Brains, genes and environment of suicide attempters

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Brains, genes and environment of suicide attempters.

A study of clinical characteristics, stress-response, the serotonin transporter, and brain lateralization.

by

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Brains, genes and environment of suicide attempters.

Abstract

Identification of symptoms or biological abnormalities that predispose to suicide or identifies specific vulnerabilities, may one day improve allocation of resources or help tailor treatment to the patient.

Paper I: We compared the predictive value of symptom-oriented questions against direct questions about suicidality in assessing risk for suicide attempts. The self-rated Suicide Assessment Scale was administered to 496 psychiatric patients, whose medical records were analyzed a year later. Four questions directly concerned with suicidality contributed to predictive power, but not the symptom-oriented ones.

Paper II: We investigated the relationship between suicidal intent and hypothalamic-pituitary-adrenal axis dysfunction in 78 suicide attempters with depression and adjustment disorder. In depressed patients, lower cortisol was associated with more serious suicide attempts.

Paper III: We investigated how life-time adversities related to past and present morbidity, and genotype. Forty-two, suicide attempters and 22 matched control patients were followed-up after 13 years. Genotype may have affected risk of attempting suicide, but showed no signs of affecting long term prognosis.

Paper IV: Previously published SPECT data showed a correlation between temperament and serotonin transporter availability in suicide attempters. We studied whether these findings were reflected in anatomical differences. Magnetic resonance images were retrieved from 13 of the original subjects, and we found changes in the globus pallidus consistent with this hypothesis.

Paper V: Altered perceptual asymmetry measured with dichotic listening has been associated with reduced white matter integrity, prefrontal functioning and response to treatment in depression. Perceptual asymmetry correlated with clinical measures of suicidality in 20 suicide attempters.

Key words:	Suicide; Suicide, attempted; SUAS-S; serotonin transporter; 5HTTLPR; MNT; temperament; suicide assessment; HPA-axis; MRI; volumetry; perceptual asymmetry; dichotic

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Publications

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VANG FJ, Mattson E, Niméus A, Träskman-Bendz L, Sunnqvist C. "A one-year prospective study to predict suicide attempts with the Suicide Assessment Scale." Submitted.

Paper II

LINDQVIST D, Träskman-Bendz L, Vang F. "Suicidal intent and the HPA-axis characteristics of suicide attempters with major depressive disorder and adjustment disorders." Arch Suicide Res 2008;12(3):197-207.

Paper III

VANG FJ, Lindström M, Sunnqvist C, Bah-Rösman J, Johanson A, Träskman-Bendz L. "Life-time adversities, reported thirteen years after a suicide attempt: relationship to recovery, 5HTTLPR genotype, and past and present morbidity." Arch Suicide Res 2009;13(3):214-229.

Paper IV

VANG FJ, Ryding E, Träskman-Bendz L, van Westen D, Lindström MB. "Size of basal ganglia in suicide attempters, and its association with temperament and serotonin transporter density." Psychiatry Res 2010 Aug;183(2):177-179.

Paper V

VANG FJ, Johanson A. "Might dichotic listening be a useful tool to discover sub-types of suicidality?" Manuscript to be submitted.

Abbreviations

^{123}I-β-CIT	^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane
5HT	serotonin (5-hydroxytryptamine)
5HTT	serotonin transporter
5HTTLPR	serotonin transporter linked polymorphic region
ACTH	adrenocorticotropic hormone (also known as corticotropin)
AD	adjustment disorder
AUC	area under curve
AVP	arginine vasopressin (also known as vasopressin or antidiuretic hormone)
BDNF	brain derived neurotrophic factor
CPRS	Comprehensive Psychipathological Rating Scale (see Appendix)
CRH	corticotropin-releasing hormone (also known as CRF)
DAT	dopamine transporter
DHEA	5-dehydroepiandrosterone
DST	dexamethasone suppression test
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
HPA-axis	hypothalamic-pituitary-adrenal axis
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MNT	Marke-Nyman Temperament scale
MR	magnetic resonance
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
ROC curve	receiver operating characteristic curve
SIS	Suicide Intent Scale (also known as Suicidal Intent Scale, see Appendix)
SPECT	single positron emission computed tomography
SUAS	Suicide Assessment Scale
SUAS-S	Self-assessed Suicide Assessment Scale
TCI	Temperament and Character Inventory
TPQ	Tridimensional Personality Questionnaire

Foreword: Some peculiarities in suicide research

People who attempt suicide differ greatly from one another. For instance, they differ in background, previous suicidal behaviour, warnings, psychiatric history, intent to cause death, and triggers.

Suicide is popularly often attributed to hardship and depression. Even though partly true, it is far from the whole story. Some diagnoses impart a dramatically increased risk of suicide, and although depression is the most common of them, there are several others too. Hardship often precedes suicide. Yet suicide can hardly be considered a normal reaction to hardship—even when faced with considerable hardship or psychiatric illness, suicide is the exception rather than the rule. More seems to be needed for a suicide to happen.

Finding the right people to participate in studies

Even experienced clinicians have had very few chances to meet patients shortly before they commit suicide (even though they will have met some who eventually killed themselves, and even more who attempted suicide). It will naturally depend very much on the kind of patients the doctor in question sees, but an informal survey of my senior colleagues suggested that experienced psychiatrists have typically met 1–10 patients (probably closer to 1) shortly before their suicide. This small number makes it very difficult to learn to recognize suicidality. It also makes it hard to know if you actually can recognize suicidality, or if you just think you can. Most of what we think we know about suicidal patients is inferred from patients having injured themselves without actually killing themselves, or expressing the urge to kill themselves, but not from patients who actually take their lives.

In the research setting too, getting sufficient numbers to draw robust conclusions is challenging. Although suicide is not a rare cause of death (accounting for ~1% of deaths) it is unpredictable. The research data we work with is the result of over two decades of work, by a large body of people, and still we find it difficult to draw firm conclusions because the patients are so diverse in relation to their number. Even in one of our finest data sets, consisting of approximately 300 suicide attempters, followed for up to 25 years from the time of a suicide attempt, only 30 people actually ended up taking their own lives. That is 30 people differing considerably in age, symptoms, personality characteristics, sex, social background, and a multitude of other factors all known to affect suicidality. This figure is fairly typical, with 3%–4% of people attempting suicide during their lives, and roughly 10% of survivors actually killing themselves within the decades to follow [1], [2]. To date, the best predictor of future suicide is actually a past suicide attempt combined with chronic or recurring psychiatric illness.

You will need to observe approximately 5 000 members of the general public for a year, to see a suicide. In a broad psychiatric sample, we observed one suicide in 500 patients observed for a year. If you observe patients after a suicide attempt, you will need to observe approximately 10–50 to see a suicide within the next year. After a couple of years, the suicide rate in suicide attempters drops, and, while remaining elevated, start to approach the general psychiatric population. These figures are approximate, but indicate a window for research in the year or two following a suicide attempt. By sampling this high-risk group, actual suicides can be studied within a reasonable timeframe and moderate sample sizes; and by studying recent suicide attempts, something might be learned that can be generalized to actual suicides.

When studying recent suicide attempters, the primary trade-off is representativity. There is no guarantee that suicide attempters who later commit suicide resemble the ones that died on their first attempt (which ~50% of suicides do [3]), or who have no recent psychiatric contact (which ~75% of suicides do not [4]). Suicide attempters as a group differ in many ways from suicide completers, most

notably in sex, diagnosis and method of the suicide attempt. Therefore it is sometimes desirable to identify the suicide attempts that resemble actual suicides most, for instance by selecting patients that only survived by pure chance. There is also no guarantee that information recorded after a suicide attempt accurately informs us of the processes that precipitated the suicide attempt.

For practical reasons, we are often forced to sample from psychiatric populations. Indeed, suicide occurs most often in the psychiatrically afflicted, but also seems to occur in people without identifiable psychiatric illness. In Western Europe and the United States, no diagnosis is found when trying to reconstruct the lives of approximately 0%–20% of suicide victims[5], with perhaps up to 50% not having an identifiable diagnosis in rural China [6]

The intent to die in suicide attempters

Some people injure themselves repeatedly, with behaviours ranging from self-cutting to frank suicide attempts [7]. While there is typically a low risk of death per attempt, they still have an elevated risk of eventually killing themselves [8], [9]. They generate a lot of activity and attention around their self-injurious behaviour, are very visible, and probably shape popular ideas about why people attempt suicide (see Figure 22, p. 145). It has been estimated that for every suicide there are 5–20 suicide attempts, and this group of patients contributes heavily to that statistic. Most can be diagnosed with a personality disorder (which in itself is a complex issue presenting many paradoxes). This behaviour is often ascribed to anxiety-reducing motives (many describe a relief upon injuring themselves) or social motives (e.g. attention seeking, communication of distress, or even manipulation). Even though these motives may not intuitively seem as serious as a genuine desire to surcease, many of these people will ultimately die by their own hands. This makes them an important group to try to understand, one which numerically dominates a sample of suicide attempters, but one which probably has a very different suicidal process than other suicide attempters.

Some people injure themselves explicitly without the purpose to die, others demonstrate a clear purpose to die, but many fall into the continuum between these two extremes. Had the two groups been very distinct, it would allow us to describe self-injury as suicidal or non-suicidal, and resolve some of the confusion described above. The distinction is often made, and "non-suicidal self injury" has in fact been suggested as a new diagnosis in upcoming revisions of the American Psychiatric Association's diagnostic system. The problem is that the two groups are not easily distinguished on closer inspection. Many people who repeatedly injure themselves express desire and plans to die, and often in fact ultimately kill themselves; and at the same time, many people who make serious suicide attempts express ambivalence towards dying.

Although it is common for victims of suicide to have discussed their intention to commit suicide, a lot of suicide victims keep their plans to themselves. "One-third to one-half of all victims" have expressed suicidal intent to their family or doctor during the preceding months [10]. However, that leaves half to two-thirds having kept their plans secret. It also seems that more lethal suicide attempts tend to be associated with fewer suicide warnings and more efforts to prevent discovery (and hence rescue). The intent to commit suicide can fluctuate, or be more static, which affects the opportunities to plan the attempt or communicate the intent. Some suicide attempts are well-planned, others are impulsive spur-of-the moment actions.

The problem of predicting suicidal acts

With many roads to suicide, predicting suicide becomes difficult. Textbooks and articles often state that no single clinical characteristic will ever to be able to predict suicide. Such a statement is of course impossible to prove, but I am not aware of anyone who believes the opposite.

Can we combine observations of different kinds to produce better predictors? Despite many attempts over the past decades, no combination of clinical characteristics has been found that predicts suicide very well. Inventing ways to build a strong classifier from several weaker ones has been attempted in many other fields (including how to build internet search engines), but is generally difficult with "noisy data" like those we can obtain [11].

Clinical predictors of suicide are often correlated (e.g. people who express the wish to die, also often express hopelessness and sadness). This leads to the situation where many characteristics are somewhat associated with suicide, but none stand out, and most cannot easily be analyzed (or even understood) independently of the others.

What is the relevance of biology?

Suicide runs in families[12], and genes seem to explain some of that familial transmission. If there are genetic risk factors, biology has to be relevant at some level. But to what extent? Is biology clinically relevant to suicide? Unfortunately, we cannot boast of any current clinical applications of the study of biology in suicidality.

Are there any known biological abnormalities in people who attempt or commit suicide? There are findings linking biological characteristics (e.g. specific genes or certain neurotransmitter metabolites) to both suicide and suicide attempts, but even the findings that have been replicated have only been replicated inconsistently (see introduction). The heterogeneity of suicide attempters in combination with clustered characteristics may be both the cause of false discoveries, and failures to replicate true findings. Many studies report significant mean differences in some biological parameter, but where only a minority of the sample actually differs from controls. Such findings could indicate real and important differences in a sub-group of suicide attempters, but they could also just reflect greater heterogeneity of suicide attempters relative to controls.

Is biology specifically relevant to suicidality? Many psychiatric illnesses show clear signs of having a biological substrate. But surely, for biology to be relevant to suicidality, it is not enough for biology to play a part in certain suicide-promoting diseases. For example, it would not be enough for a gene to predict depression which in turn confers an elevated suicide risk; the gene would need to predict suicide in depressed patients. This leads to the question if there are any plausible biological mechanisms by which suicide risk can be specifically conferred.

Certain kinds of brain dysfunction may explain how some people are capable of going through with the frightening and painful prospect of killing themselves. For example, some types of brain injury [13] are thought to make people impulsive, and perhaps impulsivity could explain why some people go through with a suicide. Other types of dysfunction that allow barriers to be overcome can be imagined, such as quick habituation to fear [14]. Such abnormalities in suicide attempters—if they exist—would be examples of "specific vulnerabilities".

If a specific vulnerability were found to be ubiquitous (or at least very common) in people who attempted suicide, it would advance our ability to predict suicide risk. As discussed, this is probably not a realistic goal, because the paths to suicide are so many—or, said another way, probably no single vulnerability will prove both common and important. If we are lucky, however, identifying specific vulnerabilities, may suggest particular treatment options, targeted training or therapy, or, as the pharmacological repertoire expands, specific medicines.

Introduction

Self-assessed Suicide Assessment Scale (SUAS-S)

SUMMARY: Scales can be used in suicide risk assessment, research, suggesting therapeutic options, or to provide medico-legal protection. Examples of scales include those measuring suicidal ideation, brief scales, reasons for living, psychological antecedents, or clinical characteristics of past suicide attempts. SUAS/SUAS-S attempts to combine direct questions about suicidality with symptoms thought to be relevant in the context of suicide.

Recommended reading

[15–17] Reviews suicide assessment instruments.

[18] In developing a scale (NGASR), the authors review the rationale for different risk indicators and how to weight them.

[19–21] Discuss assessment of suicide risk.

[22] Compares several scales in relation to the decision of admitting patients.

The role of scales in suicide risk assessment

Why would it be useful to develop a scale to assess suicide risk? Psychiatrists and clinical psychologists are often required to assess suicide risk. It has been suggested that suicidality is under-estimated when structured instruments (such as scales and structured interviews) are not used. However, in reality, little is known about the positive or negative effects of experienced clinicians incorporating such scales into clinical practice, and local traditions and experiences vary.

When patients unexpectedly kill themselves, the clinician may (rightly or wrongly) face medico-legal consequences if a clear and accepted procedure for assessing suicidality has not been documented in the patient records. Structured instruments may provide some medico-legal protection, regardless of their effect on the standard of care.

Sometimes other professionals are expected to assess suicide risk (e.g. policemen taking suspects into custody or primary care physicians), even though they cannot be assumed to have expert knowledge, experience or routine. A structured instrument (like a scale) might help them, particularly by ensuring that the most relevant questions are asked, and that risk factors are appropriately weighted.

Structured methods to assess suicidality can be useful for research purposes. This is usually done with the implicit understanding that higher scores would translate into more suicide attempts in the population studied, or a higher risk for the individual studied. (Recall that the actual events are rare, and cannot always be studied because of sample size limitations. Furthermore in clinical trials there is an obligation to protect the participant from adverse effects of a treatment, like suicide attempts.) But, unless it actually predicts suicidal behaviour in large materials, a scale's value is limited, or even counterproductive.

What is the problem with suicide assessment scales? There is no scale that sticks out as being clearly superior to its competitors at predicting suicide. With suicides being rare events (a few cases per 10 000 per year in the whole population), the positive predictive values tend to be poor when used on low or intermediate risk groups. Although several instruments show some predictive validity, they might not contribute incrementally to assessments made by experienced clinicians, and may be a second-rate substitute for one. In light of this, a valid criticism is that for clinical use we would be better off with instruments to suggest options for treatment, than trying to predict the unpredictable.

Suicidal ideation

One family of scales descends from Beck's Scale of Suicidal Ideation and includes several modifications (e.g. for self-report, administration by

paraprofessionals, computerized administration, or worst-time ideation). As the name implies, their focus is suicidal ideation, and their general content explores this very broadly: wish to live/die; active/passive desire to commit suicide; frequency/duration/intensity of ideation; distress caused by thoughts, and whether they feel congruent; control/resistance against thoughts; control over behaviour; deterrents and reasons to live/die; planning of a suicide attempt; seriousness of plans, in terms of violence, availability of means, and medical lethality; perceived lethality; sense of courage/competence to kill self; sense of likelihood of killing self; talking/writing about suicide or death; preparations or suicide notes.

Brief scales

Brief scales avoid asking redundant questions, and are usually intended for quick clinical screening, for instance by the primary care physician. These include SAD PERSONS and the Paykel scales. SAD PERSONS simply counts risk factors (e.g. sex, age, depression, previous attempt, etc.), under the dubious assumption that they can simply be added up in a meaningful way. The Paykel Suicide Scale contains five items that follow a rising staircase-model: (1) feeling life is not worth living; (2) wishing to be dead; (3) thinking about suicide; (4) seriously considering or planning suicide; and (5) having attempted suicide.

Positive scales

Other commonly used scales ask about reasons for living (e.g. Reasons for Living scale). Identifying specific reasons for living has direct clinical applicability regardless of the scale's total score or the patient's suicide risk.

Clinical characteristics

The Suicide Intent Scale measures the seriousness of a suicide attempt, as manifested by planning, determined execution and belief in its lethality (see Appendix III, p. 131). It is an example of a scale that measures clinical characteristics of past suicide attempts.

One half is based on the objective circumstances surrounding the suicide attempt (with a focus on planning), and the other is based on the patient's subjective reports. These two halves often do not agree, however [23]. The objective indicators predict later suicide in women subsequent to deliberate self-harm roughly as well as any other suicide scale you can find (AUC = 0.76) [24]. Alas, the subjective indicators do so less well, and the SIS does not perform well at all in males.

SIS scores are often said to correlate negatively with low-intent repetition, and positively with completed suicide, although results have not been quite so clear-cut. However, it is important not to simply take the SIS as a suicide prediction instrument. See it instead as a formative (not a reflective) scale, based on a series of diverse indicators that select suicide attempts of a specific quality, that may be prototypical for suicide completers.

Psychological antecedents

Some scales attempt to assess purported psychological antecedents of suicidality. For instance, hopelessness is commonly assessed in the context of suicidality, usually with Beck's Hopelessness Scale. Not surprisingly, questionnaires about depressive symptoms, hopelessness, suicidal ideation and several others tend to correlate in patients. While an optimist may see this as a sign of convergent validity, it also creates a problem in that the different scales provide more or less the same information.

Symptom-oriented questions

SUAS and SUAS-S (see Appendix II, p. 128) attempt to assess suicide risk by combining five direct questions about suicidality (wish to live/die, suicidal thoughts/plans, purpose of suicide) with fifteen questions about psychiatric symptoms thought to be relevant to suicidality (e.g. hopelessness, impulsivity). It is unclear, however, if this is a good strategy. There are both theoretical and statistical concerns about the way we have previously understood the contribution of the fifteen symptom-oriented questions (see Paper I).

The hypothalamus, pituitary & adrenal axis

Summary: The hypothalamic-pituitary-adrenal axis is normally activated under stress, but seems dysregulated in depressed patients. A multitiude of explanations have been proposed for this dysregulation, which has also been proposed to be relevant to suicidal behaviour.

Recommended reading

[25] Reviews old and new theories about HPA-axis dysregulation in depression.

[26] Discusses potential deleterious effects of corticosteroids on the brain, and reviews some of the biology of the HPA-axis.

[27] Discusses the effect of corticosteroids on the brain.

[23] Reviews the Suicide Intent Scale.

The normal HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis is colloquially often referred to as the body's stress system. Under physiological or psychological stress, the HPA-axis is activated. (See Figure 1, p. 4.) This is a perfectly normal physiological response, even to mundane stressors. (E.g. placing someone's feet in ice-water for a couple of minutes produces a measurable HPA-axis response.) In healthy individuals, the hormones fluctuate over the day, peaking two hours after waking up, and are closely connected to the human circadian rhythm. Cortisol alters cellular processes in possibly every tissue type in the body, and induces changes in cognition and behaviour [28–31].

The HPA-axis in depression

If you administer a synthetic glucocorticosteroid to a person, the normal physiological response is for that person's body to produce less of its own corticosteroid, cortisol. There are certain illnesses where people do not respond normally in this way, because their bodies are committed to over-producing cortisol. Some of these illnesses are endocrinological (e.g. an adenoma in the pituitary gland, or an adrenal tumour) or paraneoplastic (e.g. a small-cell carcinoma of the lung producing ACTH). It is also seen in depression. The synthetic glucocorticoid often used to test if cortisol produc-

tion is reduced is dexamethasone, hence giving name to the dexamethasone suppression test.

"Around 50% of depressed patients (80% if severely depressed)"[32] over-produce cortisol, and fail to lower their cortisol production as they should when given a glucocorticosteroid. HPA-axis abnormalities are over-represented in several other psychiatric conditions, but not to the same extent as seen in depression. Many depressed patients normalize their HPA-axis dysfunction with successful treatment, but HPA-axis normalization is neither necessary nor sufficient for treatment response.

The observed phenomenon embodies more than just hypercortisolemia, and is often referred to as HPA-axis dysregulation in depression. Abnormalities have been described through the entire chain of hormones (vasopressin, CRH, ACTH) culminating in elevated cortisol. Because of the multiple feedback systems involved, the HPA-axis response to pharmacological challenges can seem paradoxical. CRH given in isolation causes a surge in ACTH production in the normal person, but a bluntened response in depressed patients. When a steroid (like dexamethasone) has been administered some hours earlier, the reverse happens: there is a surge in ACTH production in the depressed patient, and only a minor increase in healthy controls.

Though the classic finding in depression is non-suppression of cortisol (sometimes called escape from suppression) during the dexamethasone suppression test, other response patterns have been observed. They include hyper-suppression (reducing cortisol production more than normal), and early versus late escape from suppression (with some people initially suppressing the cortisol production, but unusually quickly returning to normal or high levels). Their relevance, if any, is unknown.

It is still unknown if the HPA-axis hormones: (1) participate in causing depression, or (2)

Figure 1. The HPA-axis
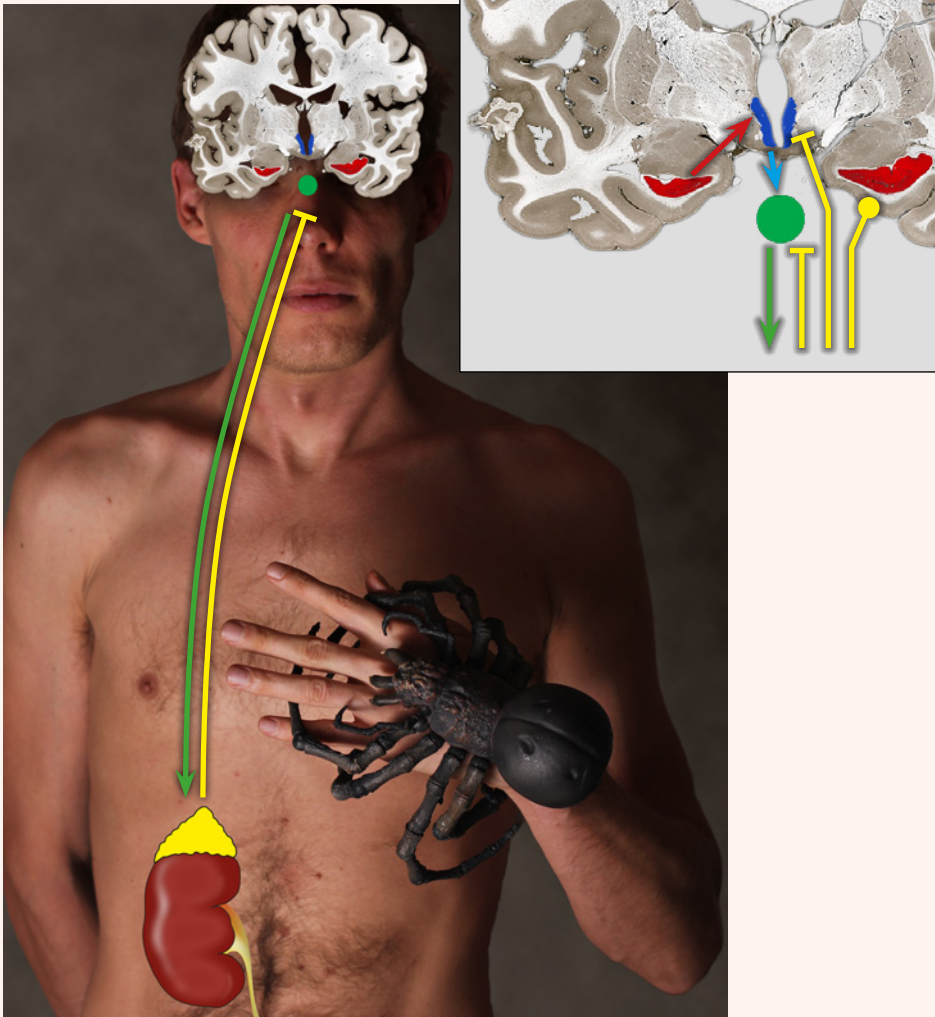
Both mundane and not-so-mundane stressors activate the HPA-axis.

Stimulated by other parts of the brain (e.g. hippocampus), the hypothalamus produces AVP and CRH. These stimulate ACTH production in the pituitary, which triggers cortisol production in the adrenal cortex. The cortisol produces negative feedback at the hypothalamus and pituitary.
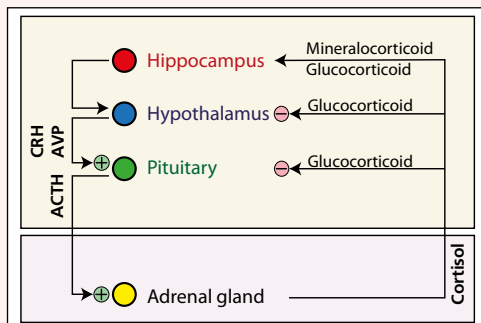
Image of the brain adapted with permission from *http://www.brains.rad.msu.edu*, and *http://brainmuseum.org*, supported by the US National Science Foundation. Photo by Fredrik Vang and Gabriel Kroon.

their dysregulation is caused by depression, or (3) the dysregulation is a "manifestation of persistent neurobiological abnormalities that predispose to depression"[25]. Some propositions are listed in Table 1.

Currently, the HPA-axis dysregulation is usually explained in terms of reduced glucocorticoid receptor signalling. Some even suggest that the cause of that reduction in signalling might be found in the receptor itself (e.g. genetic variation, or epigenetic modification of its expression) [33], [34]. However, there exist several other plausible explanations too. For example, the HPA axis interacts with the serotonergic system. It has been pointed out that 5HTTLPR (a DNA region modulating the expression of the serotonin transporter, studied in paper III) knock-out mice show a dysregulated HPA-axis, and there are a few reports of 5HTTLPR genotype affecting the cortisol stress response in humans [35–37]. The glucocorticoid receptor signalling might not be awry in depressed patients, but responding physiologically normally to other modulatory input.

The HPA-axis in suicide

Several studies have reported some ability to predict suicide from HPA-dysregulation (reviewed in [46]). In one study, around half of male suicide attempters with HPA-axis dysregulation ended up taking their lives in the decades that followed. HPA-axis dysregulated suicide attempters may also have a higher long-term risk of suicide (e.g. see illustrative survival curve in [47]), suggesting constitutional (or trait) differences. Most studies have reported high cortisol levels to be associated with suicidality.

It is unclear if this predictive power has anything specific to do with suicide, or simply comes from detecting more severe, persistent, recurrent or endogenous forms of depression. Sometimes, HPA-axis dysfunction is said to predict suicide regardless of diagnosis (which slightly favours the former explanation), and sometimes only for mood disorders [47] (which strongly favours the latter).

Table 1. Proposed explanations for HPA-axis dysregulation in depression

Explanation	Reference
HPA-axis dysregulation is caused by depression.	
High levels of cortisol cause depression. E.g. dramatic effects on mood (both towards depression and mania) are occasionally seen in patients receiving high doses of steroids.	[33]
The HPA-axis dysregulation is a "manifestation of persistent neurobiological abnormalities that predispose to depression".	[25]
Hypercortisolemia may be toxic and cause depression by affecting neurogenesis, or other changes, in the hippocampus (believed to shrink in depression), possibly mediated by BDNF levels.	[33]
CRH or vasopressin may have a direct effect on behaviour or mood.	[38]
HPA-axis dysregulation is caused by impaired glucocorticuosteroid receptor signalling.	[25], [26], [33], [34], [39]
Both glucocorticoid and mineralocorticoid receptors are involved in HPA-feedback. Both may be important because the release of cortisol is highly variable during the day, and pulsatile. (Possibly mineralocorticoid signalling is increased, while glucocorticoid signalling is decreased.)	[25], [33]
HPA-dysregulation results from lower glucocorticoid receptor signalling. Since the mineralocorticoid receptor is almost fully occupied at physiologically normal levels of steroids, it is probably not important.	[33]
Blocking glucocorticoid receptor signalling (e.g. mifepristone) reduces the toxic effects of hypercortisolemia, and might be clinically useful against depression.	[33]
Enhancing glucocorticoid receptor signalling or combined gluco/mineralocorticoid receptor signalling (e.g. dexamethasone, prednisolone) normalizes the HPA-axis, and might be clinically useful against depression.	[33]
Antidepressants exert their clinical effect by modulating the glucocorticoid receptor. The precise effect depends on tissue type and time-frame considered. In some cells the glucocorticoid receptor is up-regulated, and in others down-regulated, due to differences in second messenger systems.	[33]
Early stressful life events program the HPA-axis (possibly through epigenetic mechanisms), leaving it more or less sensitive in adulthood.	[25], [33]
Entry of antidepressants and cortisol to the central nervous system is controlled by the blood-brain barrier.	[25]
Variations in the CRH receptor 1 gene can explain constitutional HPA-axis dysregulation, and maybe suicidality, possibly by central effects of CRH in interaction with other systems.	[40], [41]
Neuroactive steroids (like estrogen, testosterone, DHEA) interact with both the serotonergic system and HPA-axis. Like cortisol, they are synthesized from cholesterol and low cholesterol has been associated both with suicide and depression, and affects serotonin metabolites.	[42–44]
Steroids affect extracellular serotoin levels in the brain, by affecting rate of clearance.	[45]

The 5HTTLPR genotype, adversities and suicide attempts

SUMMARY: The 5HTTLPR genotype has been proposed to affect sensitivity to stressful events, and may be relevant to suicidality. There is an association between stressful life-events and suicide attempts.

Recommended reading:

[48] Discusses several the problems of using questionnaires, especially checklists, to measure stressful life events.

[49] Discusses the problem of checklists encompassing events with very individual effects on people. Provides references to a number of landmark studies.

[50] Discusses adverse life events and suicidal behaviour.

[51] Argues for the effect of the 5HTTLPR gene, and reviews the literature broadly with the intent to support the claim.

[52] Positive meta-study about the effect of 5HTTLPR on depression, with critique of some negative meta-studies.

[53] A critical review of several details pertaining to the original study, including the effect of time-frame considered and chronicity of illness on the results.

[54–56] The original article reporting an interaction between adversities and 5HTTLPR genotype in evoking depression by Caspi et al., and two notable failures to replicate.

Genetic studies of suicidality have generated the over-all view that: (1) there is familial transmission of suicide by some mechanism; (2) genes seem to account for some of this familial transmission; (3) one mechanism is that genes transmit psychiatric maladies (e.g. affective disorders or psychoses); (4) apart from this, a specific component of suicidality may be transmitted; and (5) this might turn out to be mediated by traits like impulsivity, anger, hostility, impaired decision making, reduced cognitive flexibility, altered stress response, or something yet unknown [57].

The most studied genes in suicidal behaviour relate to monoaminergic neurotransmission, especially serotonergic. Several other genes have been considered too, with the BDNF gene being the most notable. (Recently reviewed in [40], [41], [58–60].) To date, the genetic findings in suicide have been inconsistent, as for all other complex traits. Over-all, they point to a role for the 5HTLPR genotype, the gene coding for tryptophan hydroxylase, and possibly the BDNF gene [40], [57], [60], [61]. However, the 5HTTLPR genotype has been found to be implicated in a wide array of psychiatric disorders, and may not affect suicidality specifically.

Description of the 5HTTLPR genotype

The 5HTTLPR refers to a promotor region in the proximity of the gene for the serotonin transporter (which is particularly relevant to depression since the transporter is the target of several successful antidepressants). There are a number of variations [62], but we distinguish between the two most common, short (S) and long (L), alleles (differing by a tandem repeat). The S-allele has been shown to reduce the expression the serotonin transporter in cell cultures, although the results in vivo are contradictory [63]. Hence, in the living person, the 5HTTLPR genotype may affect expression of the serotonin transporter only under specific physiological conditions (speculatively, perhaps early development or in interaction with specific hormones).

5HTTLPR genotype in psychiatric illness

Caspi et al. [54] originally reported that both the number of recent adverse life events and the 5HTTLPR genotype in synergy affected various measures of depression and a history of suicidal ideation/attempts. The presentation of the results carried popular appeal because people without the S-allele seemed virtually unaffected by stressful events, whereas S-allele carriers showed increasing morbidity with more stressful events. Since then there have both been a number of notable suc-

cesses and failures to replicate Caspi's findings.

It has been proposed that the way in which adverse events are measured strongly affects the results. Concerning the 5HTTLPR, stress and depression, two meta-studies concluded that there was no effect of the 5HTTLPR genotype [64], [65], but were very restrictive in their choice of studies to include. A third meta study [52] concluded there was an effect, and that failure to replicate occurred in questionnaire based studies (which also happened to be the largest studies). All the same, a recent study, very similar to the original study, could not replicate the effects of the 5HTTLPR genotype either [55].

A lot of research provides further evidence in favour of the 5HTTLPR genotype being linked to vulnerability to psychiatric illness. Table 2 summarizes some recent findings, with the purpose of illustrating the breadth of findings. Since the question of the 5HTTLPR genotype has become so extensively researched, some findings probably a good deal more than one in twenty are likely to be false positives. All the same, there is a considerable corpus of findings relating 5HTTLPR to cognitive and neuroendocrinological processes relating to the fear/stress response (also reviewed in [51]).

There is an increasing sense communicated in the literature that the actual manifestations of the genotype-by-stress interaction may also interact with sex or gender, social support, and other genes. It is, of course, reasonable to include interactions with sex/gender and social support in any statistical model with the sample size to support it, given how these parameters affect the baseline incidence of various psychiatric disorders. Under the circumstances, however, it is unclear whether the reports of complex interactions represent a true effect, or the increased rate of type I errors under the practice of testing interactions when main effects are not significant.

5HTTLPR and suicidality

Since the 5HTTLPR has been associated with such a broad panorama of psychiatric morbidity, we need to supply a reason why we think it deserves attention in the study of suicidality. In a recent review [103], the authors state the opinion that: (1) the serotonergic system has been implicated in suicidality; (2) 5HTTLPR has been implicated in hopelessness, hostility and impulsivity. Another reason (as discussed more fully in Paper III) is that the genotype may affect suicidality across diagnostic boundaries. One possible mechanism is by affecting the trait-like life-long tendency to easily react with anxiety and low mood regardless of identifiable psychiatric illness—which is, of course, the essence of personality traits like high harm avoidance, low validity, or high neuroticism.

Adversities and suicidality

Both recent adversities and childhood adversities have been associated with psychiatric morbidity, including attempted suicide (e.g. [50]). Psychological autopsies also support the importance of recent adversities in suicide completers [104]. Whereas some suicide completers have a long history of difficulties beginning in childhood, others have a relatively brief period of difficulties before committing suicide [105]. Relatively little is known specifically about the role of childhood adversities in this latter group. It is also quite possible that childhood adversities are more strongly associated with suicide attempts, than actual suicides [106].

Although some adversities preceding suicide fall outside the range of normal human experience, most are not extraordinary in that respect. Examples include bereavement, breakdown of important relationships, interpersonal conflicts, financial or legal trouble, or difficulties at work/school.

Childhood neglect, emotional abuse, physical abuse and sexual abuse have repeatedly been associated with suicidal ideation and behaviour [107–109]. These "occur in families characterized by a range of adversities that might also contribute to the development of psychopathology, such as familial conflict, parental psychopathology, and suicide attempts in abusing parents"[50] and absence of protective factors. This makes it difficult to differentiate between the effects of reported adversities, and the effects of unrecorded psychosocial stressors and disadvantages that coincide with them. It is also very difficult to know whether adversities cause or are caused by the patient's mental illness. In fact, the advent of recognizable symptoms that are serious enough to warrant a diagnosis may have been preceded by

Table 2. Selected findings about the 5HTTLPR genotype

Specific psychiatric illnesses	
5HTTLPR associated with alcohol abuse	[66]
5HTTLPR associated with violent suicides and antidepressant triggered hypomania/mania in bipolar disorder.	[67], [68]
5HTTLPR associated with binge eating.	[69]
5HTTLPR associated with chronicity in depressed patients.	[70]
5HTTLPR is probably not associated with panic disorder, but may be associated with symptom profile consisitent with depressive comorbidity	[71–74]
5HTTLPR is associated with post-traumatic stress disorder	[75], [76]
Amygdala	
Amygdala activation in certain tasks affected by 5HTTLPR in healthy peolpe.	[77–79]
5HTTLPR affects amygdala volume, both in patients and controls.	[80]
5HTTLPR affects connectivity between amygdala and prefrontal cortex, with differences between depressed patients and controls.	[81]
Hippocampus	
Smaller hippocampus volume in depressed patients with SS genotype	[82]
Thalamus	
Enlargement of limbic parts of the thalamus	[83], [84]
Attention	
EEG shows interaction between attentional effort and 5HTTLPR on evoked potential.	[85]
5HTTLPR affects attentional bias to negative words and faces, and threatening stimuli	[86–89]
Impulsivity	
Serious life events associated with increasing impulsivity in LL, and decreasing impulsivity in SS/SL borderline patients.	[90]
Increasing impulsivity of healthy subjects during tryptophan depletion, where 5HTTLPR predicts increase in impulsivity.	[91]
5HTTLPR associated with impulsive/disinhibited traits in inmates.	[92]
HPA activity	
5HTTLPR genotype affects the cortisol response to stress	[35], [93]
5HTTLPR genotype interacts with BDNF genotype in affecting response to stress	[94], [95]
Risk aversion	
5HTTLPR affects risk-taking in community sample	[96]
5HTTLPR affects social reward and risk taking in macaque monkeys.	[97]
Personality and temperament	
D4 receptor and 5HTTLPR genotypes interact to determine negative affect in infants.	[98]
BDNF and 5HTTLPR genotypes interact in determining conscientiousness in adolescents.	[99]
Infant's 5HTTLPR genotype modulates correlation between infant's irritability (Mother & Baby Scale) and mother's anxiety	[100]
5HTTLPR affects self-directedness (TCI) and interacts with other serotonergic genes and education in affecting novelty-seeking (TCI)	[101]
5HTTLPR associated with neuroticism in a healthy sample	[102]

Some findings reported with regard to 5HTTLPR genotype (see Supplementary Method, SM305). In several cases, there have been both positive and negative findings, and many will probably not withstand the scrutiny of time. However, there seems to be a robust cluster of findings around the fear/stress response, attentional bias to negative/fearful stimuli, amygdala reactivity and the HPA-axis.

years, or a life-time, of sub-clinical manifestations that insidiously interfere with the afflicted person's life.

How far back in time should we search for events that contribute to mental illness? The reported impact-duration of adverse life events is also considerably shorter (e.g. 1-3 months in depression [110]) than the interval of years or decades often considered in research. Adversities occurring years before onset of illness probably do not cause illness directly, but may indicate vulnerability [53] or chronic illness. However, there is reason to suspect that early life events may be particularly important in determining vulnerability to mental illness [111], or may boost the effect of later adversities [112]. This has been most convincingly demonstrated in animals, which can be experimentally subjected to childhood stress. In that sense, a distant adversity may still be considered part of the cause, without being the trigger that caused the illness.

Subcortical structures in suicidality

Summary: Although various parts of the pre-frontal cortex has most often been implicated in suicidal behaviour, there are also reasons to consider the basal ganglia.

Recommended reading:

[113] The original SPECT study, from which this study descends.

[114], [115] Organization of the pallidum and striatum, and its relevance to psychiatric disorders.

[116–119] Case studies of personlity changes following basal ganglia lesions.

Subcortical structures in psychiatric illness

We studied volumes in deep grey-matter regions of the brain: hippocampus, amygdala, putamen, caudate and globus pallidus. Loss of hippocampal volume is very often found in depressed patients and may be present as a marker of vulnerability to both depression and anxiety disorders [120]. We are increasingly becoming aware that the basal ganglia, usually associated with movement disorders, may also be important in psychiatric disorders, especially impulse control related (like obsessive-compulsive disorder). The theoretical rationale for considering the basal ganglia in emotional (not just impulse control) related disorders is that parts of the basal ganglia participate in loops involving areas like the orbitofrontal cortex, cingulate cortex and the limbic system[114], [115], [121]. Some parts of the basal ganglia are also clearly important in representing reward [122].

There is a considerably body of evidence demonstrating volumetric changes in the basal ganglia in: schizophrenia (usually reductions when never treated with anti-psychotic medication, and increases in medicated schizophrenics [123–129]), attention-deficit hyperactivity disorder (reductions in children, [130], [131]), obsessive-compulsive disorder and Tourette's (mostly increases, especially in caudate [120], [132]), unipolar depression (reductions, [120]), bipolar disorder (possibly increases, [120], [129], [133]). There is also reason to suspect that anti-psychotic medicines can alter the size of the basal ganglia [127], [128], [134]. Importantly, the size-correlations observed between different parts of the brain (including the basal ganglia) differ between healthy controls, unipolar depression and bipolar disorder (and most likely other diseases too) [133]. We know very little about the cellular nature of the changes that affect the sizes of basal ganglia in psychiatric illness, which neural circuits are affected, or whether they cause or are caused by changes in other brain areas (including white matter). We also know very little about which parts of the individual structures are affected, which is important, because different parts of each structure project to different brain areas. It is often assumed that parts of the basal ganglia with frontal or limbic connectivity would be involved in psychiatric disease.

It is worthwhile to note that lesions/stimulation of both the caudate (more certainly) and globus pallidus (less certainly) have been observed to produce psychiatric symptoms. "Effects such as hypomania, merriment, and laughter have been reported with [deep brain stimulation in humans] in the STN [subthalamic nucleus], GPi [globus pallidus internus], and zona incerta."[135]. There have also been experiences of "substantial anti-depressant effects, as well as depression rebound with cessation of therapy"[135] when stimulating the ventral caudate, known to be involved in processing reward/pleasure. There have been reports of suicide after deep brain stimulation to the globus pallidus [136], [137]. Some patients have presented with lesions in the globus pallidus following anoxia after a drug overdose, with reports of "anhedonia" [116], and "flat affect, social withdrawal, loss of interest, inability to "feel," and lack of concern"[138].

The brain in sucidality

Commonly cited findings in suicide attempters include: (1) HPA-axis dysregulation; (2) Increased prolactin production after fenfluramine is given to boost serotonin release; (3) less serotonin transporter and more 5HT2A receptor binding on

blood platelets; (4) altered serotonin metabolites in cerebrospinal fluid; (5) low cholesterol; (6) 5HT1A and 5HT2A receptor binding increased pre-frontally in post-mortem studies [139], [140]. All these findings suffer from lack of consistent replication, and are difficult to tease apart from underlying psychiatric morbidity (e.g. depression).

Neuroimaging studies of suicidality have together reported differences in most areas of the brain (recently reviewed in [141]). The most consistent findings using several imaging techniques involve frontal areas of the brain (usually taken to reflect impaired decision making, selection of short-term over long-term reward, risk-taking, or impulsivity) [141], [142]. A novel and interesting re-interpretation of the pre-frontal alterations is to understand them as being related to mental pain [143]. Another novel line of inquiry is white matter integrity, as white matter hyperintensities (especially periventricular) are over-represented in suicide attempers [144–146]. (These hyperintensities were even over-represented in young suicide attempters, which is important because hyperintensities are non-specific radiological findings of unclear origin, more abundant with higher age.)

A minority of studies have implicated the basal ganglia, but research might simply not have focused on this area that features in most textbooks for its motor functions. One study found altered diffusivity in white matter bordering the basal ganglia, and the area of the putamen and globus pallidus itself, associated with suicidality (history of attempt) in depression [147]. Another study found grey matter reductions in the caudate and anterior cingulate gyrus to be associated with suicidality (own attempts vs. first-degree relatives with sucide attempt vs. no suicide attempts) in depressed patients [148]. A post-mortem study of serotonin receptors and their second messengers found the caudate to be the area with "highest alteration of the serotonergic system"[149] in violent suicide victims. An older study found altered density of serotonin receptors in the globus pallidus in depressed suicides [150].

Figure 2. Some subcortical structures
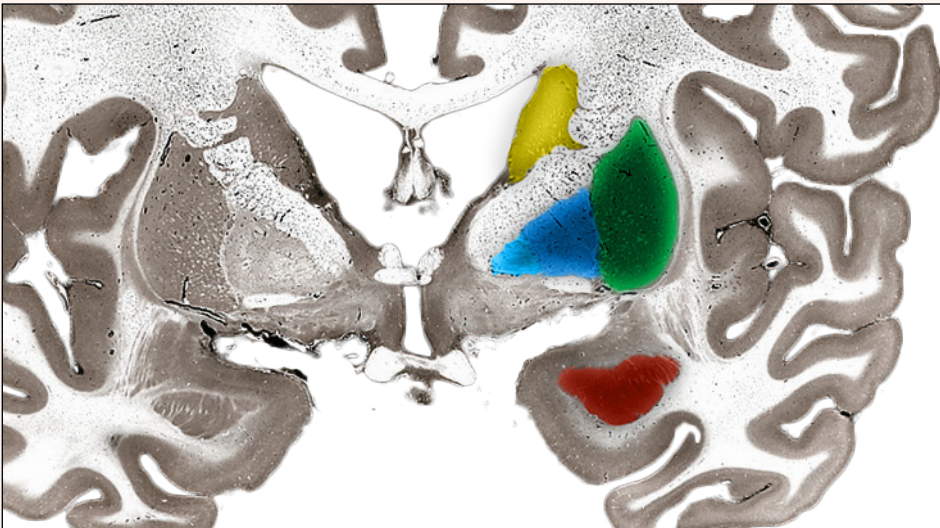
This diagram shows: the globus pallidus (blue), putamen (green), caudate (yellow) and amygdala (red).

Image of the brain adapted with permission from *http://www.brains.rad.msu.edu*, and *http://brainmuseum.org*, supported by the US National Science Foundation.

Dichotic Listening

SUMMARY: Dichotic listening is an experimental method using sounds, and can be used to probe functional lateralization of the brain. Depending on the task at hand, a right-ear or left-ear advantage appears, as a result of hemispheric specialization and attentional processes. Dichotic listening has not previously been used to study suicidality.

> **Recommended reading:**
>
> [151–154] Review explanations for the dichotic ear advantage.
>
> [155], [156] Depression, treatment response and dichotic ear advantage.

Dichotic listening refers to an experimental procedure where two different sounds are presented simultaneously, but in different ears.

The ear advantage (also called perceptual asymmetry) in dichotic listening tasks refers to participants performing better on one ear than the other, probably because of differences between the left and right brain hemispheres. Interestingly, perceptual asymmetry (as well as EEG asymmetry) has been linked to treatment response in depression, white matter integrity and pre-frontal functioning.

Explaining the ear advantage

In one precedure, we present two consonant-vowel utterances dichotically (for instance /ba/ in the left ear and /pa/ in the right ear). Because the sounds are quite similar, they compete with each other, and usually one utterance is perceived more clearly than the other. With well-designed sounds, this interference can be so pronounced that the participant only perceives a single sound—i.e. the two sounds fuse into a single percept.

Because most people have a left brain hemisphere advantage in processing speech-like sounds, participants usually perceive more utterances presented in the right ear, than in the left. This is the so called right ear advantage in verbal dichotic listening tasks. The procedure we use is usually referred to as the consonant-vowel dichotic listening task, and a commonly used alternative is the fused dichotic words test where specially synthesized rhyming words are presented dichotically [157]. The right ear advantage in verbal material is the most robust, and most studied, example of perceptual asymmetry.

In other tasks, there is a left-ear advantage. We first present two tones dichotically (i.e. a different tone in each ear), and after a brief silence, a third tone is presented binaurally (i.e. in both ears). The participant then needs to decide if the third tone was identical to one of the first two. In this task, there is a slight left ear advantage. Tasks that tend to produce a left ear advantage include those demanding recognition of pitch, timbre, and loudness.

When particular qualities of speech or music are considered, the picture becomes somewhat more complex. Language prosody—the "music" of speech—is often impaired by lesions in the right hemisphere language areas, and dichotic tests of prosody detection yield a left ear advantage. Similarly, not all musical tasks produce a left ear advantage. For instance, comparing the duration of notes or speech produces a right ear advantage [158]. One theory is that processing of sounds carrying linguistically relevant information is left-hemisphere lateralized; another theory is that purely acoustic qualities determine lateralization [159], perhaps with the left hemisphere providing better temporal and the right better spectral resolution.

Ear advantage and brain lateralization

The dichotic ear-advantage is probably caused by cortical lateralization, asymmetrical relay of input in the brain stem, or both [151], [160].

The classical way of determining lateralization of important brain functions is to inject a barbiturate into either the left or right carotid, and study the effect on the patient [161] (the Wada test). Language lateralization measured with the Wada test predicts left ear or right ear advantage on a verbal dichotic listening task [162]. Similar results are found when comparing ear-advantage

to fMRI-based measures language lateralization [163]. These studies looked at small groups of patients about to undergo neurosurgery, and may not generalize to a healthy population. Nonetheless, since the left-hemisphere language specialization is a robust finding even in healthy groups, it remains a compelling account: somehow, left-hemisphere specialization in language coincides with specialization in speech-like sound.

Co-lateralization between language and speech-like sound is not perfect. In the consonant vowel task which we use, only 85%–90% of right-handed persons and 65% of left-handed persons have a right ear advantage (compared to about 95%–99% and 65%–70% respectively being left-hemisphere dominant for language according to the Wada test), with a slightly greater right-ear advantage in males [164]. In some groups of people, there may be also be a correlation between the anatomical planum temporale asymmetry (involved in language processing, and usually larger in the left hemisphere [165]) and perceptual asymmetry on a verbal dichotic listening task. (Described in right-handed males and dyslexic patients [166], [167].)

Hemisphere specialization has classically been studied in patients where communication between the hemispheres has been disrupted. For information to be passed between the brain hemispheres, the neural activity has to be coordinated through the fibres of the corpus callosum or the minor commissures that connect the two halves of the brain. In the auditory pathways, both contralateral and ipsilateral input reaches the cortex, although the contralateral input is dominant. This means that a split brain patient can hear on both ears as long as only one sound is presented, but only on one ear during dichotic presentation of sounds. The dichotic competition is thought to block the ipsilateral input. (This differs from the visual pathways, most studied in split-brain patients, where the projections are strictly contralateral for most of the visual field.) Damage to the posterior parts of the corpus callosum increases the perceptual asymmetry when presenting speech-like sounds dichotically. Consistent with theory, there is almost no effect on the number of correct right-ear reports, but there can be a dramatic fall in the number of correct left-ear reports.

This has been demonstrated consistently in split-brain patients and in several conditions affecting white-matter integrity [152], [168]. (However, in patients with callosal agenesis, the perceptual asymmetry is not altered greatly, probably because the brain adapts.) Importantly, left-right connectivity (measured using MR based white-matter tractography) seems to account for left ear performance in healthy persons too [169]. Additionally, performance on verbal dichotic listening tasks increases in children and decreases starting in the fifties, in parallel with age-related changes in the corpus callosum.

The mechanism behind perceptual asymmetry has mostly been studied in speech-like sound. There is, however, evidence to suggest that the right hemisphere is specialized in melody or spectral resolution [165], which would also make the explanation applicable to tonal dichotic stimuli.

Explanations beyond brain lateralization

It is intuitively appealing to think that the processing of speech-like sounds and language co-lateralize, and several studies support the claim [165]. However, even if it turns out to be true, this cannot be the whole story.

The right-ear advantage in verbal tasks can be extinguished or even reversed under certain experimental conditions (see [151] for details). Examples include attending to certain spatial locations, responding non-verbally [170], or arousal in anticipation of electrical shocks. Perceptual asymmetry is also affected by stress, the menstrual cycle [171], and smoking [172], [173], which is not believed to affect the brain structurally. Also, the frontal lobes seem to play an important role too, with unilateral lesions causing a considerable performance drop on both ears, but primarily the contralateral one [174].

Several experimental results suggest that the brain might pre-activate the left-hemisphere in anticipation of verbal material, leading to an inadvertent shift of spatial attention to the right [151], [168]. The corpus callosum might then be necessary to coordinate attention/activation, rather than transferring auditory information, and the

left hemisphere might not be better at processing speech-like sounds (although still specialized in language). The left hemisphere still has an advantage during a verbal dichotic listening task, but only because it is primed in anticipation.

Shifting attention

If the participant is asked to listen to both ears, the experiment is said to be performed under divided attention. If the participant is asked to pay attention to only one ear, it is said to be forced left ear attention or forced right ear attention. Some chronically ill psychiatric patients are only able to shift their attention to the advantaged side. In the case of the consonant-vowel task, that would concretely mean that they would perform well during conditions of forced right ear attention, and poorly under conditions of forced left ear attention. Inability to shift attention is thought to reflect deficits in top-down attentional modulation.

Relevance to psychiatric illness

Both perceptual asymmetry and EEG asymmetry have been investigated in depression, with the suggestion that they are altered in depression, can predict response to treatment, or can guide treatment selection [155], [175–179]. A shift of perceptual asymmetry towards the right ear has been found to be associated with treatment response in fluoxetine [156], [180], bupropion [155] and cognitive-behavioural therapy [181]. There are unfortunately complex interactions between sex and EEG/perceptual asymmetry, that make interpretation difficult [156], [176]. Ear advantage on verbal dichotic listening tasks and EEG asymmetry are probably correlated both in depressed and non-depressed patients [182], [183]. There is also a small positive association between verbal right ear advantage and plasma cortisol after dexamethasone [175].

Transient changes in performance have been observed during manic episodes, that then appear to normalize, perhaps in association with specific symptoms [184], [185]. Anger/suspiciousness was found to be associated with an isolated improvement of the left-ear performance on the tones task; elation/grandiosity was related to a bilateral performance drop most evident on the right-ear on the verbal task [185]. The performance increase is interesting because it cannot easily be explained by a "manic response style", and occurs only on one ear, and the non-dominant one at that. Usually, a drop in the ability to deploy attentional resources leads to a drop in performance on the non-dominant ear. Differences in early auditory processing, already evident in the brainstem, are believed to exist in schizophrenics and possibly their relatives, and differences in perceptual asymmetry in psychotic disorders may require a completely different interpretation.

Originally based on behaviour observed in unilateral lesions and seizures, it was proposed that the right hemisphere was specialized in emotional processing [153]. The idea of an "emotional hemisphere" or "sad hemisphere" squares poorly with the current zeitgeist in neuroscience, but there is undeniably a large body of publications that suggest some sort of emotional lateralization (e.g. [186]). Later proposals were that the two hemispheres differ in activation when confronted with emotions having positive versus negative valence, prompting activation versus inhibition, or approach versus withdrawal [153].

Relevance to suicide

EEG asymmetry has been studied in suicide attempters [187] and related to suicidal ideation during treatment of depression [188]. To our knowledge, however, dichotic listening has not been used to study suicidality. Three reasons to consider dichotic listening in the study of suicidality are that: (a) perceptual asymmetry has been linked to prognosis in the treatment of depression [156]; and (b) adequate frontal-lobe functioning may be important in modulating the perceptual asymmetry [174], [189].

Aims

Paper I

AIM: To investigate if SUAS-S (a self-rated scale for assessing suicide risk) predicts suicide attempts within one year.

MOTIVATION: Assessing suicide risk is an important clinical concern. SUAS-S is a self-rated scale (questionnaire) that attempts this by combining questions about general psychiatric symptoms with specific questions about suicidality. It remains a subject of research how and when symptoms should be taken into consideration.

Paper II

AIM: To investigate if neuroendocrinological abnormalities are associated with seriousness of suicide attempts.

MOTIVATION: Another aspect of suicidality is suicidal intent, the intent to actually cause death when injuring oneself. Depressed patients often show a dysregulated cortisol production, but little is known about if this dysregulation—typically worse in serious, melancholic depression—is independently associated with more serious suicide attempts.

Paper III

AIM: To investigate if genotype affect probability of a suicide attempt or long-term prognosis.

MOTIVATION: There have been reports of the 5HTTLPR genotype affecting sensitivity to stress, resulting in different rates of depression, suicide attempts, and measurable differences in HPA-axis activation. The finding has been contested, and even if true, it is unknown whether this translates into differences in long-term prognosis of suicide attempters.

Paper IV

AIM: To investigate if anatomical differences in the brain explain the correlation between temperament and serotonin transporter availability seen in suicide attempters.

MOTIVATION: Research has both implicated the basal ganglia and limbic structures in mood regulation. A previous study found a correlation between temperament and serotonin transporter availability in suicide attempters. By analyzing the magnetic resonance images of the brain from that study, we wish to determine if the temperament–neurobiology association is also reflected in anatomy.

Paper V

AIM: To investigate if dichotic ear advantage correlates with clinical measures of suicidality.

MOTIVATION: Dichotic ear advantage may be clinically related to treatment response in depression, white matter integrity, and pre-frontal functioning, but has not been studied in suicidality. It may prove to be a useful tool to detect sub-types of suicidality.

Materials and methods

Participants

An overview of participants is given in Table 3, and more detailed descriptions are given in the individial articles. The participant overlap between the studies is shown in Figure 3 (p. 18).

In paper I, the patients were 496 psychiatric patients (out-patients, in-patients, and psychiatric emergency room consultations). Most patients had either mood or anxiety disorders, but the whole spectrum of psychiatric disorders was represented.

In papers II–IV, patients were taken from a pool of approximately 300 suicide attempters that entered the research programme between 1987 and 2001. Suicide attempts requiring medical care (either at the psychiatric emergency room, the main hospital emergency room, or at a somatic ward) routinely triggered a psychiatric consultation. During this period, roughly half of the suicide attempters receiving a psychiatric consultation were referred to a particular ward specializing in suicide attempts. Approximately 90% of them were offered to participate in a research programme, and 90% in turn accepted. Reasons for not offering participation typically included

very short stay or very serious condition, implying exclusion of the extremes. Patients could choose to participate in some or all of the research.

In paper II, patients were selected on the basis of only having an axis I diagnosis of depression or adjustment disorder, and no somatic disease known to affect the investigations carried out.

In paper III, 102 patients were tracked down who had been hospitalized in the interval 1986-1992, and had participated in all of the research. Seventeen patients had died (of which 11 were confirmed suicides), 43 declined to participate, and 42 participated in the follow-up. Psychiatric controls were matched for sex, approximate age, diagnosis, and time of hospitalization, based on 270 medical records reviewed. Of these 71 were contacted, 23 agreed to participate, one was excluded, leaving 22 controls. The intention was to find 42 controls, but proved infeasible.

In paper IV, the patients had made a serious suicide attempt (as measured by a cut-off score of 18 on the SIS, with patients studied in paper II effectively scoring 20–24), and had not

Table 3. Participants

	Study				
	I	II	III	IV	V
N	496	78	64	15	20
Patients	Heterogeneous clinical sample	Admitted suicide attempters	Admitted suicide attempters.	Admitted suicide attempters.	Admitted suicide attempters.
Patients' diagnoses	Mixed	Depression and adjustment disorder.	Mixed	Mixed	Mixed
Patients' level of suicidality	Mostly low.	All made recent attempt(s)	All made previous attempt(s).	All made serious recent attempt(s).	All made recent attempt(s)
Control group	None	None	Admitted psychiatric cntls.	Healthy controls.	None

Overview of important differences between participants in the five studies.

been exposed to anti-depressant or anti-psychotic drugs for at least six months prior to the suicide attempt. Healthy controls were were matched by age and sex, and were screened to exclude psychiatric disease, anti-depressants and anti-psychotic medication.

In paper V, the patients were hospitalized following a suicide attempt that led to a psychiatric consultation. They were not treated at a specialized ward, however.

Figure 3. Patient overlap between studies
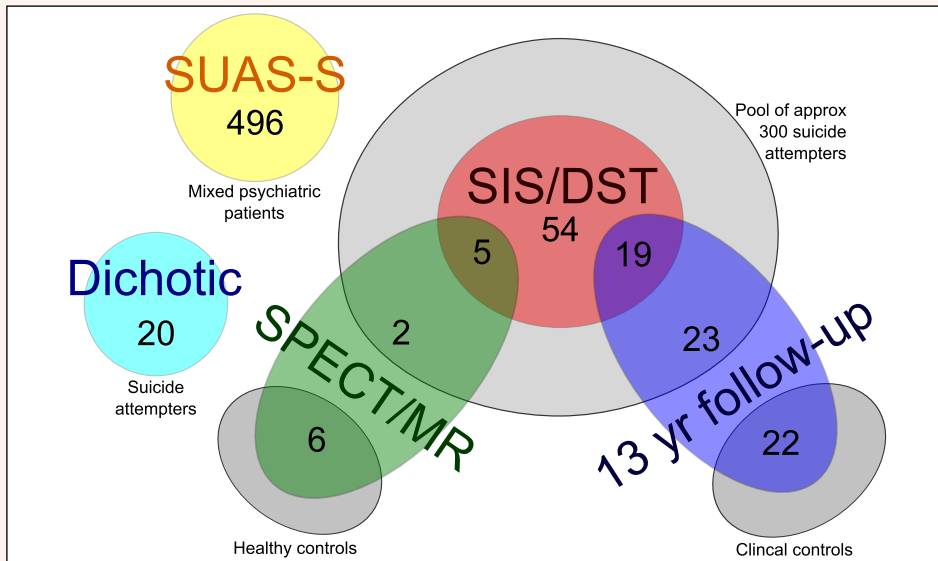
Patients participating in multiple studies. (Paper I=SUAS-S, paper II=SIS/DST, paper III=13 year follow-up, paper IV=SPECT/MR, and paper V=Dichotic Listening.)

Table 4. Methods used

Study	Method chosen	What it strives to measure
I	Suicide Assessment Scale (SUAS-S)	Suicidality
I	Review of medical records	Suicide attempts, self-injury, diagnosis
II	Dexamethasone suppression test (DST)	HPA axis dysregulation
II	Suicide Intent Scale (SIS)	Seriousness of suicide attempt
III	Custom made interview	Adversities
III	Polymerase chain reaction (PCR), bi-allelic	5HTTLPR genotype
III	Comprehensive Psychopathological Rating Scale (CPRS)	Psychiatric morbidity
IV	^{123}I-β-CIT SPECT	5HTT/DAT availability
IV	1.5 T MR imaging	Brain anatomy
IV	Marke-Nyman Temperament Scale (MNT)	Temperament
V	Dichotic listening	Brain lateralization
V	Suicide Assessment Scale (SUAS-S)	Suicidality
V	Montgomery-Åsberg Depression Rating Scale (MADRS)	Depressive symptoms

Scales and questionnaires

SUAS and SUAS-S

SUAS and SUAS-S try to assess suicidality, using fifteen questions about symptoms thought to be relevant to suicidality, and five questions about desire to live/die and suicidal thoughts/plans (see Appendix II, p. 128).

SIS

The Suicide Intent Scale (SIS, see Appendix III, p. 131) is used to assess suicidal intent (the intent to actually kill oneself) behind a suicide attempt, as manifested by planning, determined execution, and expected lethal outcome. We use it as an indicator of seriousness of a suicide attempt (study II), and believe that suicide attempters with high SIS scores may better resemble patients who actually kill themselves (study IV).

CPRS

The Comprehensive Psychopathological Rating Scale (CPRS, see Appendix III, p. 131) is used to rate psychiatric symptoms. We have used it as an indicator of global burden of symptoms. For this purpose, we used a total CPRS score, which covers a very wide range of symptoms.

MNT

The Marke-Nyman Temperament (MNT) scale attempts to assess three postulated dimensions of temperament: solidity, validity and stability. (See Table 5.) The MNT is very similar to the widely used Temperament and Character Inventory (TCI) and the Tridimensional Personality Questionnaire (TPQ). Studies using the TCI or TPQ can probably be compared to results obtained with the MNT.

Table 5. Comparison of MNT and TCI		
Low MNT solidity	**Low MNT validity**	**High MNT stability**
Changing friendships. Fluctuating opinions and interests. Seeking fun and excitement, and dislikes boredom. Casual or imaginative style. Quick to form an opinion. Quick decisions. Driven by the spur of the moment. Preferring a good story to a true one. Saying things just to shock. Bohemian. Theatrical.	Easily feeling stressed or tired. Feeling that tasks take a toll. Lack of energy. Set in habits. Low confidence in ability to take on new tasks. Dislikes taking quick decisions. Easily disturbed, and disapproves of disruptions. Anxious about future. Difficulty in catching up on lost sleep.	Confides in, and shows interest in others. Likes others to do the same. Wants to work with others, preferring to be liked over respected. Prefers a night with friends over a night alone with a book. People matter more than principles. Prefers intimate and warm contact with people. Easy to make contact with children.
Similar to TCI high novelty-seeking	**Similar to TCI high harm-avoidance**	**Similar to TCI high reward-dependence**
which is described to be composed of exploratory excitability; impulsiveness; extravagance; and disorderliness.	which is described to be composed of anticipatory worry; fear of uncertainty; shyness; and fatigability.	which is described to be composed of sentimentality; openness to warm communication; attachment; and dependence.

A description of MNT sub-scales, and corresponding TCI dimensions. TCI also contains other sub-scales not listed in this table.

Interview: life-time adversities

Adversities were recorded using a custom-made semi-structured interview after a suicide attempt that led to hospitaliztion. "The interview was divided chronologically into four sections, always administered in the same order: the period of life between [the suicide attempt] and follow-up; ages 0 – 12; ages 13 – 19; and ages 20 to the [suicide attempt]. The interview covered a wide range of areas, including negative life events and adversities (inspired by existing scales ...), living conditions, suicide attempts and psychiatric morbidity. The

interviewer filled in a response sheet during the interview, where most responses were recorded as dichotomous ... choices... If the patient reported an event, he or she was asked to expand, and additional details from the interview were liberally noted on a sheet of paper, but are not considered here. In this way, the interviewing psychiatrist could clarify ambiguities and correct misunderstandings, in the manner done during a clinical interview, and verify that a reported adversity really qualified as such" (Paper III).

Imaging

^{123}I-β-CIT SPECT

SPECT image analysis [190] was done by a collaborating group (J.-A. A. and E.R., see acknowledgements). ^{123}I-β-CIT is a radioactively labelled cocaine analogue that binds to serotonin transporters, dopamine transporters and norepinephine transporters. First, 200 Mbq ^{123}I-β-CIT was administered intravenously (at time $t = 0$). SPECT scans (taking 30 minutes each) of the brain were collected, starting at $t = 1$, 6 and 22 hours. An oral dose of 20 mg citalopram was given at $t = 1.5$ hours (i.e. right after the first SPECT scan).

      The binding potential is the concentration ratio of specifically bound ligand (e.g. to the serotonin transporter) to passively dissolved ligand in the tissue. Separate estimates for serotonin transporter binding potential and dopamine transporter binding potential were estimated

assuming: a ^{123}I half-life of 32 hours; citalopram peak serum concentration at $t = 6$ hours followed by exponential decay with half-life 36 hours; and no dopamine transporters in the cerebellum. Binding to norepinephrine transporters was not taken into account.

MR imaging based volumetry

T1 weighted images taken using a 1.5 T MR scanner were used. FreeSurfer was used to automatically segment the images. Most validation of automated methods have been done with focus on the hippocampus. For the hippocampus, automated segmentation has been verified to be produce good results, comparable to manual segmentation when there are no visible abnormalities or artefacts, but tending to produce slightly larger estimates [191], [192].

Biochemical and genetic analyses

Genotyping

Genotyping of the 5-HTTLPR (serotonin transporter promotor region) was done by a collaborating group (J. B.-R., Gothenburg, see acknowledgements). "The [region was] amplified by polymerase chain reactions (PCRs) performed on a Perkin Elmer 9700 thermal cycler. The 5-HTTLPR polymorphism was amplified by using the PCR prim-

ers 5'-ATGCCAGCACCTAACCCCTAATGT-3' and 5'-GGACCGCAAGGTGGGCGGGA-3', yielding a product of 419 bp for the 16-repeat allele (L) and 375 bp for the 14-repeat allele (S). … All reactions were carried out using 1 U of a HotstarTaq polymerase from Qiagen, in a total volume of 15 μl containing 1.5 mM MgCl$_2$, 0.3 μM PCR primers and 50 ng genomic DNA. After an initial 15-min denaturation step at 95 °C, 35

cycles were performed, including 30 s at 95 °C, 30 s at 66 °C and an elongation step at 72 °C for 1 min. … Genotyping was performed on 2% agarose gels. DNA was visualized by ethidium bromide."[193]

Dexamethasone suppression test

The dexamethasone test spans over two days. On day one, baseline serum cortisol concentrations were measured at 15:00, and then 1 mg dexamethasone was given at 22:00. The next day, serum cortisol was measured at 08:00 and 15:00. Failure to reduce serum cortisol after dexamethasone is a measure of HPA-axis dysregulation. Patients were medication-free.

Dichotic listening

The participants first adjusted the volume of their headphones. The consonant-vowel syllables and complex tones were then administered twice each under divided attention (the first being a practice round). Subsequently, they were administered once under forced left attention, and once under forced right attention. The sounds were presented by a computer using a custom written program, with responses indicated by the participant using the mouse.

Adjusting the volume

Irregularly spaced, randomized tones, in either the left or right ear, with duration between 350 ms and 650 ms and frequency 500 Hz to 1900 Hz, were presented 60 dB below maximum power, in a continuous stream at a rate of approximately 2.6 tones per second. The participants were instructed to adjust the volume using a potentiometer, until the sounds were barely audible, and the slightest further downwards adjustment would make the tones disappear completely. If the tones did not sound alike in both ears, it was noted down and the particpant was asked to turn up the volume

Figure 4. Alignment of syllables in verbal dichotic task
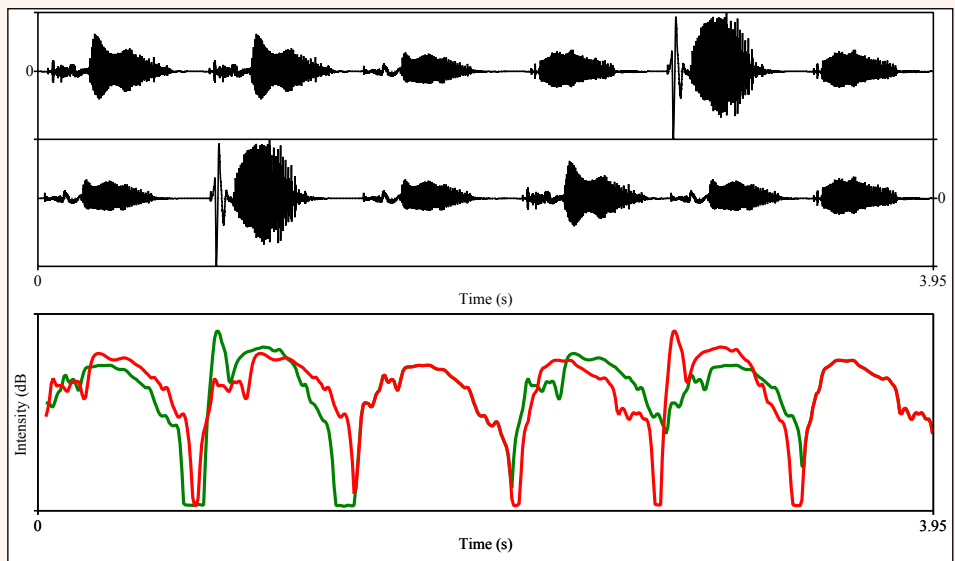
Syllables in the verbal dichotic listening task are aligned by the initial release of energy to maximize the amount of mutual interference.

slightly, until there was no audible difference. If the participants failed to indicate when the stream of beeps ended, the procedure was repeated. (A pilot study on healthy participants that included a simple hearing test, suggested this method was adequate to standardize the volume across participants.)

Dichotic listening: consonant-vowel task

Consonant-vowel syllable pairs (36 pairwise combinations of /ba/, /pa/, /ga/, /ka/, /da/, /ta/) were presented dichotically. Recorded and aligned (see Figure 4, p. 21) syllable pairs were provided by Kenneth Hugdahl, and have been extensively used and tested by his group over many years. They were presented at a volume where the peak power during the /a/ was approximately 37 dB to 45 dB above the power of the tones used during headphone adjustment.

In the divided attention condition, the participant indicated which consonant-vowel pair was heard, or if both were heard, which was heard most clearly, guessing if necessary. Under forced attention, the participant only reported what was heard on one ear, guessing if necessary. The participant reported by clicking on one of six button labelled "ba", "pa", "ga", "ka", "da" and "ta" on the computer screen, after which the computer automatically advanced to the next trial.

Tones

The task was modelled on the complex tones test [194]. First two different tones were presented dichotically, followed by a one second silence, and a third tone (probe) binaurally. In half of the trials the probe matched one of the two dichotic tones, presented a second earlier.

Pairs of tones from the equal tempered scale between 156 Hz (D#3) and 294 Hz (D4), were used to generate 40 dichotic pairs. The probe ranged from 147 Hz (D3) to 311 Hz (D#4), and was either the same as one of the dichotic tones, or one semitone above or below one. All tones were generated with waveform $y(t) = \sin(2\pi t f) + \sin(3 \cdot 2 \pi t f)/3 + \sin(5 \cdot 2\pi t f)/5$, of duration 550 ms, with 100 ms rise and decay time, at 44.1 KHz sample rate. They were presented at approximately 57 dB over the power of the tones used during headphone adjustment.

In the divided attention task, the participant was supposed to report if the probe matched any of the two dichotic tones, guessing if necessary. In the forced attention task, the participant paid attention to one ear only, and reported whether the first and second sounds were identical or different on that ear, guessing if necessary. The participant reported by clicking on a button labelled "different" or "same" on the computer screen, after which the computer automatically advanced to the next trial.

Statistics

Statistics were done using R, as described in the articles and Supplementary methods section below. Detailed descriptions and manuals for the procedures used are available on-line (*http://www.r-project.org*), or in the references given. Several methods and alternatives thereto are also described in [195–204], the R Journal (*http://journal.r-project.org*), and the Journal of Statistical Software (*http://www.jstatsoft.org*).

Supplementary methods

This section provides details about calculations presented in "Further results".

SUAS-S

(SM107) Item rsponse models were fitted with package *ltm*, using a generalized partial credit model (described in online documentation for function *gpcm* in package *ltm*). The partial credit model normally allows each item to have its own discrimination parameter, and a difficulty parameter for each adjacent pair of response categories. In the partial credit model, the interpretation of the difficulty parameters goes like this: For example, the second difficulty paramter corresponds to the transition between response category 2→3; given that a person responds either 2 or 3, that difficulty parameter is the level of the latent trait above which the person is more likely to respond "3" and below which he is more likely to respond "2". These coefficients should be successively higher for each response category in an item (i.e. 1→2 < 2→3 < 3→4 < 4→5). When the order of some coefficients is reversed, it may indicate a problem with the item.

Items 16, 17, 18 and 20 were used from SUAS-S, corresponding to items 19, 18, 16 and 20 on SUAS (in that order). The data for SUAS-S was the same as in paper I. The data for SUAS came from the pool of 300 suicide attempters, and has been analyzed before in other ways by Niméus (dissertation, 2000) and Sunnqvist (dissertation, 2009). The version of SUAS used did not have specific anchors.

The partial credit model produced unreasonable parameter estimates (with almost perfect discrimination for item 18). Hence a "1PL" constraint (see package documentation) was added to the parameters, which means that all four items were constrained to have the same estimated discrimination parameter. The same "1PL" constrained model was then fitted to SUAS. SUAS item 20 showed reversals (difficulty parameter for the response category transition 3→4 was higher than that for 4→5) . This reversal was also apparent on the discarded unconstrained fit to the SUAS material.

(SM108) Fitted using linear mixed-effects models, using function lmer in package *lme4*. The response was the sum of SUAS-S items 16-18 & 20, allowing no missing values. Age was entered as a numerical variable, with *sex* (male/female) and an *age × sex* interaction, with normally distributed random effects for diagnosis and psychiatric facility. Combinations of diagnoses were treated as separate levels (e.g. "depression", "depression & anxiety",

"anxiety", "anxiety & alcohol abuse" are all treated as unique levels).

Graphs show the regression lines (conditional effects) based on 1000 Markov chain Monte Carlo estimates of the fixed effects parameters.

(SM109) Each item was modelled using linear models, with score given by a linear combination of: total SUAS-S score; sex; age (centered on 40) with separate slopes for males and females. (Function *lm* in *stats* package with formulation *score ~ total + sex*/I(*age* − 40), in S+/R terminology; see online documentation on www.r-project.org). Confidence intervals for coefficients were then plotted, one row per item. (Coefficients for the intercept and total SUAS-S score were not shown in the plot.)

To show the effect of having made a previous attempt, this was added as a variable (formulated as *score ~ total +previous.suicide.attempt+ sex*/I(*age* − 40)), and the procedure repeated.

Since most suicide attempters had attempted suicide before, the effect of suicide attempt during follow-up period was examined, conditional on a previous suicide attempt. Outcome was added as a variable (formulated as *score ~ total + suicide.attempt.by.followup + sex*/I(*age* − 40)), and only patients with a previous suicide attempt were included in the analysis.

(SM110) ROC analysis was performed using package *pROC*, and confidence intervals calculated using DeLong's method.

The patients were asked a simple question about previous suicide attempts, and by only analyzing the subgroup that acknowledged such an attempt, we can estimate the incremental predictive value of SUAS-S given prior knowledge about a previous suicide attempt.

SUAS-S items 18 and 20 ask if the patient has thought about suicide (with score >0 implying thoughts about suicide). 47% of the sample answered >0 on both, and 6% answered yes to one only. By analyzing the subset that answered >0 to item 18 or 20, we can estimate the incremental predictive validity of SUAS-S given prior knowledge about suicidal ideation.

SUAS-S item 20 asks about planning and preparations, with score 2 indicating thoughts about methods but no plans, 3 plans without preparations, and 4 plans with preparations. By only analyzing patients with SUAS-S item 20 scores of 3 or 4, we can estimate the incremental predictive value of SUAS-S given prior knowledge of plans or preparations.

HPA-axis and suicidal intent

(SM201) 46 patients with major depressive disorder (23 with and 23 without axis-II comorbidity), and 45 patients with adjustment disorder (24 with and 12 without axis-II comorbidity) were selected from the pool of 300 suicide attempters, on the basis of not having any second axis-I diagnosis and having participated in the dexamethasone test (i.e. took dexamethasone and gave analyzable blood at 0800). This sample corresponds largely to the one analyzed in article II. However, the sample in article II was refined further by excluding patients with physical illnesses believed to affect the results of the dexamethasone suppression test, and excluding patients with incomplete data. Due to uncertainty about the exact criteria we used when article II was written, no such refinement was done here.

(SM202) Confidence intervals were estimated using 10 000 bootstrap samples, using package boot. For each bootstrap sample of paired observations, Spearman's rank order correlation was calculated, transformed using Fisher's transform (hyperbolic arctangent), the *BCa* (bias corrected) bootstrap estimator was calculated, and the confidence intervals transformed back with the inverse Fisher transform (hyperbolic tangent). Deletion of missing values was done pairwise, not listwise.

(SM203) MANOVA with objective and subjective scores modelled as a linear combination of diagnosis (MDD or AD), axis-II pathology (present or not) and sex (male or female) without interactions, suggested a significant effect of diagnosis ($p = 0.02$, Pillai's trace) and sex ($p = 0.02$, Pillai's trace). Adjustment disorder patients had a non-significant trend towards higher objective (0.7 points more, 95%CI –0.6 to 2.0) and lower subjective (1.1 points less, 95% CI –0.2 to 2.3) scores than depressed patients. Women tended to score lower on both objective (1.1 points less, 95%CI –0.2 to 2.4) and subjective (1.9 points less, 95% CI 0.6 to 3.2) halves of SIS, compared to men.

(SM204) Lines show non-parametric LOESS smoother. Each line is fitted independently of the other lines.

(SM205) Subtracting the CPRS item 20 (increased sleep) from item 19 (decreased sleep) produces a rough index of reduced sleep.

Genotype, life-time adversities and morbidity

(SM301) The number of adversities reported by Caspi et al. ($n = 263$ with zero adversities, $n = 211$ with one, $n = 161$ with two, $n = 90$ with three and $n = 120$ with four or more) represent a count of events in a period of time. It was first modelled using a poisson distribution, using maximum likelihood methods, but did not provide an adequate fit, presumably due to overdispersion. Adversities were then modelled as a negative binomial distribution, since this distribution arises when the rate parameter of a poisson distribution varies and is itself drawn from a gamma distribution. It provided an adequate fit ($\chi^2(4) = 0.73$, $p = 0.95$).

(SM302) The number of adversities were known not to be adequately described by a binomial distribution, due to overdispersion. A beta-binomial distribution was fitted, since this represents a binomial distribution with probability of success drawn from a beta distribution. Separate fits were made for the 42 suicide attempters and 22 controls.

(SM303) The prior distribution of adversities was modelled as a negative binomial distribution (with parameters chosen to match the distribution of events in Caspi et al, as described in SM1) censoring at eight events (not four, like Caspi et al.). The prior distribution of genotypes SS/SL/LL was $p(SS) = 0.2$, $p(SL) = 0.5$ and $p(LL) = 0.3$. The prior distribution of sex was $p(Male) = 0.52$, $p(Female) = 0.48$. The probability of suicidal ideation/attempt given sex, genotype and adversities was calculated according to Caspi et al.'s logistic regression (including assigning only four points to four or more events).

Based on the posterior distribution, 76% of SS, 56% of SL and 32% of LL suicide ideators would be expected to report more than two adversities. Mean (and standard deviation) of number of adverisites were 3.8 (1.9), 3.0 (2.0), 2.0 (1.9) for SS/SL/LL groups respectively. Expected posterior genotype densities were $p(SS|Suicidality) = 0.21$, $p(SL|Suicidality) = 0.47$ and $p(LL|Suicidality) = 0.32$.

Cases were then sampled randomly according to the posterior distribution. Samples of various sizes, n, were drawn, and the proportion of statistical tests yielding $p < 0.05$ was plotted against $\log_2(n)$ along with a non-parametric smoother. The number of samples needed for $p < 0.05$ in 50% of samples was determined from the graph.

The power of three strategies was explored: (1) using chi-square to test if the SS/SL/LL genotype distribution differs from the general population, when the genotype distriubtion in the general population is known (taken to be 20%/50%/30%); (2) using ANOVA to compare the number of adversities reported by each genotype; (3) using chi-square to compare the number of people reporting more than two adversities for each genotype. (Random data sets were generated, with 100 replications for each of 40 levels of simulated participants, n,

with n between 10 and 1000 persons.) Samples of approximately 50 suicide attempters should allow detection in 50% of experiments, by comparing number of adversities with ANOVA.

(SM304) The method described above was repeated using the logistic regression coefficients given by Caspi et al. for predicting major depression. In a sample of depressed patients, size needs to exceed $N > 400$, for the ANOVA (comparing the number of adversities reported by different genotypes) to be significant in more than 50% of studies. In a sample of first episode depression, the size needs to exceed $N > 85$.

(SM305) To illustrate the breadth of recent findings, keywords were mindmapped based on article titles in a PubMed search of recent literature containing 5HTTLPR or 5-HTTLPR or SLC6A4. The keywords were sorted and grouped. Representative articles were then found by browsing abstracts of recent articles containing the keywords identified together with the terms "5HTTLPR" or "5-HTTLPR" or "SLC6A4". This method is biased towards spurious positive findings.

(SM306) The distribution of events in suicide attempters and controls were modelled as two negative binomial distributions. (For non-attempters, the parameters estimated above from Caspi's data were used. For suicide attmpters, parameters chosen arbitrarily to allow for a high proportion of extreme events, to illustrate the point. Data was generated randomly, for 10000 hypothetical non-attempters, and 300 hypothetical suicide attempters (corresponding to Caspi's 3% suicide attepters). Logistic regression was performed with and without censoring the maximum number of events recorded at 4, and probabilities calculated from the regression coefficients. True probabilities were calculated from the two negative binomial probability density functions.

(SM307) Three different versions of SUAS were used. At the initial (index) evaluation, the interview-based SUAS without specific anchors were used. At follow-up, both the interview-based SUAS with specific anchors and the self-rated SUAS-S were administered.

SUAS-symptoms refers to the first fifteen items. Of the last five questions on suicidality, the question about the purpose of the suicide was not used in calculating SUAS-suicidality, for the reasons described in the analysis of SUAS-S (paper I). Only the 42 suicide attempters (not the 22 controls) were analysed.

There is only a small correlation ($r_S = 0.27$, 95% CI: –0.08 to 0.55) between adversities reported att follow-up and SUAS-suicidality at index (four direct SUAS items). There is a trend towards better correlation ($r_S = 0.40$, 95% CI: 0.10 to 0.64) between adversities and SUAS-symptoms at index (fifteen first SUAS items).

The correlation between adversities and SUAS-symptoms at index for those who remained ill by follow-up was $r_S = 0.54$ (95% CI 0.0 to 0.78). For those who recovered by follow-up, $r_S = 0.04$ (95% CI –0.45 to 0.50).

Confidence intervals for Spearman's r_S were calculated as in SM202.

Summary of results in papers I-V

Paper I: SUAS-S

Using factor analysis, and comparing with previous factor structures reported for SUAS, we identified four questions out of twenty that were valuable in predicting suicide attempts. These were the four questions that asked directly about suicidality.

Using these four questions, SUAS-S predicted suicide attempts with area under curve (AUC) 0.76 (95% CI: 0.67 – 0.85), which was better than using the traditional total score. Regardless of which score was used, SUAS-S could not differentiate between patients who injured themselves non-suicidally and patients who attempted suicide, as both groups had elevated SUAS-S scores.

Based on semi-exploratory factor analysis, it seems the best way to describe the factorial structure of SUAS-S in the studied population was as: (1) fourteen questions about symptom load; (2) two related questions about wish to live/die; and (3) two related questions about suicidal thoughts/plans.

Paper II: HPA-axis and suicidal intent

We hypothesized a positive correlation between suicidal intent and endocrinological disruption in depressed suicide attempters, but not in patients with adjustment disorder (if HPA axis hyperactivity is associated with depression but not suicidality specifically).

We found a significant negative correlation in depressed suicide attempters, significantly different from the slight trend towards positive correlation found in adjustment disorder. This suggests that hypercortisolemia is not independently associated with suicidality. The unexpected negative correlation needs further explanation.

Paper III: Adversities and 5HTTLPR genotype

We hypothesized that the number of adversities reported by suicide attempters would depend on their 5HTTLPR genotype, and predict outcome at follow-up.

Suicide attempters reported more adversities than controls, and patients who recovered by follow-up reported less than those who did not. Genotype affected the number of adversities reported in suicide attempters, but did not measurably affect long-term prognosis.

Paper IV: Subcortical volumes, 5HTT and temperament

Unmedicated suicide attempters with high suicidal intent had in a previous study undergone ^{123}I-β-CIT SPECT and MR scans, and filled in scales to assess temperament. Results showed a correlation between temperament and dopamine transporter and serotonin transporter binding potential. We hypothesized that same suicide attempters would show volumetric abnormalities in the deep grey matter of the brain (amygdala, hippocampus, basal ganglia), correlating with the previously reported SPECT findings.

MR scans from seven suicide attempters and six controls could be retrieved. Suicide attempters had smaller globus pallidus (bilaterally) and smaller caudate (right). In suicide attempters, but not controls, there was a negative correlation between globus pallidus volume and: (a) serotonin transporter binding potential (measured using SPECT); and (b) solidity (a personality trait akin to low novelty-seeking/impulsivity)

Paper V: Dichotic ear advantage and suicidality

Patients who had attempted suicide were administered a Dichotic Listening test, SUAS and MADRS. The verbal dichotic listening asymmetry correlated with the suicidality questions in SUAS-S, even after correcting for depressive symptomatology using MADRS. Dichotic listening may be a useful tool to detect subtypes of suicidality.

Further results

SUAS-S: Hopelessness and suicidality

SUMMARY: Hopelessness and suicidality are most tightly coupled in suicide ideators or past suicide attempters.

Hopelessness was the symptom that loaded most on the expressed suicidality factor (see Paper I). Might heterogeneity in age, sex, global morbidity, and previous suicide cloaked the internal structure of SUAS-S? Might hopelessness be connected to suicidality only in certain patient groups?

All items are positively correlated, with a prominent cluster around the direct suicidality questions (Figure 5, p. 28). This is the effect of the first principal component (a general positive correlation, or, heuristically, a *g*-factor of ill-being) and a prominent residual structure around suicidality.

After partialling out total score (comparable to disregarding the first principal component), age, sex and age × sex, the ultrastructure becomes more visible, revealing a hierarchy of interrelated symptoms. However, none of the symptoms appear to bear a particular relationship to suicidality, even at this level of pre-processing (Figure 6, p. 28). Only when patients with previous suicide attempts or known ideation are analyzed separately, does one of the symptoms (hopelessness) show a positive partial correlation with the cluster of suicide questions (Figure 7, p. 29)

Each SUAS-S item's contribution to prediction

SUMMARY: No single symptom is strongly predictive of suicide attempts. The four direct questions (wish to live/die and suicidal thoughts/plans) are elevated by approximately half a point each in patients who later attempt suicide, compared to non-attempters with the same SUAS-S score. Hopelessness does not seem to make an independent contribution to predicting a suicide attempt.

In some situations, an item may help predict suicide attempts, even if the factor it loads on does not. After correcting for age and sex, which items make independent contributions to predicting attempted suicide, above and beyond total score? In particular, we have à priori reason to believe hopelessness may be of interest (see Paper I and previous section).

We can consider the item score profile. Figure 8 (p. 30) compares people who attempt suicide with people who do not, but have the same age, sex and total SUAS-S score. We can see that items 16-20 each score approximately half a point higher than could be predicted by total score alone. Clearly the amount of independent information provided is small, in relation to the total number of points. Figure 9 (p. 31) shows the elevated hostility, impulsivity and poor frustration toler-

ance associated with non-suicidal self-injury.

The majority of patients who attempted suicide during the study period acknowledged previous attempts. Figure 10 (p. 32) shows symptom profile associated with a previous suicide attempt. Figure 11 (p. 33) shows the symptom profiles of suicide attempters, only considering those with a past attempt. This tells us which items provide information, given that we are considering a patient known to have previously attempted suicide.

Impulsivity seems connected with previous suicide attempts, but neither impulsivity nor hopelessness demonstrate any clear ability to pick out future suicide attempts.

Figure 6. Partial correlation between items
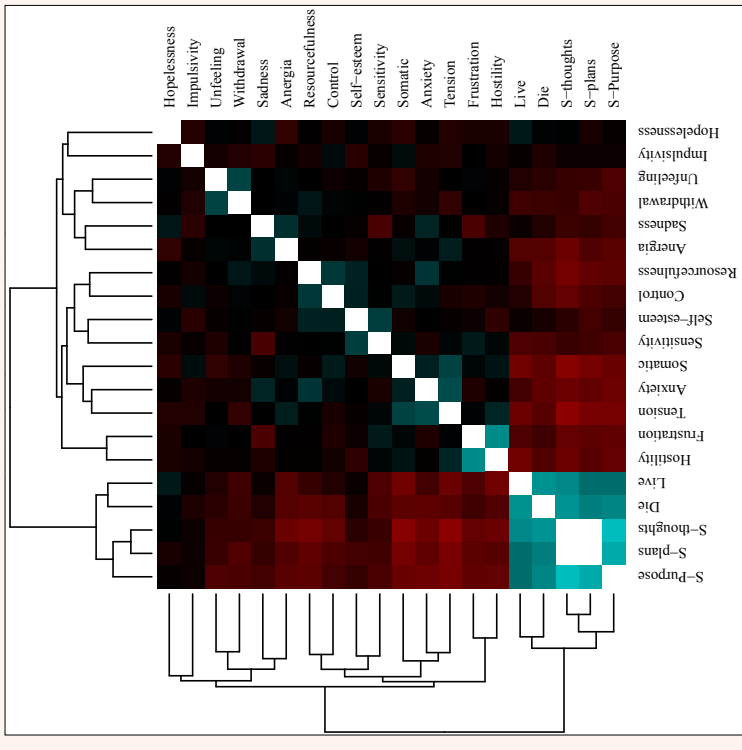
After partialling out total score, age, sex and age × sex, the ultrastructure becomes more visible, revealing a hierarchy of interrelated symptoms. However, none of the symptoms appear to bear a particular relationship to suicidality. (If any variable had, there would have been a blue line where that variable intersects with the specific suicide items.)

Figure 5. Correlation between items

All items are positively correlated, with a prominent cluster around the direct suicidality questions. (Discussed in "SUAS-S: Hopelessness and suicidality" on page 27.)

Figure 7. Partial correlations (given previous attempt or suicidal ideation)
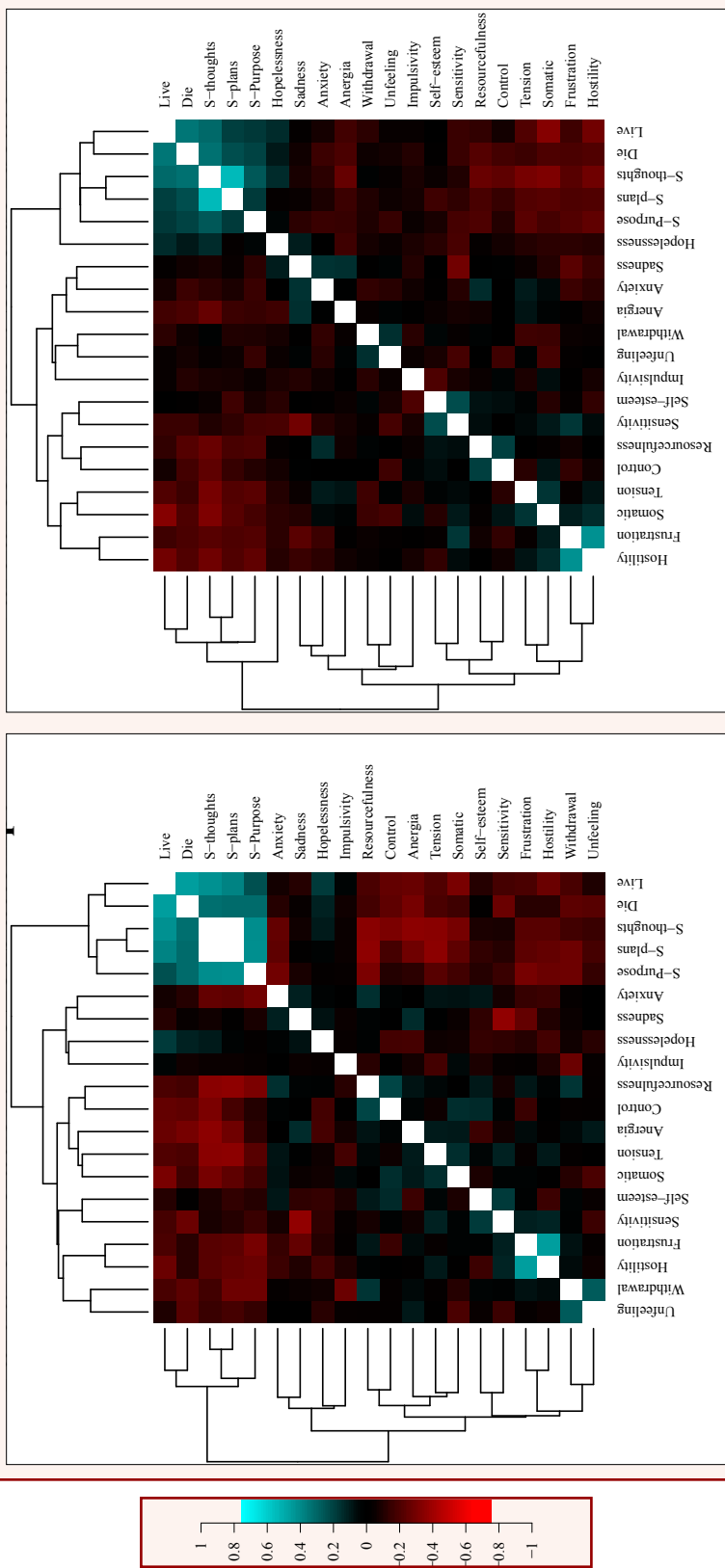
After also restricting the analysis to patients with a previous attempt (top) or suicide ideators (i.e. >0 points on item 18 or 20, bottom), hopelessness begins to appear as a thin blue line across the suicide question cluster. (Equivalent to loading more on the expressed suicidality factor.)

Figure 8. SUAS-S conditional item profile: attempted suicide during the study
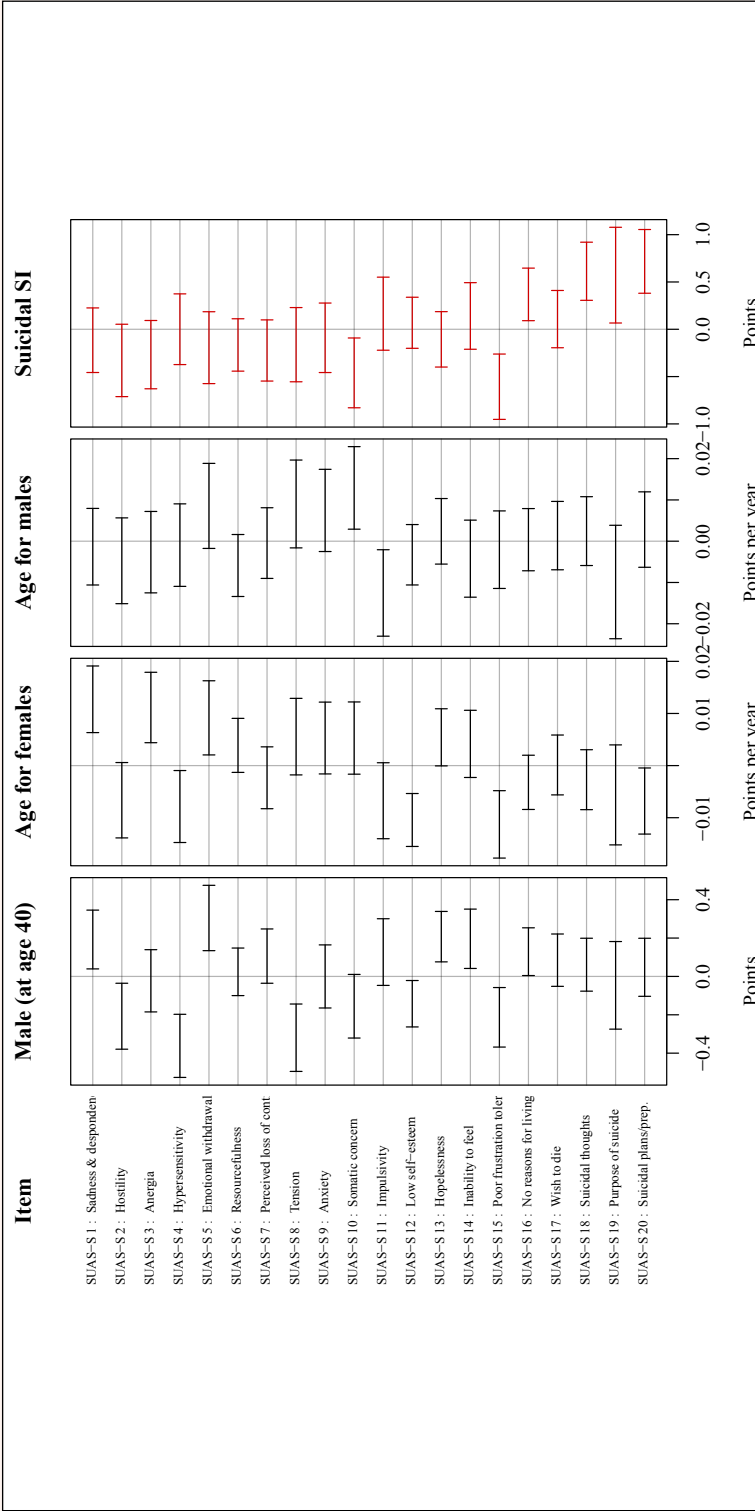
Difference in item scores between those who do and do not attempt suicide during the study (shown in red), controlling for total SUAS-S score (not shown), age (black) and sex (black). People who attempt suicide score ~0.5 points higher on items 16-20 than people with the same age, sex and total SUAS-S points who do not attempt suicide. (Correspondingly, they score lower on other items, since the total SUAS-S score has to be the same.)

Figure 9. SUAS-S conditional item profile: self-injury during the study
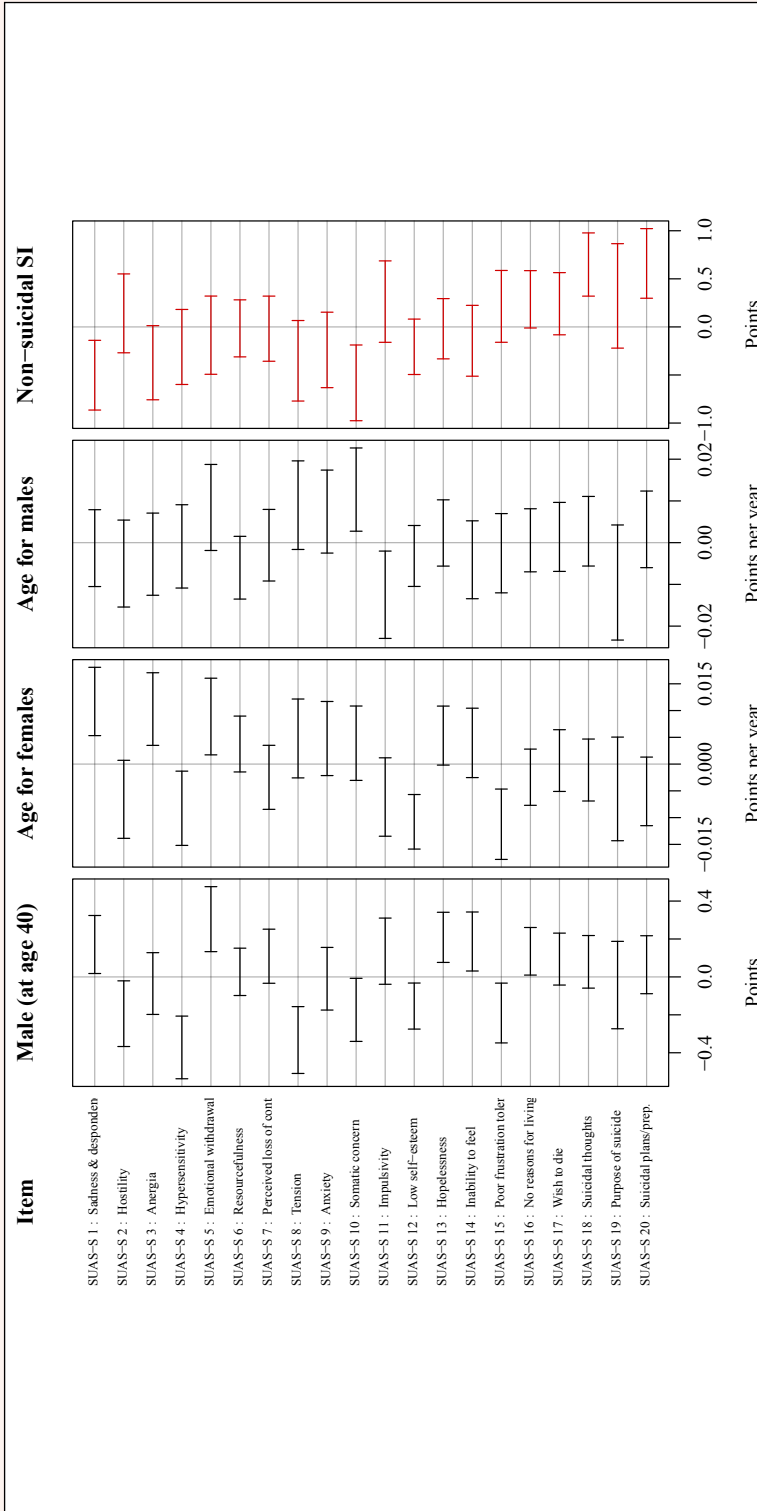
Difference in item scores between those who do and do not injure themselves non-suicidally during the study (shown in red), controlling for total SUAS-S score (not shown), age (black) and sex (black).

Figure 10. SUAS-S conditional item profile: previous suicide attempt
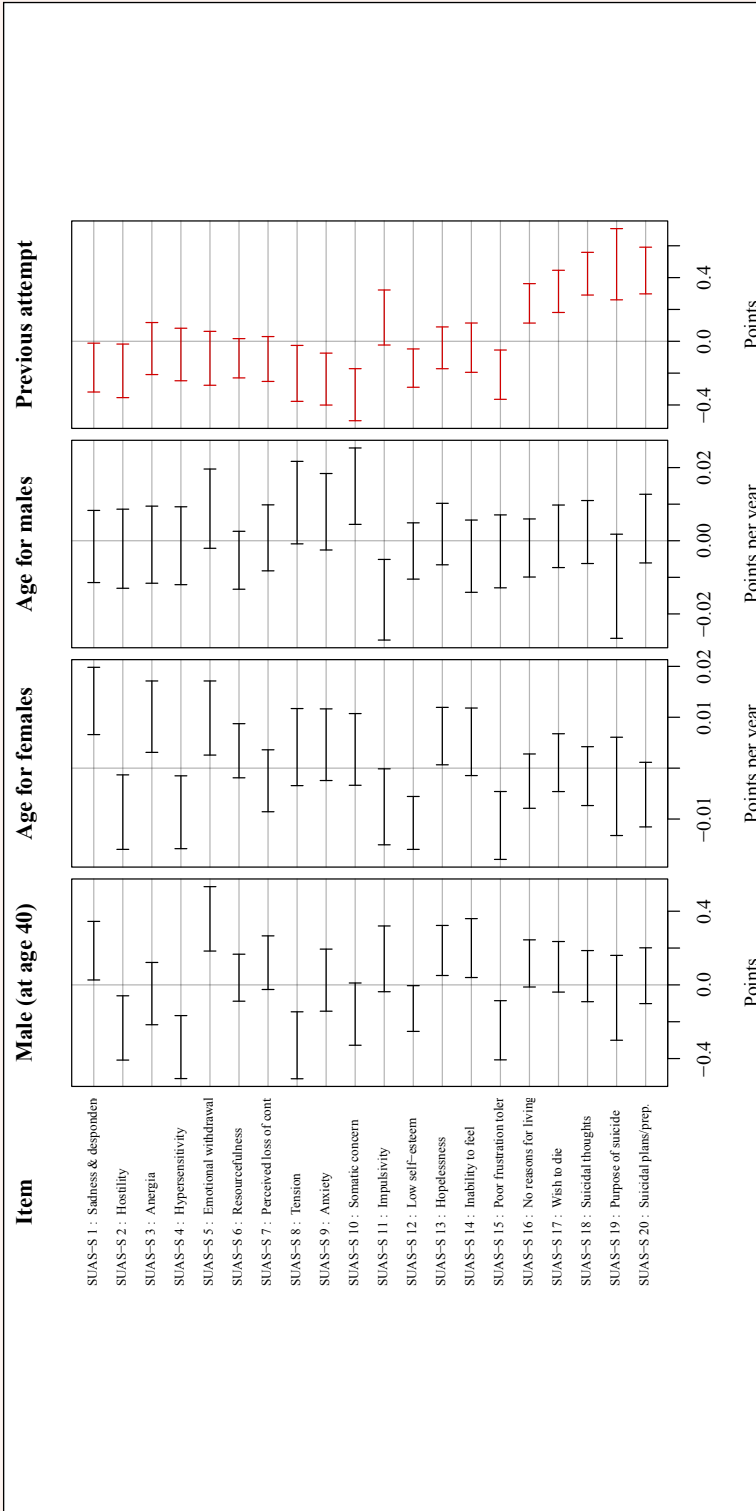
Difference in item scores between those who have and have not attempted suicide before the onset of the study (shown in red), controlling for total SUAS-S score (not shown), age (black) and sex (black).

Figure 11. SUAS-S conditional item profile: suicide attempt, given a previous attempt
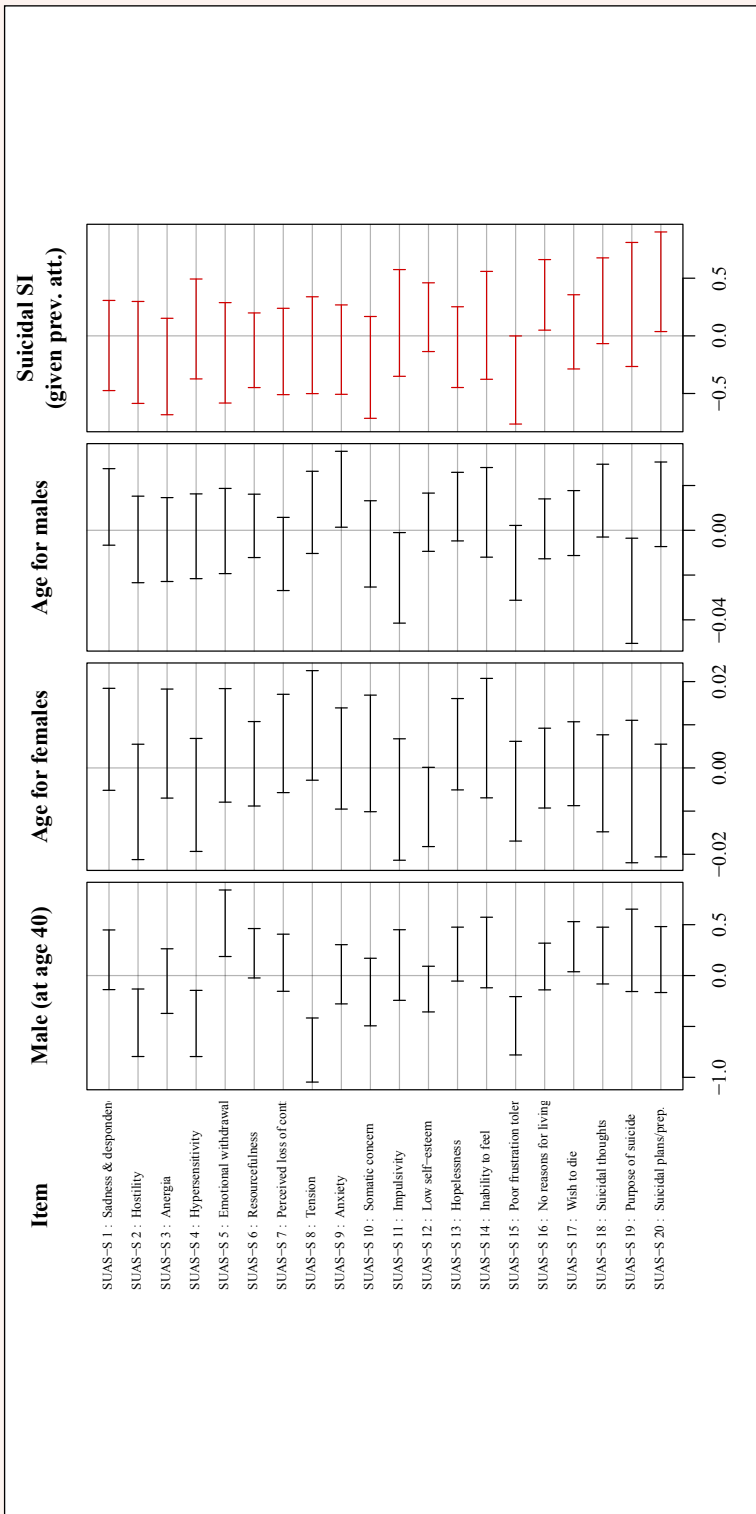
Difference in item scores between those who do and do not attempt suicide during the study (shown in red), controlling for total SUAS-S score (not shown), age (black) and sex (black), given that they already had attempted suicide at the onset of the study.

Figure 12. Effect of age, sex and diagnosis on score
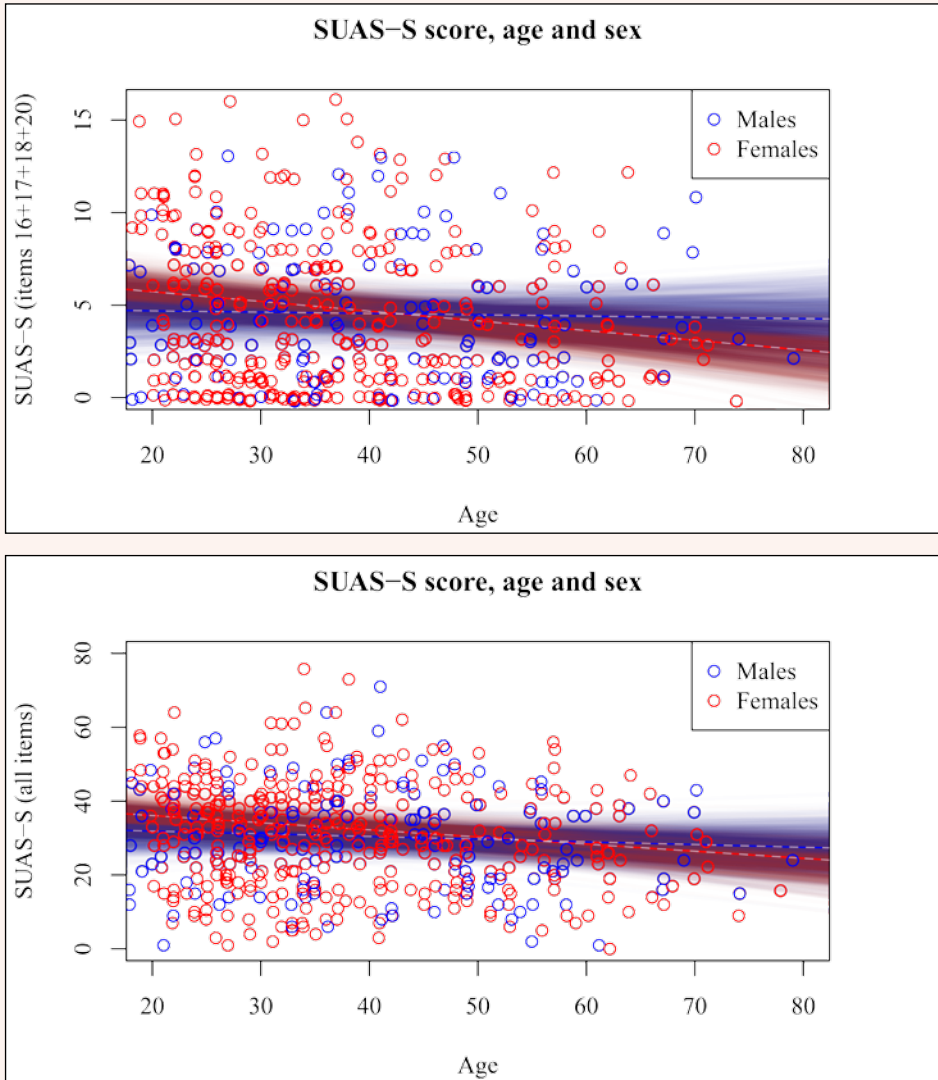
Difference in item scores between those who do and do not attempt suicide during the study (shown in red), controlling for total SUAS-S score (not shown), age (black) and sex (black), given that they already had attempted suicide at the onset of the study.

Top: There was a small but significant decrease in score on the four direct questions with age in females (95% CI −0.09 to −0.02 points per year), but not in males (95% CI −0.06 to 0.04). The difference between men and women in the regression slope is verging on significance (95% HPD −0.01 to 0.10).

Bottom: The age × sex effect is similar to total SUAS-S score, and of comparable magnitude after dividing by standard deviation. (Supplementary Methods, SM108)

Figure 13. Predictive ability of four items in SUAS
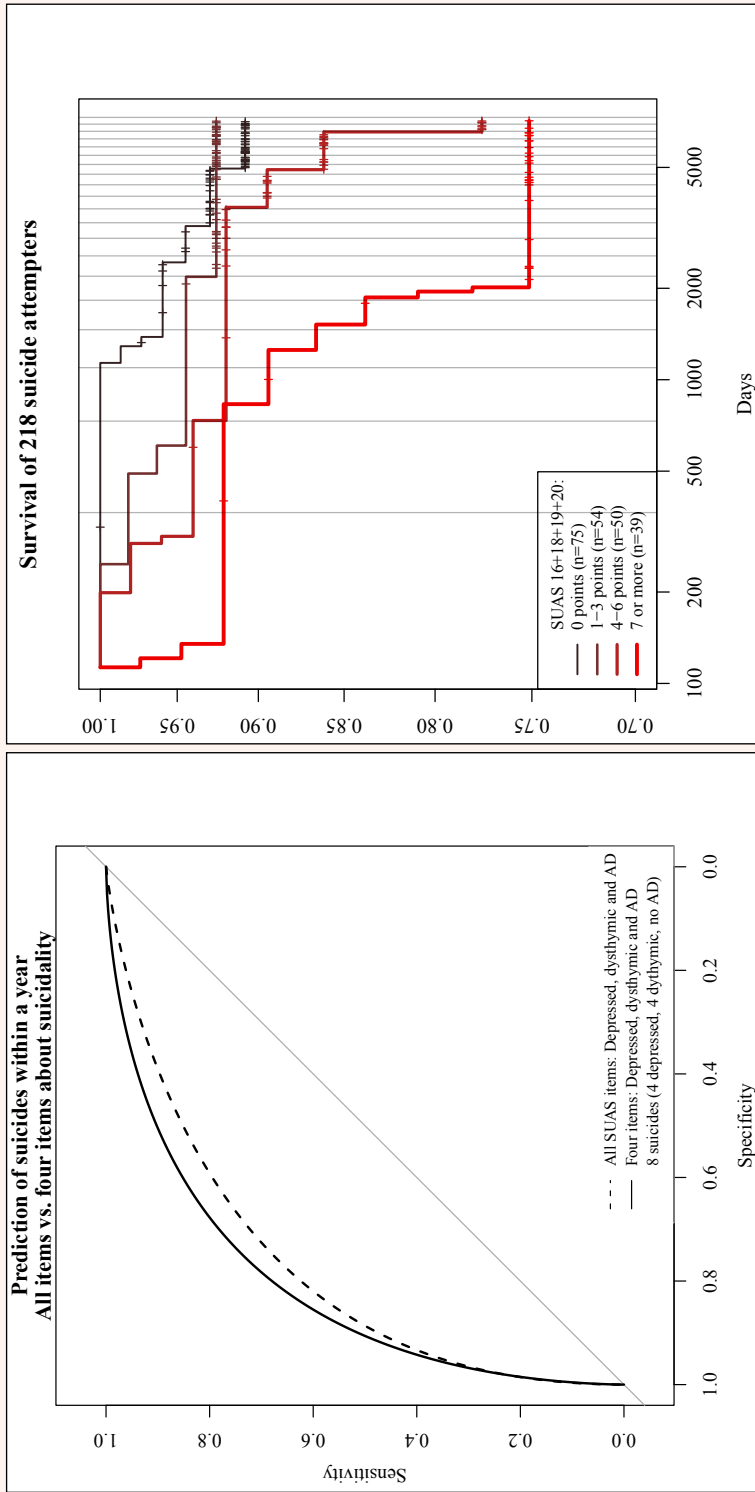
In the SUAS-S study, we recommend focusing on four direct questions about suicidality. In this figure we re-analyze how these four questions performed in the SUAS material originally analyzed by Niméus. Left: The four items did not do much better than total score at predicting actual suicide within a year in hospitalized suicide attempters. Right: High scores are associated both with acute (<1 year) and long-term (>1 year) risks. There may be a floor effect, where the pool of at-risk individuals is exhausted after some years (plateau seen in highest risk group).

Figure 14. Item Response Theory model: SUAS-S suicide items
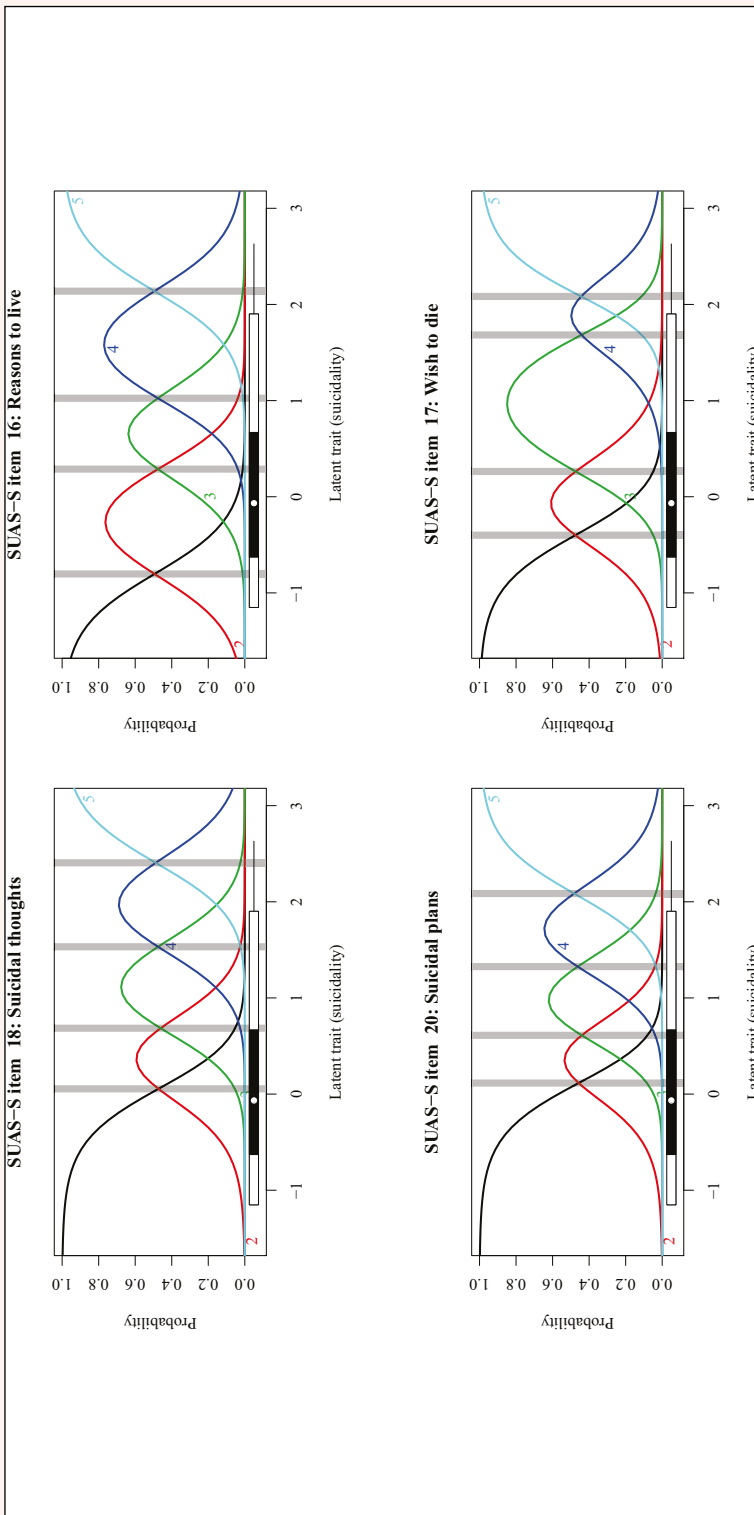
Item characteristic curves for items 16, 17, 18 and 20 on SUAS-S (the four direct questions about suicidality). Curves indicate probability of choosing a particular response, grey bars indicate difficulty parameters. Horizontal bar shows distribution of latent trait (i.e. suicidality-"scores" for the 496 participants), with range shown as thin line, 2.5% to 97.5% quantiles as a white box, 25% to 75% quantiles as a black box, and median as a white dot. (Supplementary Methods, SM107).

Figure 15. Item Response Theory model: SUAS suicide items
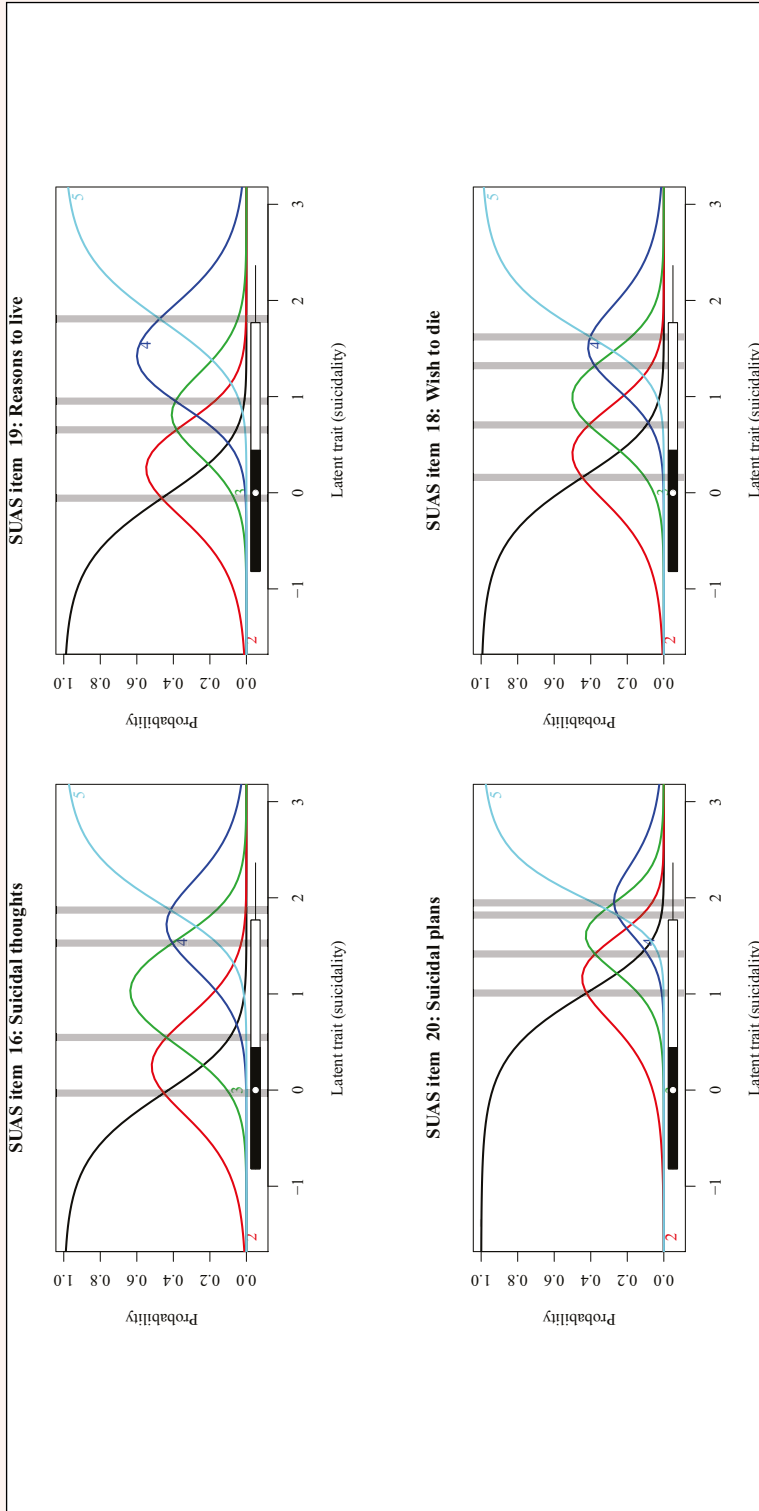
Item characteristic curves for items on SUAS directly asking about suicidality (based on older data from hospitalized suicide attempters). In this interview-based version of SUAS without explicit anchors, item 20 (about plans and preparations) seems to probe the high-end of the suicidality spectrum. (Supplementary Methods, SM107).

Figure 16. Mediation of suicidal thoughts/plans in SUAS-S
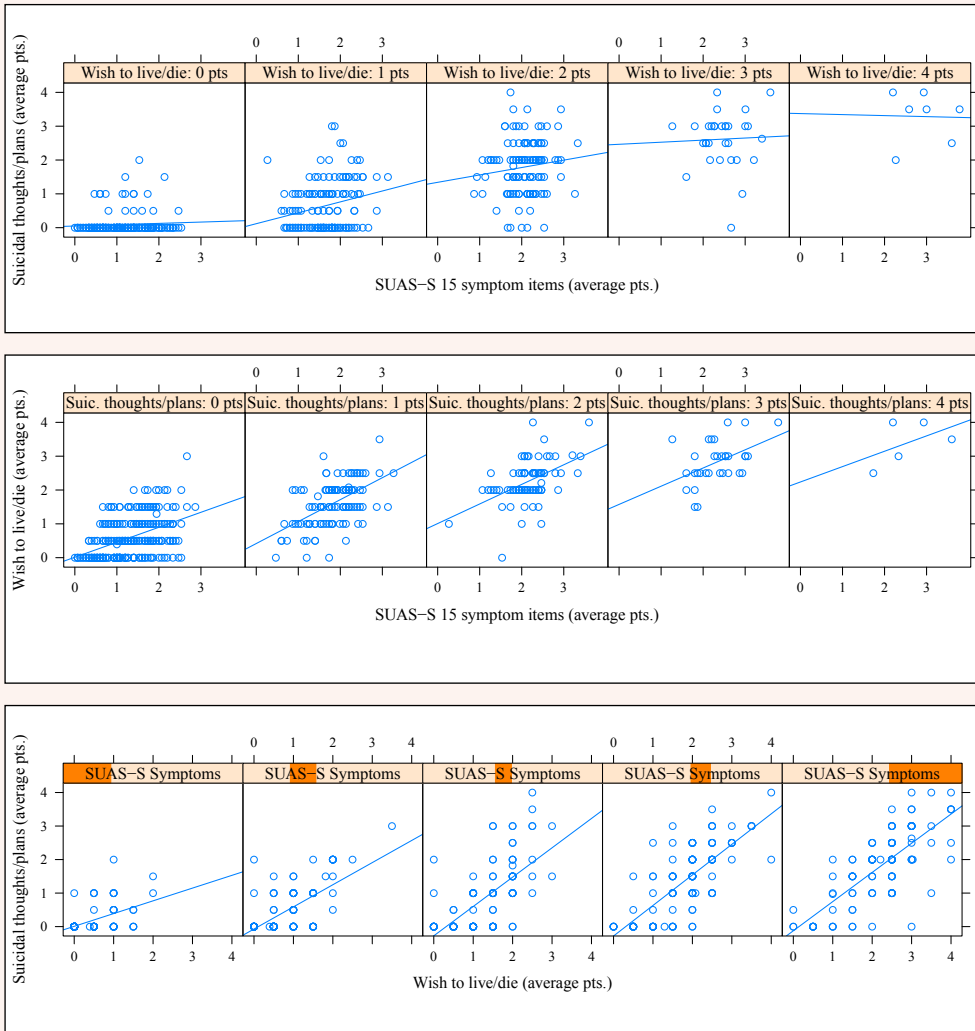
Mediation analysis of SUAS-S in a heterogeneous psychiatric sample: symptoms → suicidal thoughs/plans (top); symptoms → wish to live/die (middle); wish to live/die → suicidal thoughts/plans (bottom). Wish to live/die largely mediates the impact of symptoms on suicidal thoughts/plans (manifested by horizontal lines in top panel, parallel lines in bottom two panels).
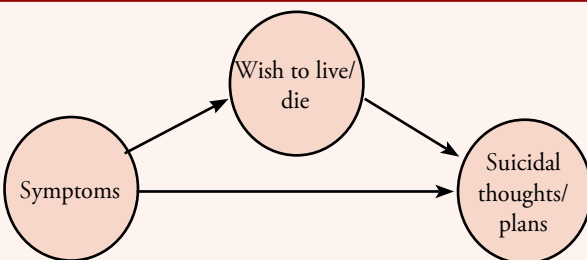
Explanatory note: The graphs are a way of visually examining a proposed causal relationship between symptoms, wish to live/die and suicidal thoughts/plans. Note that the direction of causality is assumed, not proven/known.

Figure 17. Mediation of suicidal thoughts/plans in SUAS
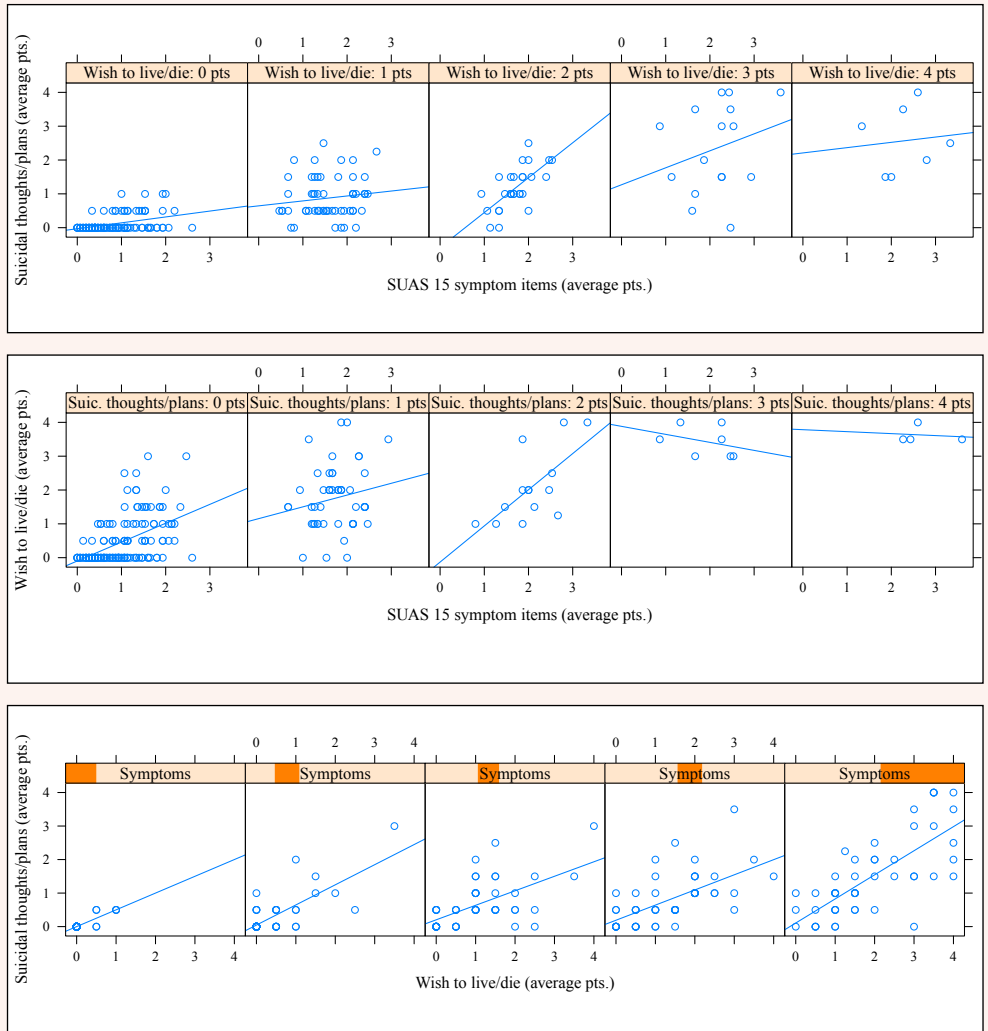
Mediation analysis of SUAS in hospitalized suicide attempters showing: symptoms → suicidal thoughs/plans (top); symptoms → wish to live/die (middle); wish to live/die → suicidal thoughts/plans (bottom). The pattern is much more complex than for SUAS-S. At intermediate levels of wish to live/die, there is a considerable direct effect of symptoms on suicidal thoughts/plans (top). At high levels of suicidal thoughts/plans, there is always a high desire to die, irrespective of symptoms (middle).

SUAS-S robustness to age, sex and diagnosis

Summary: The specific questions about suicidality in SUAS-S are not more robust to age, sex and diagnosis than total score.

With 15 of 20 questions asking about diverse symptoms, total SUAS-S score will be affected by diagnosis, and in a heterogeneous sample, by age and sex. Is, then a composite of the four specific questions about suicidality more robust to demographic background variables than total score? In both cases there is a small decrease in score for women with age (~0.1 standard deviations per decade for females, less for men), and in both cases the magnitude of the random effect for diagnosis is greater (~0.3 – 0.4 standard deviations). (As shown in Figure 12 (p. 34) some items are associated with higher age, and some with lower age, with most apparent differences in women.)

The direct questions in SUAS and completed suicide

Summary: The four direct questions about suicidality perform only marginally better than total score in SUAS, for predicting completed suicide in hospitalized suicide attempters.

In the SUAS-S study, we recommend focusing on four direct questions about suicidality. Does that hold for the interview version of SUAS too? Figure 13 (p. 35) shows a re-analysis of the SUAS material originally analyzed by Niméus (dissertation, [205]), based on a subset of the 300 suicide attempters described in Methods. In this material the version of SUAS without specific anchors was used. Just using the four specific questions produced a marginally (but not significantly) better predictor of suicide, and high scores seemed to indicate a more immediate risk.

Top points in SUAS versus SUAS-S.

Summary: Compared to SUAS-S, the four direct questions about suicidality on SUAS become geared towards more extreme symptoms, when assessing hospitalized suicide attempters.

Whereas SUAS-S has anchors for each likert-style response, the original version of SUAS (considered in the previous section) did not. Therefore SUAS and SUAS-S scores might not be comparable, because the unanchored SUAS responses could take on extreme interpretations in extreme clinical samples.

To investigate this, an item response model was fitted to SUAS-S (Figure 14, p. 36) and to the SUAS (Figure 15, p. 37) material. Over-all, the SUAS interview seems to probe more in the high ends of suicidality than the self-rated SUAS-S.

Interpretation should be cautious since both the sample and measuring instrument differ. However, in support of the aforementioned, note that the SUAS sample should, if anything, have higher levels of suicidality, consisting entirely of hospitalized suicide attempters.

The last item about plans and preparation seems to assess suicidality at a particularly high level in the SUAS interview without anchors. This suggests differences between the clinical assessment of plans/preparations and the self-assessment of the same thing. (The same item in SUAS shows a reversal of third and fourth difficulty parameters, alerting us to potential problems in rating the two top response categories in SUAS without anchors.) Indeed, in later versions of SUAS with anchors, a maximum score on that item indicates that the patient needs to actively prevented from attempting suicide.

Table 6. Incremental predictive validity of SUAS-S

Clinical background knowledge	SUAS-S AUC (95% CI)		Estimated from
	Items 16, 17, 18 and 20.	All 20 items (total score)	
Nothing known.	0.76 (0.67 to 0.85)	0.68 (0.58 to 0.77)	Whole sample.
"Have you ever tried to kill yourself?" "Yes. Etc…"	0.67 (0.55 to 0.78)	0.59 (0.47 to 0.70)	19 suicide attempters of $n = 158$ with previous suicide attempts
"Have you thought about killing yourself lately?" "Yes. Etc…"	0.61 (0.46 to 0.76)	0.50 (0.37 to 0.62)	19 suicide attempters of $n = 260$ acknowledging suicidal ideation.
"Have you thought about killing yourself lately?" "Yes. Etc…" "Have you ever tried to kill yourself?" "Yes. Etc…"	0.58 (0.43 to 0.72)	0.52 (0.38 to 0.67)	17 suicide attempters of $n = 111$ acknowledging previous suicide attempts and current ideation.
"Have you been thinking about killing yourself lately?" "Yes. Etc…" "Have you thought about how?" "Yes. I am going to…"	0.56 (0.38 to 0.74)	0.63 (0.44 to 0.81)	8 suicide attempters of $n = 59$ acknowledging current suicide plans or preparations.
"Have you been thinking about killing yourself lately?" "Yes. Etc…" "Have you thought about how?" "Yes. I am going to…" "Have you ever tried to kill yourself before?" "Yes. Etc…"	0.53 (0.33 to 0.73)	0.43 (0.23 to 0.63)	8 suicide attempters of $n = 41$ acknowledging previous suicide attempts, and current plans or preparations.

Although SUAS-S may predict suicide when no other information is available, complete ignorance of clinical information is not a realistic assumption in practice. At the very least, we may choose to ask the patient about previous attempts and current thoughts/plans, and then the incremental predictive value of SUAS-S rapidly plummets to chance level. (AUC of 1 is perfect, 0.5 is chance level. Supplementary Methods, SM110.)

Figure 18. HPA-axis and depression severity, sex and sleep

Left: The association between SIS and cortisol remains similar at high and low levels of depressive symptoms (MADRS). (Supplementary Methods, SM204.)

Top right: Using the CPRS items about increased or decreased sleep, we see a trend towards higher cortisol being associated with reduced sleep

Bottom right: Males score higher on SIS, and may differ endocrinologically. However, the overall pattern seems to be similar for men and women.
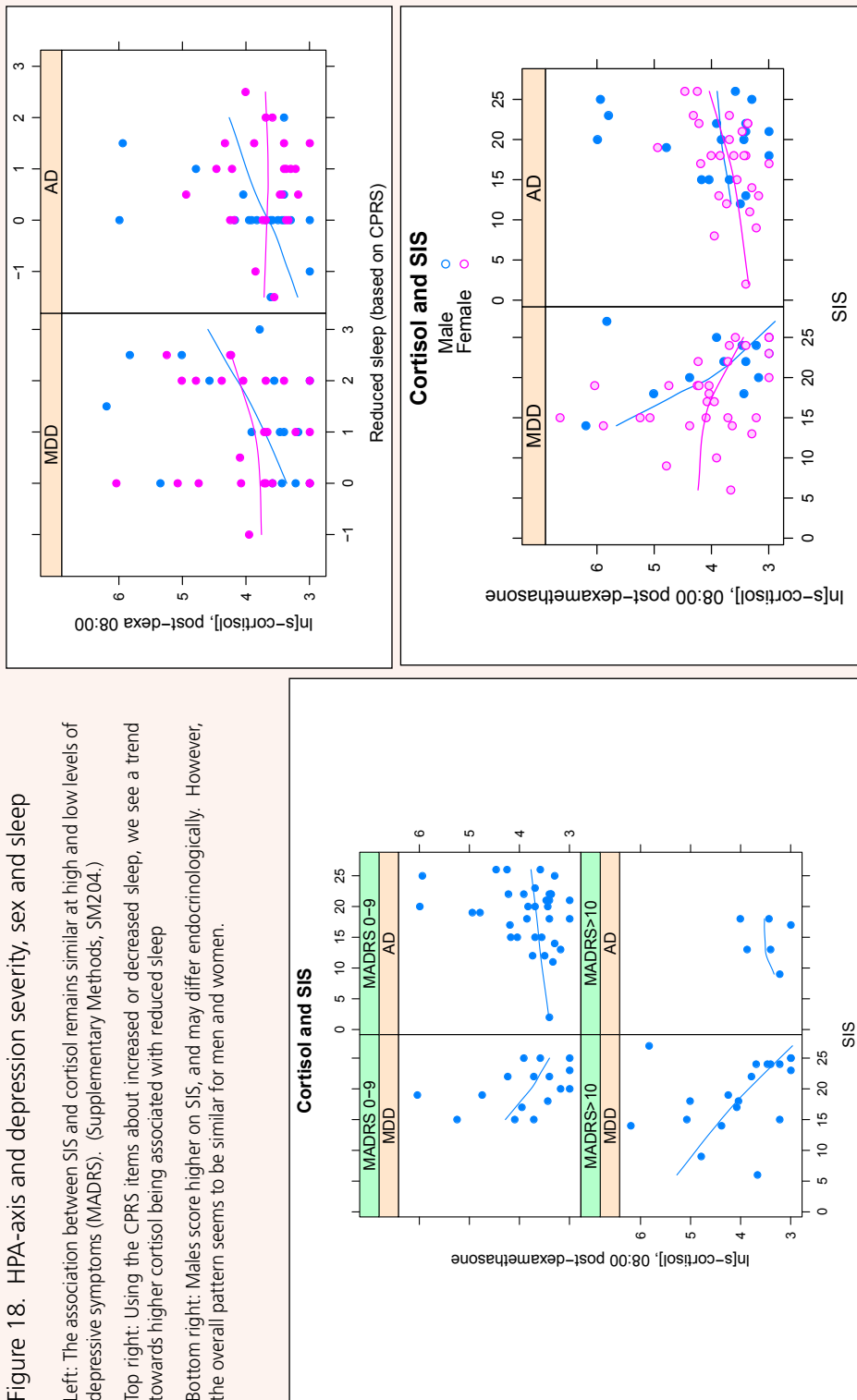
Mediation analysis in SUAS and SUAS-S

Summary: In SUAS-S, but not SUAS, the wish to live/die mediates the effect of symptoms on suicidal thoughts/plans.

Intuitively it seems plausible that wish to live/die should precede and perhaps explain suicidal thoughts/plans. Mediation analysis suggested that the wish to live/die almost completely mediated the correlation between symptoms and suicidal thoughts/plans when using SUAS-S on a heterogeneous psychiatric sample (Figure 16, p. 38). This was not the case for SUAS in hospitalized suicide attempters (Figure 17, p. 39).

The incremental predictive ability of SUAS-S

Summary: The incremental predictive ability of SUAS-S drops in the presence of trivial clinical information.

Although SUAS-S may predict suicide when no other information is available, the reality is usually that some clinical background information about a patient is available. At the very least, we may choose to ask the patient about previous attempts and current thoughts/plans. The important question is then: given background knowledge of a patient, does SUAS-S improve our decision?

As shown in Table 6 (p. 41), the predictive value of SUAS-S falls rapidly in the presence of background information. The drop in predictive ability occurs both for the four specific questions about suicidality and the total score, suggesting that the inclusion of symptom-oriented information is not a solution. This is almost certainly not a problem which is unique to SUAS-S, since risk indicators are correlated.

Depression severity, sex and sleep as HPA-axis confounders.

Sleep disruption, severity of depression and sex are possible confounders when examining the correlation between HPA-axis dysregulation and suicidal intent.

The association between SIS and cortisol remains similar at high and low levels of depressive symptoms (MADRS; see Figure 18, p. 42). This suggests that the severity of the depression does not account the results. (Supplementary Methods, SM204.)

Males score higher on SIS, and may differ endocrinologically. This may have contributed to the results. However, the overall pattern seems to be similar for men and women ($r_S = -0.38$, $p = 0.04$ for depressed men; $r_S = -0.29$, p = 0.13 for depressed women. See Figure 18). The sample is too small to investigate the matter properly while still taking Axis-II pathology into account.

The diurnal rhythm regulates cortisol production, and disturbed sleep is a central symptom in depression, and sleeping complaints common in hospitalized psychiatric patients generally. page 42 also shows cortisol versus a rough index of reduced sleep based on CPRS. The trends were not statistically significant, but associations should be assumed to exist based on other research. (Supplementary Methods, SM205.)

Table 7. Subjective and objective parts of SIS

| Axis-II comorbidity | Diagnosis | Measurement | Rank-order correlation (95% CI) between ln[s-cortisol] and Suicide Intent Scale | |
			Subjective part	Objective part
Mixed	MDD	Pre-dexa	−0.17 (−0.47 to 0.17)	−0.32 (−0.57 to −0.01)*
		Post (08:00)	−0.30 (−0.57 to 0.02)	−0.44 (−0.64 to −0.13)*
		Post (15:00)	−0.28 (−0.55 to 0.05)	−0.36 (−0.61 to −0.02)*
	AD	Pre-dexa	0.30 (0.04 to 0.52)*	0.04 (−0.23 to 0.31)
		Post (08:00)	0.40 (0.11 to 0.64)*	0.07 (−0.23 to 0.35)
		Post (15:00)	0.27 (−0.08 to 0.54)	0.19 (−0.11 to 0.43)
None	MDD	Post (08:00)	−0.44 (−0.73 to −0.02)*	−0.58 (−0.75 to −0.29)*
		Post (15:00)	−0.38 (−0.70 to 0.09)	−0.46 (−0.76 to −0.02)*
	AD	Post (08:00)	0.32 (−0.21 to 0.71)	−0.39 (−0.71 to 0.08)
		Post (15:00)	0.25 (−0.38 to 0.72)	0.16 (−0.32 to 0.59)
All	MDD	Post (08:00)	−0.12 (−0.60 to 0.42)	−0.33 (−0.76 to 0.28)
		Post (15:00)	−0.16 (−0.64 to 0.54)	−0.28 (−0.77 to 0.46)
	AD	Post (08:00)	0.32 (−0.15 to 0.66)	0.14 (−0.31 to 0.50)
		Post (15:00)	0.14 (−0.39 to 0.56)	0.07 (−0.34 to 0.47)

In patients with major depressive disorder (MDD) without personality disorders, both objective and subjective parts correlate negatively with SIS, but mostly the objective part. In adjustment disorder (AD), the positive correlation seems due to the subjective component of SIS. (But the confidence intervals are wide, and this interpretation is tentative. Supplementary Methods, SM202)

Table 8. Age and adversities recalled during the interview

| | Adversities (reported by all 64 participants) | | |
	Ages 0 – 13	Ages 13 – 19	20 – index
Correlation with age (95% CI)	−0.20 (−0.4 to 0.05)	−0.22 (−0.4 to 0.02)	0.20 (−0.04 to 0.4)
Proposed mechanism	Longer time ago in old patients → more forgetting		Longer time-span in old patients → more adversities.

Age affects number of adversities recalled for different time-spans.

Table 9. The meaning of childhood neglect

Ages 0 to 13	Ages 14 to 19
Was not allowed to live with parents; had to arrange for somewhere to live him/herself.	[Nothing noted]
Father away. Felt abandoned when mom had miscarriage.	Mother's hysterical behaviour. Let down.
Father would have wanted to hit. Father was not nice.	Father would have wanted to hit, but did not dare.
Mother cared, but cold.	[Nothing noted]
[Nothing noted]	Not noticed as much as her six siblings. Shy.
No contact with father. Neglected by mother.	Very neglected by mother.
Given away when mother gave birth. Thoughts about sexual abuse appeared during psychoanalysis.	Not appreciated by parents for her achievements.
Parents often absent. Father sometimes behaved bizarrely, and there were threatening situations.	Parents often absent.
Father did not help raise her. Mother worked. Not emotionally neglected, just practically.	[Nothing noted]
Siblings moved early, mother fled, alcoholic father.	Mother visited once in three years, but he/she often visited mother and was welcome.
Bad relationship to father	Bad relationship to father.
Neglected by both parents, but most by father. Hard discipline. Were not allowed to have friends. Much control.	Grandmother died.
Many times by father, who did not have time for the children. The patient was not seen.	Parents.
[Nothing noted]	Mother was not understanding, and beat her.
Felt ashamed about mother, who was a substance abuser (alcohol/drugs?). Was not allowed to bring home friends.	Mothers substance abuse. Father looked the other way.
Mother out at night, while she was watched by relatived	Mother spent more time on men.
Father physically absent	Father physically absent
Lived in Indian reserve, not believed, child labour, beaten.	Husband beat her. [Comment: Married early. Pregnant three times during this period.]
Beaten. Stayed in home or with family so that parents could rest. Mother worst, father agreed with mother.	[Nothing noted]
You did not talk about feelings.	You did not talk about feelings.
Emotionally. [Comment: father did not care when she was forcibly kissed in front of him(?) by two foreigners.]	[Nothing noted]
Parents did not care	[Nothing noted]
Important teacher stopped.	Father ignored him/her, and was negative about his/her firends.
[Nothing noted]	Father got a new woman (sister-in-law or brother's wife [Unclear because of terminology used])

Responses noted down to the question about neglect by parent or significant other in suicide attempters. Several times the interview protocol noted "see above" (or something to that effect) presumably indicating that the participant had reiterated concrete events noted elsewhere in the protocol.

Table 10. Index – follow-up correlations for different scales.

			Correlations (Spearman's r_s)								
			Adversities	Index			Follow-up				
				SUAS		CPRS	SUAS		SUAS-S		CPRS
				Suic.	Sympt.	Total	Suic.	Sympt.	Suic.	Sympt.	Total
	Adversities		1								
Index	SUAS	Suicidality	0.27	1							
		Symptoms	0.40	0.61	1						
	CPRS	Total	0.29	0.58	0.78	1					
Follow-up	SUAS	Suicidality	0.36	0.25	0.44	0.36	1				
		Symptoms	0.52	0.35	0.44	0.41	0.72	1			
	SUAS-S	Suicidality	0.37	0.22	0.35	0.18	0.70	0.52	1		
		Symptoms	0.34	0.30	0.41	0.26	0.65	0.78	0.49	1	
	CPRS	Total	0.55	0.30	0.52	0.48	0.66	0.86	0.56	0.70	1

Correlation between adversities and various scales at index and follow-up. Four groups of correlations are highlighted. Confidence intervals are wide, no coefficients differ significantly, and interpretation must be tentative. SUAS-S symptoms refers to the first fifteen questions, and suicidality to the four specific questions about suicidality. (Supplementary methods, SM307.)

Yellow: Adversities reported at follow-up correlate better with clinical symptoms assessed with SUAS thirteen years earlier, than with CPRS.

Blue: Clinical observations at index and follow-up are correlated (with only a weak correlation for suicidality).

Green: All scales inter-correlate strongly at each given time of measurement.

Red: The trend is for SUAS to show better agreement with CPRS than SUAS-S.

Figure 19. Effect of 5HTTLPR on recovery measured with SUAS-S and CPRS.

Using SUAS or CPRS leads to the same conclusion: no sizeable long term effect of genotype on prognosis.

Bottom left: Difference in total CPRS score between index and follow-up.

Bottom right: Difference in SUAS symptoms (first fifteen questions) between index and follow-up.

Top right: Difference in four SUAS items asking directly about suicidality (wish to live/die and suicidal thoughts/plans) between index and follow-up.
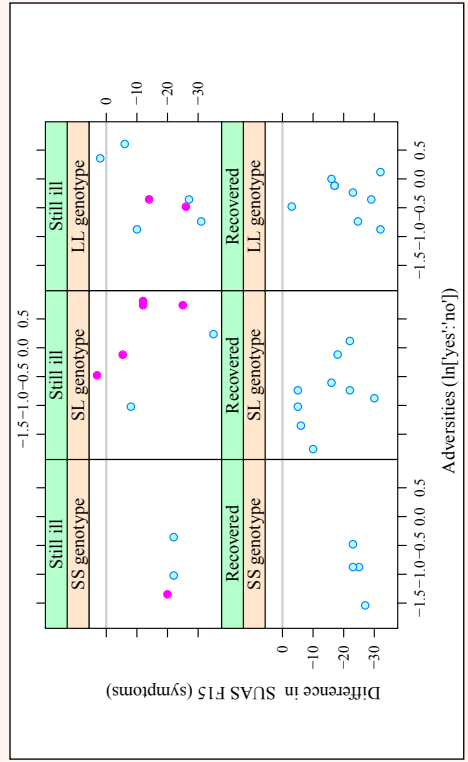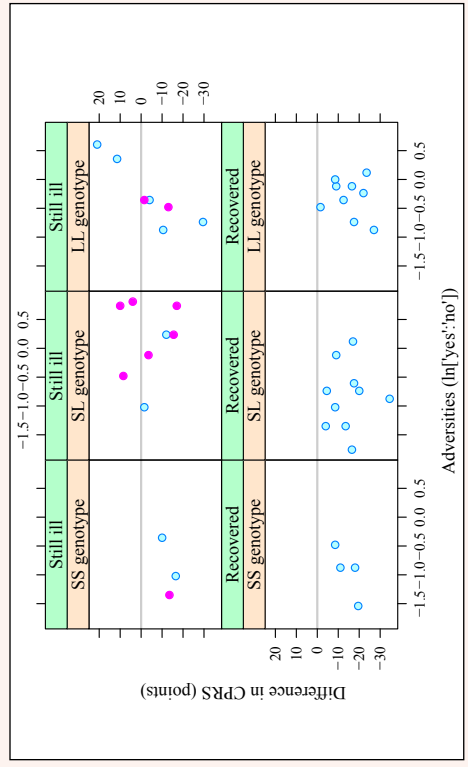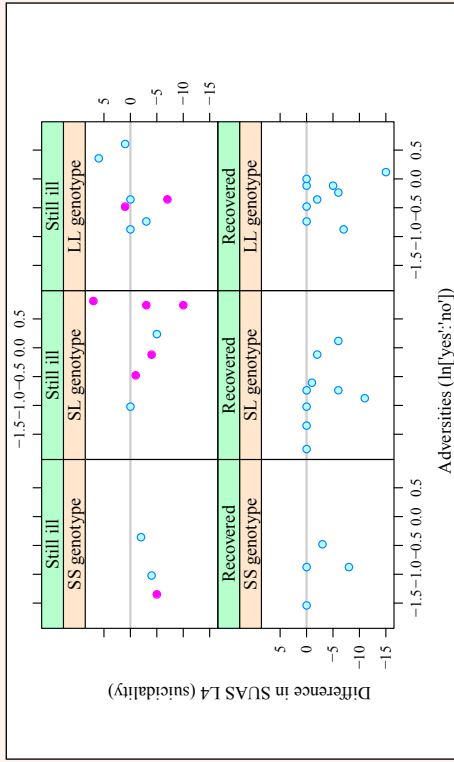
Objective versus subjective halves of SIS in HPA-axis dysregulation

SUMMARY: Cortisol correlates mostly with the objective part of SIS in depressed patients, and the subjective part in adjustment disorder.

SIS consists of an objective and a subjective half, which behave slightly differenctly with regard to HPA-axis dysregulation (see Table 7, p. 44). In depressed patients without personality disorders, both objective and subjective parts correlate negatively with SIS, but the objective part most consistently so. In adjustment disorder, the positive correlation seems due to the subjective component of SIS, and is more inconsistent. The presence of a personality disorder complicates the picture further, suggesting that we should rely on the clean diagnostic groups for interpretation. In this material, there is a trend for adjustment disorder patients to score higher on the objective, but lower on the subjective half (by about one point, on average) and a trend for the two halves to correlate less well than for depression (Supplementary Methods, SM203).

Measuring morbidity after a suicide attempt: SUAS versus CPRS

SUMMARY: Reported adversities correlate both with past and present morbidity, when morbidity is measured using SUAS, as it should, but only poorly so when using CPRS.

If adversities at follow-up only correlated with psychiatric morbidity at follow-up and not index, we might be tempted to think that the adversities reported mainly reflect recall bias. However with SUAS (but not CPRS) there is a significant correlation between adversities reported and symptoms at index ($r_s = 0.40$, 95% CI: 0.10 to 0.64, for first fifteen items), suggesting the first fifteen questions on SUAS might be more appropriate for evaluating morbidity following a suicide attempt than CPRS. (Table 10, p. 46. See Supplementary methods, SM307.)

Table 11. Power analysis

Prediction		Sample size needed for $\beta > 0.5$	Finding in our study
If Caspi et al. holds	If no effect of genotype.		
Suicide ideators/attempters with SS genotype report most adversities, and LL least.	Same number of adversities.	N > 50	Significant, but opposite. (SS < SL < LL)
SL genotype slightly under-represented in suicide ideators/attempters.	Estimated Hardy-Weinberg equilibrium based on our data predicts approximately 15%/47%/38%. Expected rates based on other studies are approximately 20%/50%/30%.	N > 1200	None. ($n = 7/18/17$ for SS/SL/LL.)

Power analysis based on results by Caspi et al. Simulations have been used to approximately determine the sample size needed to detect this difference in approximately half of studies conducted. (See Supplementary methods, SM303, for details.)

Figure 20. Limitations of power analysis
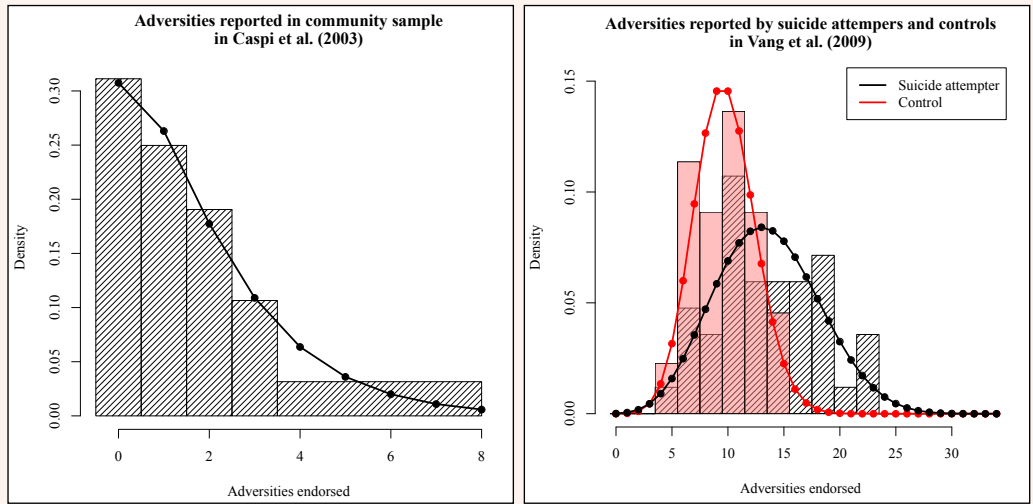
Distribution of adversities in Caspi et al. (left) and our study (right) with fitted distributions (dotted lines). We may be studying patients with more exposure to adversities, or we may have inquired about more, or more diverse, adversities than Caspi et al. All three are probably true. (Lines show negative binomial and beta binomial models of responses. See Supplementary methods, SM301-2 for details.)
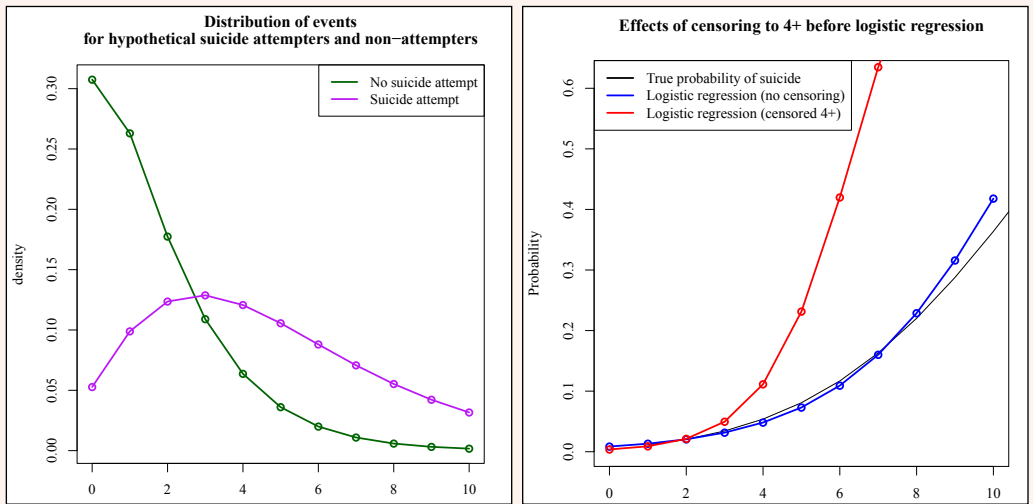
Caspi et al. may have overestimated the effects of adversities on suicidality by collapsing events into a "4 or more" group. If their suicide attempters reported an extreme number of adversities (like ours did) their data may have been distributed a little like the left panel. The right panel shows what happens when a logistic regression is fitted to the hypothetical data in the left panel after collapsing "4 or more" events into a single group, but still treating it as a numerical variable (red line). The red line clearly overestimates the probability of suicide at high exposures, and underestimates it at low exposures. (For details, see Supplemetary Methods SM306.)

5HTTLPR and long-term outcome on measured with SUAS

Summary: Using SUAS instead of CPRS to measure morbidity also fails to show any long-term benefit of any particular 5HTTLPR genotype to hospitalized suicide attempters.

CPRS asks about a wide array of symptoms—perhaps too wide. If the target group has been hospitalized for suicide attempts, why not use some measure of suicidal ideation, or the symptoms in SUAS chosen to be relevant to suicidality?

SUAS was in fact administered to these patients. Regardless of whether you consider the change in CPRS between index and follow-up or the change in SUAS (see Figure 19, p. 47), there is no evidence of the L-allele conferring an advantage.

What did the patients mean by childhood neglect?

Summary: Reported childhood neglect appeared to function like a subjective summary variable, where participants often referred to perceived toxic events reported elsewhere in the interview.

Childhood neglect was strongly associated with suicide attempts, but neglect is a very vague concept. Protocols from the interview were reviewed

to determine what informants meant by it (see Table 9, p. 45). The patients often recapitulated answers elsewhere in the protocol.

Reports of adversities are complicated by age effects on recall.

Summary: Age-related effects complicated the number of adversities reported.

The interview asks about adversities from childhood, right up to the suicide attempt, in people of varied ages. This may introduce age-related confounds, because of memory-effects.

Correlations between age and adversities during different stages of life are shown in Table 8 (p. 44). Probably older people report fewer childhood adversities because they forget, and more adult adversities because of the longer time at

risk. However, alternative explanations exist, e.g. type of psychiatric affliction may vary with age.

A further difficulty is that repeated events are also handled inconsistently. We ascribed points to the presence or absence of an adversity, irrespective of repetition—but we asked separately about ages 0–12, 13–19, 20–index. Hence being imprisoned at age 17 and at age 21 would count double, but not ages 21 and 25.

Power analysis of the 5HTTLPR study

Summary: The sample may be big enough to detect an effect of the 5HTTLPR genotype. This requires that the effect size for hospitalized suicide attempters is only a little bit larger than reported by Caspi et al. for a history of suicide ideation/attempts.

Most studies of the effect of 5HTTLPR on stress-sensitivity have had sample sized of hundreds or even thousands of people. With a sample of only 42 suicide attempters, can we really expect that a significant effect in our study is anything but a

type I error? I will argue, "Yes, maybe."

Caspi et al. report a logistic regression model predicting suicidal ideation/attempts based on adversities and genotype, from which we can

make a power analysis. A sample size of $N > 50$ suicide ideators/attempters may be sufficient to detect differences in the number of adversities reported by SS, SL and LL genotype (see Table 11). By comparison, a sample of $N > 400$ MDD patients, or $N > 85$ first-episode MDD patients, would be needed. (See Supplementary methods, SM303-4).

Caspi et al. studied suicide ideators/attempters in a community sample, and although speculative, it might be reasonable to suspect even greater differences in a sample of hospitalized suicide attempters, which we are studying (implying lower N needed). Conversely, Caspi et al. may have overestimated some regression coefficients (implying greater N needed) by censoring more than four adversities into a "4+" group but still treating it like a numerical covariate (see Figure 20), but sufficient details are not given in the article to ascertain this.

The validity of the power analysis is also limited by differences in how adversities were measured. Important differences are evident in the distribution of our data, when compared to Caspi et al. (see Figure 20), and from their method description.

Discussion

SUAS-S

SUMMARY: There was no evidence to suggest including any of the symptom-oriented items to predict suicide attempts, even when adjusting for age and sex, and score profiles. The specific questions perform marginally (not significantly) better than total score on SUAS too. The interview version of SUAS may discriminate better at high levels of suicidality, and there may in particular be differences in how suicide plans and preparations are judged. In SUAS-S, wish to live/die mediates the association between symptoms and suicidal thoughts/plans, but in SUAS the association is more complex. There is a disconcerting drop in incremental predictive value, as basic clinical information becomes available, which probably is not unique to SUAS-S. In SUAS-S, suicidal thoughts/plans are mediated by wish to live/die, but SUAS administered to hospitalized suicide attempters behaves differently.

Interpretation and relevance

Paper I shows a clear benefit to dropping symptom-oriented questions in heterogeneous patient groups, where patients are tested only once. Unfortunately, the four specific questions can still not differentiate between future self-injury and suicide attempts.

The result stands in contradiction to conventional wisdom, which would dictate that hopelessness, and perhaps also impulsivity, are important symptoms to evaluate. Certainly, hopelessness was the symptom most closely and most consistently loaded on expressed suicidality in the original factorial structure of SUAS/SUAS-S (see Paper I). Hopelessness has an even closer relationship to expressed suicidality in than other symptom-oriented variables in suicide ideators or patients with a previous suicide attempt (see further results).

It is possible that the factorial structure (describing which questions are associated) is not suited for prediction. Specifically, a specific symptom could be over-represented in suicide attempters, even though the factor it loads on is not. However, hopelessness was not elevated more than would be expected based on total score, in suicide attempters (see further results). Hence, in SUAS-S, hopelessness does not emerge as a useful independent predictor.

Symptom-oriented items behave very differently with regard to age and sex, for instance with hostility/hypersensitivity being a young female's symptom (see further results). The four direct questions about suicidality show more consistent relationship to age and sex (see further results). This is desirable for cconsistency among items. Even so, the score based on the four specific questions remains similarly affected by age, sex and diagnosis as the total score (see further results).

SUAS-S compared to SUAS

The evidence in favour of only asking direct questions about suicidality comes both from the factorial structure and ability to predict suicide attempts. However, suicide attempts are not the same as completed suicide, and factorial structure depends on the origins of variability in the sample. It was therefore important to revisit an older data set where SUAS was administered to hospitalized suicide attempters.

Using SUAS on hospitalized suicide attempters, the symptom-oriented questions only had a marginal advantage in predicting actual suicides (see further results). One reason may be that the items performed differently in SUAS and SUAS-S. It seems that "top marks" on several items are reserved for much more serious manifestations of suicidality (see further results). Symptoms may automatically be interpreted in the context of suicidality by the interviewer, and also reflect observable behaviour (as opposed to an internal feeling). In this particular study of SUAS, the interview was conducted after a suicide attempt, and the symptom load (first fifteen items) may be an indicator of whether symptoms subsided rapidly after the suicide attempt.

Mediation analysis suggested that symp-

toms on SUAS-S affected suicidal thoughts/plans almost completely through wish to live/die. This was not the case for SUAS in hospitalized suicide attempters, where the conditional relationship between the three variables is much more complex.

Limitations

We cannot exclude the possibility that items about symptoms would turn out to be more important if measured with other, better or more questions. Furthermore, asking about specific symptoms may prove relevant in specific patient groups, or if used to assess suicidality repeatedly, where it makes more sense to compare aggregate symptom load. Information about suicide attempts were obtained from medical records, and participation was quite variable between different clinics. We did not gather information about the timing of suicide attempts, or the number of visits made by each patient, or whether they were still in treatment at follow-up. Like any study looking att suicide attempters, the results must be extrapolated very cautiously to actual suicide.

Suicidal intent, cortisol and depression

Summary: This author's interpretation of the results and their relevance differs from those emphasized in the article. Hypercortisolemia is probably not a specific indicator of suicide risk, but may herald more severe, persistent or recurrent depression. There is an unexpected inverse relationship between SIS and HPA-axis dysfunction, maybe because the ability to plan and execute a suicide is suppressed at the worst point of depression, or because high serum cortisol is an adaptive reaction that reduces suicidality. The difference between the objective and subjective halves of the SIS were explored, with SIS–cortisol correlations in depressed patients seeming more related to the objective half, and in adjustment disorder to the subjective half. Despite the difficulties reconciling subjective and objective halves of SIS, it is a useful scale because it provides information that is largely independent of the information provided by other scales. Differences between men and women may have contributed to the results, but the trends are similar for men and women. The combined CRH-dexamethasone test might be more sensitive and robust, and 24 hour cortisol is another alternative to consider.

Interpretation and relevance and results

The research question is: Does the dexamethasone suppression test tell us anything specific about suicidality, or does it just identify more severe, persistent or recurrent depression?

The bulk of suggestions in the literature associates hyperactivity (high cortisol) with suicide. Our finding was: (1) a non-significant slightly positive correlation between suicidal intent and HPA-axis dysfunction in adjustment disorder; and (2) a significant negative correlation in depression. This slightly favours the explanation that previous reports of an association between HPA-axis hyperactivity and later suicide is best explained as the result of vulnerability to depression, and not by some direct suicidogenic effect of HPA-axis hyperactivity.

Had HPA-axis hyperactivity been associated with suicidal intent specifically, we would have expected significant correlations in both diagnostic groups. If HPA-axis hyperactivity is associated with depression, but not suicidality, we would expect a significant correlation in the depressed group, and a weak or zero correlation in non-depressed groups. The weak correlation would be expected in most study designs as a result of blurred diagnostic boundaries. For instance, depressive symptoms may be masked (e.g. long-standing dysphoria may not be noticed or difficult to assess in the aftermath of a crisis or in company of a psychotic disorder). Similarly in follow-up studies of non-depressed patients HPA-axis dysfunction may still indicate vulnerability to later depression (which could explain long-term suicide risk regardless of current diagnosis). Fortunately, in this particular study, the interpretation is eased by finding that the associations were in opposite directions for depressed and non-depressed patients.

Explaining the negative correlation

We are left with an unexpected finding to explain: a negative correlation between suicidal intent and HPA-axis dysregulation in depression. It is argued in the article that long-standing depression "burns

out" the HPA-axis. Let us consider some other possibilities, too.

Even though most results implicate hyperactivity (high cortisol levels) with suicidality, others have implicated hypoactivity (low cortisol levels) with suicidality (e.g. [206]). Whereas this should raise suspicions of publication bias, another possibility must be considered. Hypercortisolemia may be an adaptive response (e.g. [207]) that potentially suppresses suicidality. At the same time hypercortisolemia can predict a clinical course with more severe, persistent or recurrent depressions, thereby raising long-term suicide risk. If both forces are at work, we would expect a positive correlation in some populations (e.g. long-term follow-up of mixed diagnostic sample) and negative in others (e.g. depressed patients without comorbidity and homogenous clinical characteristics).

Another possibility is that the patient's ability to plan and execute a suicide may be suppressed because of the general behavioural and cognitive inhibition at the nadir of depression. There are many anecdotal accounts of suicides occurring as the severely depressed, cognitively and conatively impaired patient improves. With the strength of volition, power of planning returning, but residual depressive symptoms still present, the patient may be at greater risk for making a well-planned high-intent suicide attempt. This explanation is somewhat inconsistent with the fact that the correlation is similar at lower and higher levels of depression (see Further Results). However, MADRS assesses symptoms of depression broadly, and not specifically those that relate to volition and planning. Furthermore MADRS does not differentiate between anhedonia (the inability to feel pleasure) and avolition (the inability to "want to").

A psychologically blunted response to the mental rehearsal of suicide might facilitate the acquisition of capability for suicide (i.e. overcoming the fear). HPA-axis hypo-activity could be an indicator of a blunted response to threat and other stress. A blunted HPA-axis response to social stress has indeed been described in first-degree relatives of suicide completers [208]. (Antithetically, there are suggestions that cortisol facilitates learned fear extinction under some circumstances [29], [207],

[209]. HPA-axis hyperactivity might then facilitate "unlearning" the barriers to suicide through mental rehearsal.)

Unintentional selection

We cannot exclude the possibility that unintentional selection bias caused the results. The patients with high SIS and severe HPA-axis dysfunctions might be under-represented if, contrary to our claim, but in line with conventional wisdom, a much greater proportion of them actually died during their suicide attempts. Furthermore, an unmistakable depression with melancholic features (associated with an aberrant HPA-axis regulation) might lower the threshold for hospitalization and inclusion in the research programme, where a low-intent suicide attempt otherwise would have escaped invitation to participate.

Limitations

Caffeine and nicotine intake were not measured or controlled. Duration of illness is not known. Age and sex are possible confounders, although the results seem consistent across the sexes. There may be selection bias if the probability of death or hospitalization following a suicide attempt are affected by the symptoms associated with HPA-axis dysfunction. Waking times were not recorded or controlled for.

Confounders in the dexamethasone test

Caffeine, nicotine, and nicotine withdrawal have all been described to activate the HPA-axis [210], [211]. Age (see article) and sex (see Further results) may also be confounders. The timing of the cortisol sampling may be critical, both with respect to the subject's normal diurnal rhythm, and with respect to awakening on the day of sampling [25]. Waking times relative to sampling may affect the result, as well as circadian disruption. All the same, it is unclear whether correcting for waking times would be useful or counterproductive. Circadian disruption could be so central to the pathophysiology of depression that correcting for it may not make sense.

Figure 21. Suicial intent, not ideation, is independent of symptoms
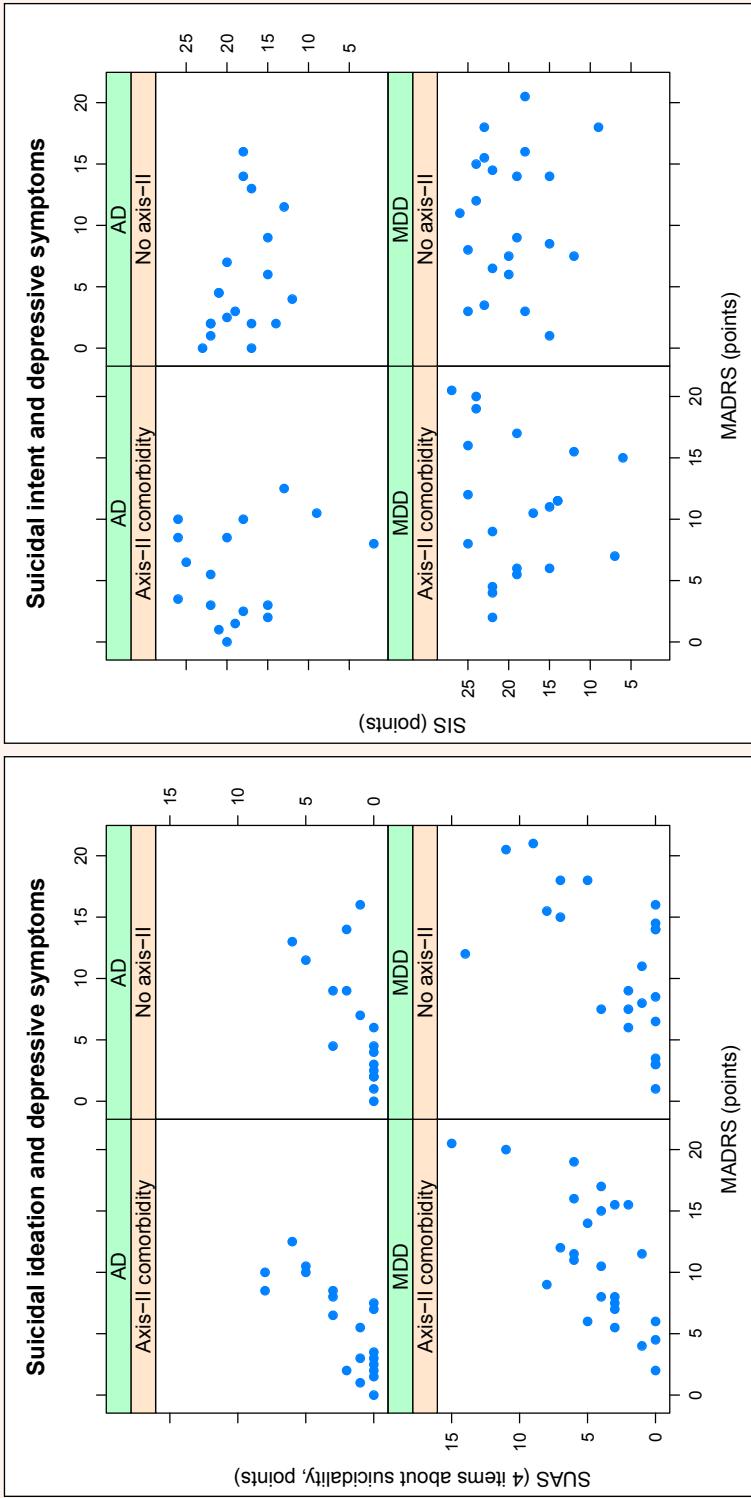
While suicidal ideation (here score on SUAS items 16, 18, 19 & 20) is related to depressive symptom severity (here measured by MADRS), the same is not the case for suicidal intent. Yet, a high SIS-score means having made a serious suicide attempt that almost ended in death by design, and it has some relationship to future completed suicide. This suggests suicidal intent provides independent information, and makes it an interesting parameter to measure.

Alternatives to the dexamethasone test

The combined CRH-dexamethasone test is more recent version of the dexamethasone suppression test. Dexamethasone is given to suppress the HPA-axis, and some hours later CRH is given to stimulate the HPA-axis. This is currently the test that most sensitively discriminates between depressed and non-depressed people. It also seems to be reasonably robust to effects of nicotine and caffeine [210]. A simpler alternative, also useful in differentiating depressed and non-depressed patients, is to simply sample cortisol every half-hour between 10:00 and 12:00 [212]. Of course, there is no guarantee that a test of HPA-axis function capable of detecting depression is suited for discovering HPA-axis aberrations associated with suicidality.

The production of CRH, ACTH and cortisol are all pulsatile, mostly at the beginning of the chain (CRH) and least at the end (cortisol). (See [213] for illustrative diagrams.) This suggests that single measurements might better be replaced with repeated measurements for more accuracy. Moreover, it suggests that other summaries of the cortisol concentration may be meaningful. The mineralocorticoid and glucocorticoid receptors have different affinities for cortisol, with the mineralocorticoid receptor being activated at average physiological levels, and the glucocorticoid receptor at higher concentrations achieved during the pulses. Hence it may be informative to measure time above and below appropriately chosen concentration thresholds. It also highlights that concentrations of other steroid hormones might need to be taken into consideration. Measuring serum cortisol at a given time of day, serum cortisol under stress (e.g. social stress, or inhalation of carbon dioxide), serum cortisol after suppression with a synthetic corticosteroid, salivary cortisol, or twenty-four hour urine cortisol capture different aspects of this dynamic process. The psychiatric relevance of these issues has not been extensively explored.

Why suicidal intent, and not suicidal ideation?

The research question was: Does the dexamethasone suppression test tell us anything specific about suicidality, or does it just identify more severe, persistent or recurrent depression? Naïvely taking the correlation between cortisol levels and some measure of suicidal ideation is problematic, however. The first reason is that (as, for instance, shown in the article on SUAS-S) suicidal ideation largely reflects general symptoms (including depressive ones). The second reason is that it is associated with both suicidal and non-suicidal self-injury. The suicide intent scale provides an appealing alternative in this case, since it measures planning, determined execution and belief in lethal outcome of a suicide attempt, and is a construct is slightly apart from most others (see Figure 21).

Objective vs. subjective halves of the suicide intent scale

The subjective and objective parts of SIS seem to function differently in depression compared to adjustment disorder (see Further results). With the the reactive nature of adjustment disorder, the notion of suicidal intent might be complicated by the person attempting suicide having more to communicate to those left behind, more ambivalence towards wanting to die, and less time to plan. If the respondent overstates or understates the seriousness of the attempt, it quickly leads to numerically big changes in score on the subjective items.

When administering the SIS, one often becomes aware of objective items being misleading in the individual being assessed. For example, some suicide methods require no efforts to conceal (e.g. crashing the car you own and drive every day into an obstacle), or may require minimal preparation for some people (e.g. a rope and a fixture may be very conveniently available in some homes), and some people have less cause to make final preparations (e.g. the will may already be in order) or communications (e.g. no living close relative). Perhaps the relevant items simply ought to be assigned missing values under such circumstances so as not to underestimate intent, or some other means of contextualizing the information should

be added.

Alternatives to suicidal intent

Seriousness of a suicide attempt can also be measured with the Risk-Rescue Rating Scale [214]. "This scale assesses the lethality of a [suicide attempt], defined as the probability of inflicting irreversible damage. The underlying hypothesis is that lethality can be expressed as a ratio of factors influencing risk and rescue. This scale consists of ten items (scored 1, 2 or 3): five items describe risk factors (method used, impaired consciousness, toxicity, reversibility and treatment required) and five describe rescue factors (location, person initiating rescue, probability of discovery, accessibility to rescue and delay until discovery)."[215]. In some respects, it is a simpler construct to understand than suicidal intent, but clearly says very little about the state of mind at the time of the suicide attempt.

Negative life events and 5HTTLPR

SUMMARY: The findings using CPRS are compared to the findings that would have been made using SUAS. There is a better correlation between adversities recorded at follow-up and SUAS at index, than for CPRS at index. This supports the validity of the life-time adversity reports, which otherwise might simply have reflected illness-correlated memory bias. The interview method chosen is susceptible to age-related confounds. By reviewing interview notes, the patients' understanding of neglect was examined. The question might have served as an opportunity for the patient to provide an over-all subjective summary. A power analysis suggests that, despite it's small sample size, the results may not be the result of a type I error. The extreme scores seen in suicide attempters may require a qualitatively different interpretation.

Morbidity measured with SUAS

We used CPRS because we wanted a very comprehensive assessment of psychiatric morbidity. However, creating an aggregate score (i.e. summing up the items, in this case) is problematic for the same reason that it is desirable: the diversity of symptoms considered. Items in a scale should ideally only be aggregated if this makes sense, either because psychometric analysis demonstrates that the items measure a sufficiently unitary construct (in a reflective scale), or there exists some expert opinion or rationale to support it (in a formative scale).

One alternative to CPRS is to use broad measures of functioning, such as Global Assessment of Functioning or the Sheehan Disability Scale (separately asking about work, social and domestic functioning). Another choice is to use more specific measures of symptom severity. If the target group has been hospitalized for suicide attempts, why not use some measure of suicidal ideation, or SUAS?

SUAS/SUAS-S data was in fact available. Further analyses did not, however, suggest that using SUAS would alter the results substantively.

There was, however, a better correlation between adversities and morbidity at index measured with SUAS. This is important, because, using CPRS, a major concern was that adversities at follow-up seemed practically only to be related to morbidity at the time when adversities were reported, and not at the time of admission after a suicide attempt.

Understanding extreme number of reported adversities

The meaning of extreme scores (i.e. very low or very high) is sometimes unclear, despite these individuals often having considerable impact on the later statistical analysis.

Extreme scores may represent more than a difference in quantity of what is being measured— it may signal that there is something qualitatively different. Certainly, we saw that people reporting very many adversities were also the ones to endorse the harshest adversities (e.g. sexual abuse). People reporting very high scores may have endured a completely different level of chronicity, violence, breakdown of protective factors, or carry-over of consequences into later life. Their experiences may not be comprehendible if simply thought of as "more of what others experience".

Extreme scores may also indicate a breakdown in measurement: (1) when instruments fail completely, they typically produce extreme results; and (2) instruments fail on unusual people, because they have unusual reasons for answering as they do. For instance, a complete breakdown in trust in the interviewer and consequent unwillingness to disclose information would produce a very low score. A patient who is particularly suggestible or afraid to disappoint, may be coaxed into a very high score by an eager interviewer. Some patient groups that are over-represented amongst suicide attempters may be particularly vulnerable to measurement breakdown. For instance, the breakdown of trust may be secondary to pervasive instability of relations, or the exaggeration of events secondary to histrionic traits.

Limitations

The sample is relatively small. However, a power analysis suggest that the sample size may be sufficient, although clearly being on the margin (see Further results). Only 22 controls could be found for 42 patients.

Using total CPRS score to measure over-all morbidity may be problematic. We used bi-allelic, not tri-allelic, 5HTTLPR genotyping. We also chose to assess adversities with a custom designed interview, which has been discouraged by some. Age affected recall at various life epochs, complicating interpretation (see Further results). Memory bias may affect adversities reported in those still ill. It is unclear which adversities caused mental illness, and which ones were caused by mental illness (or antecedents thereof). Participation rates, especially amongst controls were very low, and could have biased the results.

Measuring adversities

Common alternatives ways of measuring adversities are explained in Appendix I.

Recently, it seems that a 5HTTLPR genotype × environment interaction was robustly found when using interviews and objective events, but not questionnaires [52]. If the 5HTTLPR findings survive the test of time, we may have to conclude that even the larger sample sizes possible with questionnaires do not make up for the loss of

quality of the information obtained. At the time of writing this, no research was found that addresses the question if the 5HTTLPR genotype instead affects how people react in the interview situation, a highly social, and sometimes intense, setting.

Some types of questions may reflect personality or symptomatology more than concrete events (see Appendix I for more details). Causality is often uncertain. Some people may be more prone to remember (or more willing to report) bad experiences, rather than having experienced more of them. It has long been known that recall is mood dependent, with negative mood leading to more negative events being recalled (mood bias). Psychiatric morbidity at the time the questionnaire or interview is administered will also affect the number of events recalled [49].

One alternative to enhance the objective veracity of retrospective reporting is to seek corroborating evidence (e.g. records of sexual abuse). Another is to study people prospectively after confirmed exposure to stressful events like natural disasters or disease (e.g. [216], see also reviews [51], [52]). These studies circumvent a number of memory-related problems with retrospective reports. Under the hood, however, many of the same complexities that complicate the interpretation of the gene × environment interaction remain. Sensitivity to stress remains difficult to separate from pre-existing psychiatric morbidity, and chronic morbidity is difficult to tell apart from personality. For example, people with concurrent psychiatric morbidity (even hard-to-measure subclinical morbidity) are presumably able to mobilize fewer resources (internal and external) to cope with events like earthquakes.

The examples given in their article suggest that Caspi et al. focused on concretely defined adversities that were serious enough not to be commonplace (e.g. arrest, repossession of property, break-up of a cohabiting relationship). By contrast, we looked at a large number of adversities through the entire life-span, some being less concrete (e.g. neglect). We may also asked about adversities that are more chronic stressors, unfortunately perhaps also more likely to be the consequences of psychiatric morbidity, rather than the antecedents.

Bi-allelic 5-HTTLPR genotyping

There are a number of variations of the 5HTTLPR region [62]. We report the results based on detection of the "long" and "short" versions (differing in a tandem repeat). Sometimes tri-allelic typing is reported, allowing for: a short (S) and two long (La and Lg, differing in an adenine–guanine substitution). The S and Lg alleles are probably functionally similar [217], [218], but the Lg allele is not very common in Caucasian populations (~10%–15% allele frequency).

5HTT-binding, volumes and temperament

SUMMARY: The findings suggest that anatomical changes go hand-in-hand with neurochemical changes in this select group of suicide attempters. This makes certain confounders that may have explained the SPECT findings less likely. Future research should consider looking at the globus pallidus, as well as functionally connected and anatomically adjacent areas, using carefully chosen clinical controls. The basal ganglia are a predereliction site for certain types of injury (poisoning, drugs and anoxia) that must be considered as confounders in suicide attempters. Caution should be observed in not taking volumetric differences at face value, but should be understood in the context of other signal changes in the structure itself and its neigbouring structures, including white matter. The possibility of neuroinflammation, and possible effects of cortisol, are briefly discussed.

Interpretation and relevance of findings

The paper analyzes a subset of participants who underwent MR imaging and ^{123}I-β-CIT SPECT scans [113], [190]. The progenitor study found a correlation between temperament (ascertained with self-report questionnaires) and 5HTT/DAT binding potentials (measured with SPECT) in suicide attempters but not controls. For the SPECT study, a number of confounders can be imagined, that may have introduced this correlation in suicide attempters. Finding an anatomical correlation strengthens the credibility of the SPECT findings considerably. MR volumetry also provides an anatomical target for future studies, which the low spatial resolution of SPECT does not allow.

We found changes in the globus pallidus, which is slightly awkward, because rather large changes in the size of the globus pallidus need to be explained. Disorders affecting the bulk of the globus pallidus also ought to produce symptoms related to movement, posture or speech, consistent with clinical experience. There are admittedly case reports with pallidal necrosis leading to personality change without pronounced motor symptoms (e.g. [116–119]). All the same, these cases probably reflect the exception rather than the rule. If future research cannot specifically implicate relevant portions of the globus pallidus (e.g. limbic), or suggest a credible specific mechanism whereby large portions of the globus pallidus can be involved without generating motor symptoms, the findings are best considered secondary to some other undetected changes in the brain. Future studies should probably assess neurological signs very carefully, and also need to use carefully selected clinical controls, since several psychiatric disorders are associated with size alterations in the basal ganglia.

The patients were selected by virtue of having made a serious (measured with SIS) suicide attempt. This means that: (1) all patients were suicidal, at least in the proximal past; and (2) the suicide attempts were planned, and not impulsive. The first consequence is that correlations in the patient group that do not exist in the control group should be taken to reflect differences in underlying pathology. There is no guarantee that any such detected abnormality translates into more or less suicidality. The second is that sub-solidity—sometimes explained as impulsiveness—should not be taken to represent impulsivity in the sense of making a suicide attempt at short notice, or without due consideration..

Confounders in the original SPECT findings

What could introduce a spurious relationship between 5HTT/DAT availability and temperament specifically in suicide attempters? One risk is that

patients have taken a substance that affects the SPECT results, with the dose being related to the severity of symptoms, and the symptoms in turn affect responses on the clinical scales used to assess temperament. Fortunately, we do not usually expect these substances to affect anatomy, at least in the short term.

The patients were essentially free of psychotropic medication, but a few of them occasionally received benzodiazepines during the washout period. There is unfortunately some evidence that benzodiazepines has the potential to affect the estimated DAT binding potential by inhibiting dopamine release [219–222]. In this article, however we focus on the serotonin transporter binding, and less is known about how benzodiazepine treatment may affect those results.

Smoking was largely uncontrolled and unmeasured, and conceivably correlated with symptom severity. Smoking has been reported to affect β-CIT binding, for example in patients with depression, alcohol withdrawal, and a healthy sample [219], [223], [224]. A twin study using ^{123}I-β-CIT SPECT reported higher 5HTT binding in the heavier twin. However, results using other ligands (11C-DASB PET) suggest an inverse relationship between 5HTT binding potential and body mass index after correction for covariates.

Conceivably, the patients may also have been exposed to either prescribed or recreational drugs with long-term effects on 5HTT or DAT availability. In some cases, we cannot exclude resulting anatomical changes from the same drugs, in particular with regard to antipsychotics, although we judge it unlikely to be a major contributor to the results. Additionally, individual differences in the pharmacokinetics of citalopram may have affected the results, since the separation of DAT and 5HTT binding depends on assumptions about the half-life of citalopram.

Physiological causes of volumetric changes

What causes us to see bigger or smaller structures on the magnetic resonance scans? Some physiological explanations for how differences in size can occur include:

- Growth or loss of blood vessels, or change in their diameter.

- Gain or loss of glia cells or neurons.

- Greater volume occupied by each cell (e.g. cell body volume, arborization of axons and dendrites, myelination).

- Entry or exit of fluids by altered haemodynamics or vascular permeability.

- Developmental differences (affecting number and types of cells, arborization of axons or dendrites, how densely cells are packed, myelination of axons, or cellular organization of a structure).

Trophic effects may occur in the brain under increased demands. Some brain structures have been reported to grow when used a lot (e.g. in the hippocampus of taxi-drivers [225], [226], or cortex and hippocampus of medical students [227]). Similarly atrophy is seen in the failing brain, for instance after stroke or in dementia. Nonetheless, we should probably resist the temptation of associating decreases in size with impairment, and not simply assume "more = bigger = better" (e.g. [228]).

Pathological causes

There may be pathological causes of volume reductions. The MR images would have been examined by a radiologist, as part of the research procedure, but since the MR sequences only included anatomical scans and were not directed examinations, it is fair to suspect that the ability to identify pathological changes would have been reduced. Over-all most common cause of lesions in the basal ganglia is ischemic injury (esp. stroke), with reductions in volume or lacunar loss of brain-tissue (fluid-filled islands) being the long-term consequence. Most forms of pathology in the brain leads to parts shrinking, not getting bigger (with tumours being the notable exception, and the case of neuroinflammation discussed below). In suicide attempters, we also need to consider the effects of drugs and poisons.

Toxic and hypoxic effects

The hippocampus and basal ganglia have relatively high metabolic needs but comparatively delicate

blood supply. The basal ganglia shrink as you get older [229], [230], possibly because of vascular ageing. Certainly cardiovascular pathology can affect these areas of the brain, with reduction in the putamen having been described in connection with heart failure [231], and reductions in caudate and hippocampus in chronic hypoventilation syndrome [232], [233].

The basal ganglia are a site of predereliction for toxic and ischemic injury (especially the globus pallidus, [234]). Changes can also be secondary to several toxins (like methanol, solvents or cyanide), as well as several street drugs (e.g. ecstasy). This is mediated by episodes of hypoxia (e.g. drugs affecting breathing), reduced perfusion (e.g. via vasoconstriction or hypovolemia) or direct neurotoxicity. Inhalation of carbon monoxide sometimes causes neurological sequelae. "The most characteristic neuropathological findings ... are necrosis of the bilateral globi pallidi and progressive white matter demyelination (particularly involving the periventricular white matter and centrum semiovale)" [235]. A number of other, but less relevant, causes of neuroradiological findings in the globus pallidus are also known (including metabolic [236]).

Swelling and atrophy in autoimmunity

Autoimmune reactions is an example of a mechanism that can cause both swelling and shrinkage of deep grey-matter structures in the brain (as well as other radiological manifestations not considered here). It is worth dwelling over this possibility, in light of recent evidence for interactions between the immune system and the brain in depression and suicide.

Autoimmune limbic encephalitis, for instance, is well described as a paraneoplastic phenomenon. Antibodies are produced that target the hippocampus, leading to impaired memory along with other psychiatric and neurologic symptoms. Radiologically, it begins with a swelling of the hippocampus, followed by atrophy as the the hippocampus is partially destroyed.

In other conditions, the basal ganglia may be affected. Sydenham's chorea, following streptococcal infection, presents with tics and chorea, but commonly leads to long term psychiatric sequelae like obsessive-compulsive, disruptive, depressive or anxious behaviours [237]. A syndrome has been proposed (although not conclusively demonstrated), with neurological symptoms triggered by streptococcus infections (PANDAS). It has been hypothesized that PANDAS and certain forms of obsessive-compulsive disorder and Tourette's can be caused by antibodies directed at the basal ganglia [238], [239]. One case study demonstrates swelling of the basal ganglia in a 12 year-old boy with obsessive-compulsive disorder following a sore throat, who was treated with plasmapheresis, leading to both symptom reduction and subsiding of the swelling [240]. In another case, autoimmunity seemed to cause reversible hypermetabolism of the basal ganglia, with dementia-like changes to personality and cognition, and only minor motor symptoms [118].

However, finding anti-basal ganglia antibodies does not guarantee any radiological findings in the basal ganglia, even in the presence of neurological symptoms. Antibodies against the basal ganglia are over-represented in several conditions with diverse radiological appearance [241], and are typically found in 2-10% of controls [238].

Hypotrophic effects of steroids

Reduction in volume of the hippocampus has been described in depression and post-traumatic stress disorder, both as a possible risk factor, and as a possible consequence of toxic cortisol elevation [242]. As described earlier, hypercortisolemia is associated with suicide and depression, and the connection hippocampus/amygdala size – cortisol – depression/stress has been explored extensively. There are virtually no reports of such effects on the human basal ganglia, however. A noteworthy exception is a report of that surgery to the pituitary against Cushing's disease led to volume increases in the right caudate that were correlated to reduction in depressive symptoms [243]. (In animals, however, metabolic and structural effects of corticosteroids have been described. In rats, chronic administration of steroids increases levels of the dopamine metabolite homovanilic acid in the caudate [244]. Foetal exposure to steroids in sheep affect synaptic density pre-frontally, and in the hippocampus and caudate [245].)

Neighbouring structures

Using FreeSurfer, anatomically indistinct tissues can cause us to systematically overestimate the size of a structure (see [191] for illustrative images). Lesions or artefacts or other tissue changes also cause signal variation. The true cause might also be found in the white matter bordering the structure measured. A recent study found diffusivity changes in the anterior limb of capsula interna (white matter at the intersection of the putamen, caudate and globus pallidus), associated with suicidality in depressed patients [147]. (They also reported changes in the area of the putamen and globus pallidus themselves, which of course is more in line with our results. However, the point is that we cannot be entirely sure whether the critical change is in the globus pallidus itself or the white matter beside it.)

Limitations

Only about half of the original MR scans could be retrieved. The sample was small, and the material heterogeneous. Healthy controls were used, but this kind of study would benefit greatly from carefully matched clinical controls. This type of analysis is best done using multiple MR imaging scans and scanners with higher field strength. The SPECT method relies on certain assumptions (e.g. half-life of citalopram) to separate dopamine transporter binding potential from serotonin transporter binding potential. We may confuse size variations with lesions or other tissue changes. We did not control for benzodiazepine, caffeine and nicotine intake and non-psychotropic medication. Exposure to poisoons (esp. carbon monoxide), recreational drugs or medication (esp. antipsychotics) in the past may have affected the brain both anatomically and biochemically. The neurological examination was brief.

Alternatives to FreeSurfer

One alternative to automatic segmentation of the brain is to manually trace the structures. Manual volumetry is still considered the golden standard, but only when done by people with experience. Using an automated process avoids subjective bias, but excludes the application of common sense, for instance with regard to artefacts. Manual volume-

try is also tedious and time-consuming, which in itself can be a source of errors (particularly if the rater suffers from low solidity).

The principal automated alternatives to using FreeSurfer are: (1) the voxel based morphometry module of statistical parametric mapping (SPM, *http://www.fil.ion.ucl.ac.uk/spm*); (2) FIRST from FMRIB (*http://www.fmrib.ox.ac. uk/fsl*) [192], [246]. The functionality of FIRST is comparable to FreeSurfer in that it delineates known structures and returns estimates of their volumes. VBM differs fundamentally by comparing brains voxel by voxel.

Voxel-by-voxel comparisons (as in voxel based morphometry) are attractive because macroscopic anatomic boundaries may not be meaningful. For instance, the globus pallidus is functionally related to the very nearby ventral pallidum, but the ventral pallidum is not counted as part of the globus pallidus volume because it happens to be separated from it by white matter. The difficulties with voxel based morphometry have been succinctly summarized as: "First, shape differences attributable to misregistration during spatial normalization, rather than actual group differences, can be detected. Second, global rather than local regional volume change may be more accurately detected, because of the relatively imprecise registration used. Third, the accuracy of localization is negatively affected by smoothing, which may shift the peak of the [statistical parametric map] towards regions of low variance. Fourth, spatially complex, subtle, or changes that are related to changes that occur elsewhere in the brain may not be detected by this mass univariate approach. Fifth, the exact nature of tissue changes identified with [voxel based morphometry] is still poorly understood."[134].

Some recent studies have looked at shape differences (not just size differences) of sub-cortical and cortical structures, using a variety of methods. Unfortunately, the small sample size does not permit this kind of analysis to be made meaningfully.

Alternatives to SPECT

Modern PET ligands allow the visualization of dopamine-transporter and serotonin-transporter binding (for instance with 11C-DASB to visualize

the serotonin transporter). This shortens the procedure and circumvents the problematic assumptions that the ^{123}I-β-CIT SPECT method hinges on (e.g. the half-life of citalopram, which is known to differ between individuals). Residual correlation between DAT and 5HTT binding potential in our study may suggest separation was not complete.

Dichotic listening

SUMMARY: Dichotic ear advantage may be useful in detecting pre-frontal dysfunction associated with suicidality. Future work should study the role of comorbid anxiety. Interactions with age, sex, and other factors may limit the practical applicability.

Interpretation and relevance

Wish to live/die correlates with dichotic ear advantage. One explanation is that the wish to live/die dimension is particularly associated with a kind of frontal dysfunction measured with dichotic listening. Some authors explain emotional differences between the hemispheres of an approach-withdraw heuristic, quite along the lines of wishing to live/die.

Studies of both EEG asymmetry and dichotic listening in psychiatric patients have been plagued by complex interactions with sex. For instance, in a study of fluoxetine against depression, the tones task discriminated between male responders/non-responders, but the verbal task between female responders/non-responders; depressed men exhibited less asymmetry on both tasks, but depressed women only showed altered asymmetry on the verbal task (and then less for responders but more for non-responders) [156]. This limits the practical applicability of measuring functional asymmetry.

Previous studies of depressed patients have described differences between depressed with or without anxiety. This might be the reason for the somatization item correlating with dichotic ear advantage. Other possibilities are that the patient could in fact be somatically ill, have a psychiatric disorder with very bodily manifestations (e.g. weight loss), or have a psychiatric illness that the patient prefers to view as organic not psychic.

Confounders

Males tend to show more lateralization on both tones (towards the left ear) and verbal material (towards the right ear) than females [156]. Smoking and the menstrual cycle are also believed to affect perceptual asymmetry [171], [172], [247], [248]. The ear advantage is also affected by the relative loudness of the stimuli [249], and also by hearing loss. The phonemes may be foreign to speakers with other mother tongues (e.g. Arabic does not have a /p/). In one pitch-detection task, left ear advantage was seen in musicians without absolute pitch, but not with [250], and my own unpublished results from a group of healthy participants also suggested that musical ability affects performance on both the tonal and verbal tasks.

General discussion

Summary: The symptoms chosen in SUAS/SUAS-S seem valuable in assessing morbidity in suicide attempters, but not risk. Perhaps symptoms should generally be disregarded when assessing suicidality, but this means surrendering to the problem of having to combine diverse sources of information to arrive at a judgement. Attention should be given to incorporating more independent, but relevant, sources of information, and perhaps re-assessing the format, scope and purpose of suicide-related scales. Working with clustered, heterogeneous data present certain challenges. Although matched clinical controls are desirable, such designs require thinking more about the details of the matching, and deciding if more energy should rather be spent investigating the time-course of measured variables.

Lessons from a few scales

SUAS-S has been thoroughly investigated. The results suggest that for predicting suicide risk in heterogeneous groups based on a single measurement, you should not bother looking at the questions about symptoms. At best they do not tell you anything, at worst they distract. It begs the question if psychiatric morbidity should be disregarded more generally when assessing the suicidal patient in the clinic.

Should we just resort to the Paykel scale, with its direct questions about suicidality that can sensibly be aggregated? Although it can make perfect sense to calculate an aggregate score under the right circumstances, a good case could be made that those circumstances do not apply to most suicide-related scales. In scales where it undeniably makes sense to calculate aggregate scores, such as the Paykel scale, the questions unavoidably have a very narrow scope. Unfortunately, this is a retreat in the face of a greater enemy: the need to combine diverse sources of information to arrive at a judgement.

When assessing morbidity in suicide attempters, the symptoms probed in SUAS/SUAS-S may be a good choice. The fifteen symptom-oriented questions on SUAS-S seemed to produce a more useful aggregate score than the sixty-five CPRS items, when morbidity was studied in the context of life-time adversities.

A lesson from the Suicide Intent Scale is the need for ways of obtaining new, independent, but relevant, types of information. Currently, SUAS-S offers very little incremental information once certain basic clinical facts are known, or some other scale already has been administered. This problem is almost certainly not unique to SUAS-S. Incremental predictive validity has been poorly ad-dressed in the literature generally, and needs more consideration.

How should we proceed with clinical scales from here? The experience of rating scales in life-events has been that the self-rating scales perform poorly in comparison to an interview. They are used because self-assessment questionnaires avoid spending time on the interview itself, the practical problem of scheduling them, and the result is returned in a structured format that requires very little further processing. Clinical scales may suffer from the same pit-falls, and are seductive in the same way. Perhaps the solution is to change the scope and purpose with which scales are developed. Imagine instead you were trying to create a user-friendly computer program that helps the patient compile the kind of information about himself or herself that is clinically relevant. It would offer menus, icons, the possibility to correct mistakes, the ability to click on buttons to instantly get further explanations, perhaps using multimedia. It is unlikely that you would imagine anything that resembles the fill-in-twenty-questions zero-to-four format we have inherited from early psychometric efforts.

Suicidality at the intersecion of biology and scales

A theme has been to connect clinical scales with objective biological measurements.

The achievement in the SPECT/MR study was to in vivo combine structural information with imaging of ligand binding. Advances in MR imaging have increased resolution and contrast and permitted measurement of white matter tracts, allowing better anatomical distinctions to be made, and characterizing the connections between areas. However, real insights might only be obtained

when this information is combined with pharmacologically relevant information from the same patients, such as availability of certain receptors. Unfortunately, doing such research places strain on clinical practice, since patients need to be essentially free from medication, and probably should avoid the most popularly consumed recreational drugs on a ward (nicotine and caffeine).

A challenge is to transform the results into concrete further research on clinically relevant samples. Let us assume, for the sake of argument, that we have found pre-frontal dysfunction associated suicidality in our sample, using a dichotic listening task. In this study, all participants were selected to be suicidal (if not at the moment of testing, then at least in the proximal past). Usually, however, you will want to study broader groups of people, e.g. psychiatric patients in general, or even the general public. The challenge, then, is to find a way of detecting which patients, in a heterogeneous sample, have pre-frontal dysfunction associated suicidality (as opposed to having just pre-frontal dysfunction, or just suicidality).

The risk when working with heterogeneous samples is that we might inadvertently repackage old meat in fresh wrapping. For example, we hope to have picked up signs of pre-frontal dysfunction associated suicidality or pallidal – serotonergic – novelty-seeking associated suicidality. The risk, of course, is that we are simply detecting something as trivial as the presence of bipolar patients or anxiety symptoms amongst suicide attempters. Due to clinical and practical constraints, compounded by a fundamental ontological uncertainty about psychiatric illness, concrete solutions are not forthcoming. Despite being quite costly and more challenging to organize, more longitudinal data might be helpful. The time-course may resolve the question of who in a sample really has factor-X associated suicidality.

Heterogeneous data and clinical controls

Studying suicide attempters generates heterogeneous data with clustered characteristics. For instance, repeated non-suicidal self-injury is over-represented in young females who more frequently acknowledge certain symptoms and traits, share biological features and have similar habits that can affect biological parameters (e.g. smoking). In practice, such clustering turns out to be difficult to take into account statistically.

Ideally, we would always include clinical controls. However, a lesson can be learnt from the one study where we had carefully matched clinical controls—namely that we should fight the spinal reflex to match for age, sex and diagnosis. A successful match requires a positive correlation in the variable studied between patient and corresponding control. In fact, in the study where we had clinical controls, there was actually a slight negative correlation in morbidity between patients and controls. In other words, even though matching with clinical controls is a great idea in theory, it might not work in practice because it is not obvious what to match by. Similarly, in the SPECT/MR study, healthy controls were used, but it seems unlikely that matching by age and sex was particularly valuable to the volumetric analysis, since brain anatomy is so variable. Perhaps an option is to develop a database of MR images of healthy volunteers who for some reason already have undergone an MR scan, and try to match by anatomical similarity.

Acknowledgements and contributions

Author's contribution

The author programmed the computerized tests used for dichotic listening. The stimulus material for the dichotic consonant-vowel task were contributed by Kenneth Hugdahl. The author produced the rest of the stimulus material based on published description (tones) and novel ideas (harmonic condition).

The author has tested all participants undergoing the dichotic listening test. The author has interviewed and performed lumbar punctures on several participants in ongoing efforts to collect data. The author tracked down remaining MR images from the SPECT study and analyzed them using FreeSurfer.

The author is responsible for the majority of the statistics and analysis in papers I-V. (In paper II, Daniel Lindqvist also contributed to the statistics and analysis. In paper III, Charlotta Sunnqvist and Aleksandra Wojcik had already observed that some adverities were more common in suicide attempters than controls. In paper IV, Charlotta Sunnqvist and Eva-Marie Mattson had already observed that mean total SUAS scores were elevated in both suicide attempters and self-injury patients.)

The author is responsible for the majority of the text in papers I, III-V, and contributed to the text in paper II. (In paper II, Daniel Lindqvist is responsible for the majority of the text.)

Layout, design and graphics were done by the author. (Images of the brain adapted with permission from mentioned sources. Papers II-IV are printed as published.)

Acknowledgement

Paper I: Predicting suicide attempts with SUAS-S

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Paper II: HPA-axis and suicidal intent

Suicidal Intent and the HPA-Axis Characteristics of Suicide Attempters with Major Depressive Disorder and Adjustment Disorders

Daniel Lindqvist, Lil Träskman-Bendz, and Fredrik Vang

The main purpose of the study was to investigate Hypothalamic-Pituitary-Adrenal (HPA) axis characteristics in relation to suicidal intent among suicide attempters with Major Depressive Disorder (MDD) and Adjustment Disorders (AD). The relationship between suicidal intent, assessed by means of the Suicidal Intent Scale (SIS), and serum cortisol after a Dexamethasone Suppression Test (DST) was investigated in 78 suicide attempters, divided into diagnostic subgroups. There was a significant negative correlation between suicidal intent and post DST cortisol in patients with MDD. Our findings may be attributed to pathophysiological processes, where a high suicidal intent is revealed during a potential chronic course of MDD, which in turnresults in a seemingly normal stress system.

INTRODUCTION

Abnormalities in the Hypothalamic-Pituitary-Adrenal (HPA) axis are well documented among patients suffering from Major Depressive Disorder (MDD) (Plotsky, Owens, & Nemeroff, 1998; Varghese & Brown, 2001). The relationship between the degree of suicidal intent and the HPA-axis function is however yet to be untangled.

Suicidality and the HPA-Axis

Several studies have suggested that HPA-axis hyperactivity, assessed by means of the Dexamethasone Suppression Test (DST) or 24 hour urinary cortisol samples, is associated with completed suicide among depressed patients (Bunney & Fawcett, 1965; Coryell & Schlesser, 2001; Coryell, Young, & Carroll, 2006; Jokinen, Carlborg, Mårtensson et al., 2007; Norman, Brown, Miller et al., 1990; Yerevanian, Feusner, Koek et al., 2004), while another study did not report these findings (Black, Monahan, & Winokur, 2002).

Among suicide attempters, Westrin and Nimeus (2003) found an association between high serum cortisol after dexamethasone and suicidality, assessed by means of the Suicide Assessment Scale

(SUAS). Lopez-Ibor, Saiz-Ruiz, and Perez de los Cobos (1985) found an association between an abnormal DST cortisol-response and suicidal behavior and thoughts among depressed patients. In contrast to these findings, other studies have reported a smaller activation of the HPA-axis in depressed patients manifesting suicidal behavior and ideation, compared to non-suicidal depressed patients (Pfennig, Kunzel, Kern et al., 2005; Secunda, Cross, Koslow et al., 1986).

To our knowledge, no previous studies have investigated the relationship between suicidal intent, as a means of assessing the degree of suicidality, and HPA-axis activity among suicide attempters. In our material, we employed the Suicidal Intent Scale (SIS) (Beck, Herman, & Schuyler, 1974) as a means of rating the seriousness of a patient's intent to commit suicide. The degree of suicidal intent has been associated with high lethality of the suicide attempt (Haw, Hawton, Houston et al., 2003; Kumar, Mohan, Ranjith et al., 2006). Some studies have found that high SIS-scores at the time of a suicide attempt predicted future completed suicide (Harriss & Hawton, 2005; Nimeus, Alsen, & Traskman-Bendz, 2002; Suominen, Isometsa, Ostamo et al., 2004).

The Time-Course of Illness and HPA-Axis Disturbances

Adjustment disorders (AD) are characterized by emotional or behavioral symptoms in response to a psychosocial stressor occurring within 3 months of the onset of the stressor (*Diagnostic and Statistical Manual of Mental Disorders*: Washington, DC: American Psychiatric Association). The diagnostic status of AD has been a subject of controversy, but there are several lines of evidence that confirm the descriptive and prognostic validity of the disorder, as reviewed by Casey (2001). There is a lower

risk of relapse in AD compared to MDD (Jones, Yates, & Zhou, 2002). However, there is a strong association between AD and attempted suicide (Greenberg, Rosenfeld, & Ortega, 1995), as well as completed suicide (Lönnqvist, Henriksson, Isometsä et al., 1995). The suicidal process among patients in this diagnostic group is shorter and more rapidly evolving compared to patients with MDD (Polyakova, Knobler, Ambrumova et al., 1998), and there are often no indications of emotional or behavioral issues during early adolescence in suicide victims diagnosed with AD (Portzky, Audenaert, & van Heeringen, 2005). Tripodianakis, Markianos, Sarantidis et al. (2000) investigated neurochemical characteristics in patients diagnosed with AD after a suicide attempt, and found higher concentrations of cortisol in plasma, compared with healthy controls. Our research group recently reported lower orexin levels in cerebrospinal fluid of suicide attempters with MDD compared to AD, suggesting a hypothalamic neurobiological distinction between the two diagnostic groups (Brundin, Björkqvist, Petersén et al., 2007).

Aims of the Study

Studies of various aspects of suicidality and stress-regulation have sometimes produced contradictory results, perhaps because of differences between diagnostic groups. The present study aims to investigate differences between two diagnostic groups in how suicidal intent relates to stress-regulation. More specifically, we want to compare suicide attempters with MDD to those with AD, since there is evidence that the two groups can be distinguished not only on a clinical basis, but also in some neurobiological features. We hypothesize that the groups will differ with respect to HPA-axis function, as well as the relationship between suicidal intent and the stress system.

METHODS

Materials

The psychiatric inpatient sample considered here is a subsample from a larger comprehensive study (Nimeus, Alsen, & Traskman-Bendz, 2002) of suicide attempters in a liaison-consultation situation. In accordance with the aim of the present study, we included patients who were diagnosed with either MDD or AD and with no other Axis I comorbidity.

Seventy-eight patients were admitted to the medical intensive unit of the Lund University Hospital after a suicide attempt between the years of 1986 and 2001. After admission they were briefly investigated by means of the SIS. A psychiatrist and, in many instances, a social worker from the Lund suicide research team conducted this evaluation. Within a few days, the patients were referred to a psychiatric ward of the Lund University hospital, specialized in mood disorders and suicidal behavior. The principal diagnoses were here set according to the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition* (Washington, DC: American Psychiatric Association, 1987). All patients were assessed for Axis II personality disorders. Two psychiatrists and one resident in psychiatry set the diagnoses, and they were settled after a consensus discussion. The diagnostic procedure included systematic collection of data regarding the psychiatric history of the patients, as well as thorough psychological evaluations. Since *The Structured Clinical Interview for DSM-III-R* (Spitzer, Williams, Gibbon et al., 1992) had not yet been published at the starting point of the present study, it was not used in the diagnostic procedures. Thirty-nine of the patients received the diagnosis MDD, and 39 AD. None of the patients had any Axis I comorbidity.

The patients gave written consent to participate. The study was approved by the Lund University Medical Ethics Committee.

The DST

The DST was carried out after a mean of seven days after admission to the ward. On the first day of the DST, baseline serum cortisol concentrations were measured at 3 p.m. One milligram dexamethasone was given at 10 p.m., and serum samples were drawn at 8 a.m. and 3 p.m. the following day for analysis of cortisol (Carroll, Feinberg, Greden et al., 1981). The samples were placed on ice, centrifuged at $4°C$ and $3000 \times g$ for 10 minutes within one hour of collection. If cortisol was not analyzed in serum the same day, serum was stored at $-80°C$ until analysis. Serum cortisol was measured using a commercial RIA (Orion diagnostica RIA kit). The detection limit was below 7 nmol/l, and the intra- and interassay coefficients of variation were below 5 and 7% respectively.

A patient who did not suppress cortisol to a value below 140 nmol/l at any time after dexamethasone administration, was classified as a nonsuppressor of cortisol.

None of the patients in the study had a medical condition or took any medication, such as psychotropics, corticosteroids or insulin, known to interfere with results of the DST.

Suicide Attempt

A suicide attempt was defined as "A situation in which a person has performed an actually or seemingly life-threatening behavior with the intent of jeopardizing his life, or to give the appearance of such an intent, but which has not resulted in death" (Beck, Davis, Frederick et al., 1972)

The SIS

The SIS consists of 15 items, contributing with 0–2 points each, the maximum

score being 30. The first eight items measure the objective circumstances of the suicide attempt and this information can be obtained either from the patient or from significant others. The next seven items measure the patient's own feelings and thoughts regarding the suicide attempt.

Statistics

The statistics program "R" (R Development Core Team, 2007) with additional package "lattice" (Sarkar, 2007) was used for statistical computations and graphics. The statistical tests used for group comparisons have been indicated in the relevant summary tables. Correlation refers to Spearman's ρ, where nothing else is specified.

RESULTS

Demographic characteristics of the patients and statistical details are summarized in Table 1. A significantly greater proportion of the MDD patients had made a previous suicide attempt (here denoted repeater) compared to AD patients (46% versus 18%; $p < 0.006$). The diagnostic subgroups differed significantly in age (48 ± 16 versus 34 ± 13; $p < 0.001$), mandating special attention to this variable as a potential confounder. There were no significant differences between the groups regarding sex-distribution and prevalence of Axis II comorbidity.

Differences in cortisol and SIS are summarized in Table 2. Post-dexamethasone serum cortisol at 3 p.m. differed significantly between diagnostic groups ($p < 0.04$). However, a more rigorous analysis, not reported in detail here, attributed that difference to the confounding influence of age. Graphically, the confounding influence of age is depicted in Figure 1, which shows cortisol values pre DST, post DST at 8 a.m. and 3 p.m. by age group and diagnosis. Note that post-DST cortisol increases with increasing age, and that this pattern appears to be identical for the two diagnostic groups.

TABLE 1. Background Variables for Patients by Diagnostic Group

	Group		Sig.
	MDD	AD	
Number	39	39	
Age, mean (SD)	48 (16)	34 (13)	$p < 0.001$[a]
Sex, n (%)			$p = 0.5$[b]
Male	12 (31%)	16 (41%)	
Female	27 (69%)	23 (59%)	$P = 0.009$[b,c]
Repeated suicide attempts, n (%)			
Repeaters	18 (46%)	7 (18%)	
Non-repeaters	19 (49%)	32 (82%)	
Unknown	2 (5%)	0 (0%)	
Axis II comorbidity, n (%)			$p = 0.7$[b]
Has Axis II diagnosis	17 (44%)	20 (51%)	
No Axis II diagnosis	22 (56%)	19 (49%)	

[a]Student's independent samples T-test; [b]Pearson's Chi-square test; [c]Repeaters vs. non-repeaters, chi-square with 1 d.f.

TABLE 2. **SIS Score and Results of the Dexamethasone Test by Diagnosis. Cortisol Concentration was Measured in nmol/l**

| | Group | | |
	MDD	AD	Sig.
SIS score, mean (SD)	19 (5)	18 (5)	p = 0.7[a]
Cortisol levels, median (quartiles)			
Pre-dexamethasone (3 p.m.)	310 (251–415)	326 (260–383)	$p \approx 1^{a}$
Post-dexamethasone (8 a.m.)	44 (29–98)	40 (30–61)	p = 0.4[a]
Post-dexamethasone (3 p.m.)	92 (42–148)	52 (29–90)	p = 0.04[a]
Cortisol suppression, n (%)			p = 0.06[b]
Suppressors	26 (67%)	34 (87%)	
Non-suppressors	13 (33%)	5 (13%)	

[a]Wilcoxon (independent samples) rank-sum test with continuity correction; [b]Pearson's Chi-square test.

There were no significant differences between the groups regarding pre-dexamethasone cortisol, post-dexamethsone cortsiol at 8 a.m., or SIS score (Table 2).

Correlations Between Suicidal Intent and Cortisol

In the MDD group, we found a significant negative correlation between suicidal intent and post dexamethasone cortisol vaules at 8 a.m. and 3 p.m. By contrast, a non-significant, slightly positive correlation was found in the AD group. Correlations are summarized in Table 3. There was no significant correlation between SIS score and age (Correlation coefficient = 0.08; p = 0.51). A great deal of the patients had Axis II comorbidity. Taking this fact into account, we carried out an additional group subdivision, in order to make the groups as homogenous as possible. This
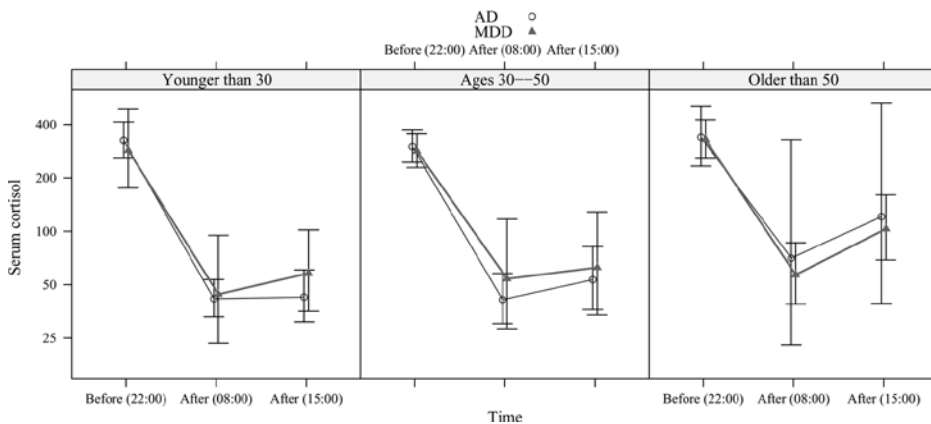
FIGURE 1. *Cortisol at different times by age and diagnosis.*

TABLE 3. **Correlation (Spearman's rho, r_s) Between SIS and Cortisol**

	MDD		**AD**	
	r_s	**sig.**	**r_s**	**sig.**
Cortisol value				
Pre-dexamethasone (3 p.m.)	−0.28	$p = 0.09$	0.14	$p = 0.4$
Post-dexamethasone (8 a.m.)	−0.47	$p = 0.003$	0.18	$p = 0.3$
Post-dexamethasone (3 p.m.)	−0.43	$p = 0.006$	0.18	$p = 0.3$

resulted in four groups; MDD patients without Axis II comorbidity (N = 22), MDD patients with Axis II comorbidity (N = 17), AD patients without Axis II comorbidity (N = 19), and AD patients with Axis II comorbidity (N = 20). Group characteristics are given in Table 4. The negative correlation between SIS score and serum cortisol (measured at 3 p.m. and 8 a.m.) remained significant in the MDD group without Axis II comorbidity. The relationship between post DST cortisol at 8 a.m. and 3 p.m. and SIS-scores is depicted for each diagnostic subgroup in Figures 2 and 3.

DISCUSSION

The main finding in this study was that there was a strong negative correlation

TABLE 4. **Demographic Variables and Cortisol Values for by Diagnosis and Axis II Comorbidity**

	MIDD		**AD**		
	Axis II	**No Axis II**	**Axis II**	**No Axis II**	**Sig.**
Number	17	22	20	19	
Age, mean (SD)	49 (18)	47 (15)	34 (15)	35 (10)	$p = 0.003^a$
Sex, n (%)					$p = 0.4^b$
Male	4 (24%)	8 (36%)	10 (50%)	6 (32%)	
Female	13 (76%)	14 (64%)	10 (50%)	13 (68%)	
Repeated suicide attempts, n (%)					$p = 0.01^{b,c}$
Repeaters	9 (53%)	9 (41%)	5 (25%)	2 (11%)	
Non-repeaters	6 (35%)	13 (59%)	15 (75%)	17 (89%)	
Unknown	2 (12%)	0 (0%)	0 (0%)	0 (0%)	
SIS score, mean (SD)	19 (6)	19 (5)	19 (7)	18 (3)	$p = 0.8^a$
Cortisol levels, median (quartiles)					
Pre-dexamethasone (3 p.m.)	290 (250–361)	357 (260–500)	370 (261–387)	306 (261–353)	$p = 0.2^a$
Post-dexamethasone (8 a.m.)	50 (30–80)	43 (25–104)	44 (30–71)	35 (30–51)	$p = 0.5^a$
Post-dexamethasone (3 p.m.)	80 (47–143)	94 (42–153)	66 (30–100)	36 (27–77)	$p = 0.5^a$
Cortisol suppression, n (%)					$p = 0.5^a$
Suppressors	11 (65%)	15 (68%)	16 (80%)	18 (95%)	
Non-suppressors	6 (35%)	7 (32%)	4 (20%)	1 (5%)	

[a]Kruskal-Wallis rank sumtest; [b]Pearson's chi-squared; [c]Repeaters vs. non-repeaters, chi-square with 3 d.f.
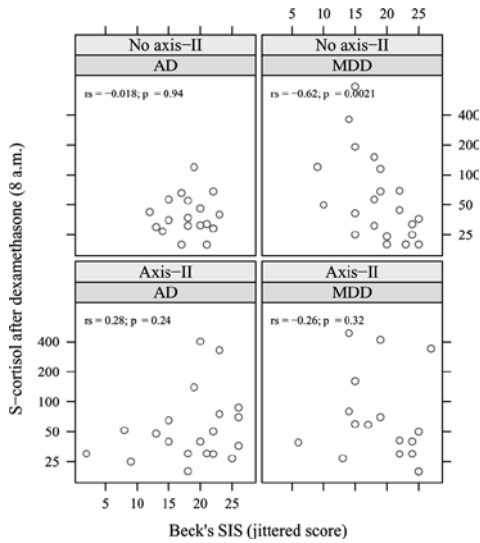
FIGURE 2. *Suicidal intent vs. serum cortisol by diagnosis.*

between suicidal intent and postdexamethsone cortisol in suicide attempters with MDD. Secondary findings, worthy of contemplation, were that MDD
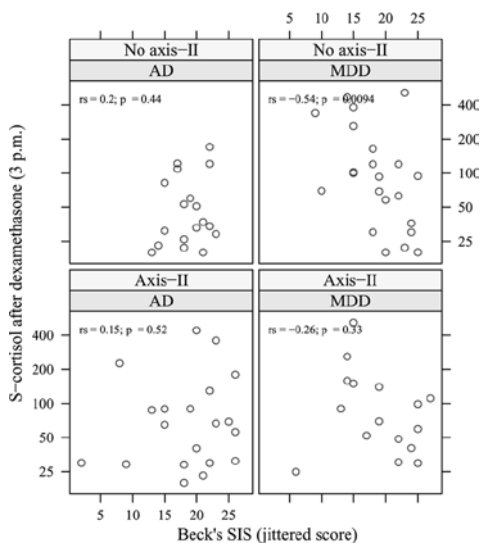
FIGURE 3. *Suicidal intent vs. serum cortisol by diagnosis.*

patients were more often repeaters, and that the groups did not differ in suicidal intent.

HPA-Axis Characteristics and Psychiatric Diagnosis

The MDD patients were significantly older than the AD patients. This is in line with a previous study by Snyder et al. (Snyder, Strain, & Wolf, 1990). Older age has been associated with higher mean cortisol levels after a DST in healthy individuals, as well as in psychiatric patients, as reviewed by Seeman and Robbins (1994). Further investigations of the relationship between age and cortisol levels showed that the between-group differences seen in post DST cortisol were likely to be attributable to the confounding factor of age. There is a large body of evidence that MDD is the psychiatric diagnosis that is most strongly associated with nonsuppression of cortisol after a DST (Plotsky, Owens, & Nemeroff, 1998; Varghese & Brown, 2001). Even though the present study was largely concordant with these findings, age proved to have a greater influence on HPA axis hyperactivity than diagnosis in our sample.

One can only speculate why we did not fully replicate the results of previous studies. A plausible explanation could be the relatively small number of patients in our sample. In addition, our findings highlights the importance of taking possible age differences into account when conducting studies related to HPA axis function.

Suicidal Intent and Psychiatric Diagnosis

There was no difference in degree of suicidal intent between the groups. This is in line with a study by Portzky, Audenaert, and van Heeringen (2005). These findings suggest that although patients with AD may suffer from a less severe illness than MDD patients, they have as high intent to die when attempting suicide. Also taking

into consideration the rapidly evolving suicidal process in AD patients (Polyakova, Knobler, Ambrumova et al., 1998), these findings should bring about careful assessment of suicidal ideation in patients with AD, in view of suicide prevention for this group.

HPA-Axis and Suicidal Intent

We found a significant negative correlation between post-dexamethasone serum cortisol and suicidal intent among the MDD-patients. When taking into account Axis II comorbidity, this correlation remained significant in MDD patients without Axis II comorbidity. Hence, the MDD patients with the highest suicidal intent tended to more often have a normal cortisol response to a DST than the patients with lower suicidal intent. These findings are to some extent concordant with the previous reports (Pfennig, Kunzel, Kern et al., 2005; Secunda, Cross, Koslow et al., 1986) in uncovering an inverse association between suicidality and cortisol. However, the overall design of our study differed from the ones just mentioned. The sample in our study consisted of suicide attempters only. We used the DST for HPA-axis assessment and the SIS in order to capture the degree of suicidality. Pfennig, Kunzel, Kern et al. (2005) studied depressed patients with or without suicidal behavior, and used both an unstructured interview and suicidality items from the Hamilton Depression Rating Scale, in order to determine suicidal behavior and ideation. Furthermore, they used the combined dexamethasone suppression/corticotrophin-releasing hormone (CRH) stimulation test in order to study the HPA-axis. They reported an assocation between suicidal behavior and a lower HPA-axis response in the Dex/CRH test.

Secunda, Cross, Koslow et al. (1986) investigated depressed patients with or without a history of suicide attempt, and employed the DST. They found that suicide attempters had lower pre- and post-DST cortisol levels than nonattempters, though only pre-DST evening cortisol differences reached significance. To our knowledge, no previous studies have applied the same design as our study, in order to investigate the relationship between suicidality and the stress system. The comparability of our findings is therefore limited, and this is an obvious weakness when trying to put our results into context.

In search for explanations to the inverse relationship between SIS and cortisol in the MDD-group, we note that it has been reported that chronic and non-chronic courses of MDD could be differentiated on a neuroendocrinological basis. Watson, Gallagher, Del-Estal et al. (2002) compared patients diagnosed with chronic MDD to healthy controls, and found no differences in post-dexamethasone cortisol concentrations. In another study (Szadoczky, Fazekas, Rihmer et al., 1994), DST-nonsuppression was less often reported in patients with chronic MDD, than for patients with a non-chronic course of MDD. Ehnvall, Sjögren, Zachrisson et al. (2004) reported that pauciepisodic patients with MDD had a more hyperactive HPA-axis than multiepsodic patients with the same diagnosis. Furthermore, they found no differences in HPA-axis activity between multiepisodic MDD-patients and healthy controls. Hence, it appears that HPA-axis function may be more normal in chronic MDD patients. The underlying mechanisms behind this phenomenon are yet to be untangled. It has, however, been discussed that a prolonged depressive illness leads to an altered set-point in the HPA axis feedback system, resulting in a shift from a hyperactive state to a "normal-like" state (Ehnvall, Sjögren, Zachrisson et al., 2004). It is plausible to assume that the duration of the depressive symptoms would influence the degree of suicidal

intent. Bearing this in mind, one could speculate that the negative correlation found between suicidal intent and cortisol among the MDD-patients in our study, reflects a tendency toward a higher suicidal intent and a more normal HPA-axis function among patients with a chronic course of their disease. However, we could not test this hypothesis, since no information on the number of previous depressive episodes had been recorded in our sample.

MDD patients with Axis II comorbidity showed the same trend in correlations as the MDD patients without Axis II. However, the correlations were weaker in the former group, and did not attain significance. This may reflect the more complex pathological processes involved in MDD with Axis II comorbidity, which might uncouple the neuroendocrinological aspects of the disease from the symptomatic aspects. Simply stated: MDD is a disease with a clear biological component, and Axis II comorbidity masks that. It may also be that SIS scores are not directly comparable between patients who have had a history of impulsiveness, or years of experience in inflicting self-harm, as many Axis II patients undoubtedly would have.

As opposed to the MDD patients, we found a non-significant, slightly positive correlation between suicidal intent and post-dexamethasone cortisol among the patients diagnosed with AD. To our knowledge, no previous studies have investigated the relationship between the HPA-axis activity and suicidality in this patient group. As mentioned earlier in the text, the suicidal process in patients suffering from AD tends to be rapid and impulsive with little prior psychopathology (Portzky, Audenaert, & van Heeringen, 2005). It is therefore reasonable that their biological reaction corresponds to that of healthy individuals, which is partly supported by our findings.

To summarize, this is the first study to report an inverse relationship between rated suicidal intent and post DST cortisol levels in MDD suicide attempters. In search for an explanation, there is some evidence that patients with chronic MDD have a more normal HPA axis, whereas patients with fewer depressive episodes have a more deranged HPA axis. Bearing this in mind, our findings might reflect an association between chronicity of illness, high suicidal intent, and a "worn-out" HPA axis. There is a trend toward the opposite relationship (increasing suicidal intent with increasing cortisol) among patients with AD. Hence, our findings suggest that MDD is biologically distinct from AD with regard to how it relates to suicidality. This may be attributed to pathophysiological processes, or different time-courses of the respective illness. In addition, patientens with AD had the same degree of suicidal intent as MDD patients, suggesting that a suicide attempt made by an AD patient should be taken seriously and dealt with accordingly.

AUTHOR NOTE

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Paper III: Attempted suicide, adversities, recovery and genotype

Life-Time Adversities, Reported Thirteen Years After a Suicide Attempt: Relationship to Recovery, 5HTTLPR Genotype, and Past and Present Morbidity

Fredrik J. Vang, Mats Lindström, Charlotta Sunnqvist, Jessica Bah-Rösman, Aki Johanson, and Lil Träskman-Bendz

In this study, we investigated how adversities related to past and present morbidity, and genotype. Forty-two, suicide attempters and 22 matched control patients were followed-up after 13 years. Life-time adversities were explored in an interview, and the patients were reassessed psychiatrically. The serotonin-transporter-linked promotor region (5-HTTLPR) was typed. More adversities were reported by suicide attempters than controls, and by still-ill than recovered suicide attempters. Adversities reported at follow-up were related to psychiatric morbidity at follow-up, but not to morbidity 13 years earlier. The 5-HTTLPR, genotype was associated with reported adversities, but not chances of recovery. Adversities potentially affected chronic morbidity. 5-HTTLPR genotype did not affect long-term recovery.

INTRODUCTION

Impact of Adversities

Recent life-events probably act to precipitate suicides, although the exact impact of a particular type of event can be anticipated to vary between contexts, cultures and the sexes (e.g., Beautrais, Joyce, & Mulder, 1997; Chen, Chan, Wong et al., 2006; Heikkinen, Isometsa, Aro et al., 1995; Kolves, Varnik, Schneider et al., 2006). Some adversities are not atomic events that happen at distinct points in time, but rather a series of happenings that stretch over a period of months or years (e.g., childhood neglect, family turmoil, or chronic illness). Such adversities have also been associated with suicidal behavior (e.g., Blaauw, Arensman, Kraaij et al., 2002; de Wilde, Keinhorst, Diekstra et al., 1992).

Heritability of Suicidal Behavior

Suicidal behavior has been consistently shown to run in families, although many mechanisms of such transmission can be imagined (recently discussed by Brent &

Melhem, 2008). Even though sample sizes have been small, twin studies support a genetic explanation (recently reviewed by Voracek & Loibl, 2007). Studies of genetics relating to the serotonergic system have yielded inconsistent results (recently reviewed by Bondy, Buettner, & Zill, 2006, and Currier & Mann, 2008).

5-HTTLPR Genotype and Suicidal Behavior

The 5-HTTLPR genotype has been shown to affect vulnerability to adversities, particularly with regards to depression (e.g., Caspi, Sugden, Moffitt et al., 2003; Cervilla, Molina, Rivera et al., 2007). The results have not always been consistent, however, and noteworthy negative findings have been presented by Surtees, Wainwright, Willis-Owen et al. (2006) and Willis-Owen, Turri, Munafo et al. (2005).

A recent meta analysis found a small, but significant, association between suicidal behaviour and the 5-HTTLPR genotype (Li & He, 2007). Even though the core findings have centered around depression, the 5-HTTLPR genotype may also affect suicidal behavior in patients primarily suffering from other disorders, like schizophrenia (Bayle, Leroy, Gourion et al., 2003).

Neves, Silveira, Romano-Silva et al. (2008) found that the 5-HTTLPR genotype did not lead to more suicide attempters being present in a sample of patients with bipolar disorder, but it did lead to a greater number and more serious suicide attempts among them.

The 5-HTTLPR genotype has also been associated with pathology of personality in ill or vulnerable populations (e.g., Lyons-Ruth, Holmes, Sasvari-Szekely et al., 2007; Steiger, Richardson, Joober et al., 2007). Some studies have even associated this genotype with differences in temperament and personality in a healthy population (e.g., Gonda, Fountoulakis, Juhasz et al., 2008). If such links exist, it would

be reasonable to consider the effect of this genotype across a range of diagnoses.

Purpose

Life-time adversities have been associated with suicide, and the psychiatrist relies greatly on patient-provided histories, derived from interviews. Therefore we studied the relationship between reports of adversities, elicited during an interview over a decade after a suicide attempt, with past and present morbidity. Since vulnerability to stressors may affect the long-term consequences of adversities, we also took into account the effect of the 5-HTTLPR genotype.

METHOD

The study was approved by the Lund University Medical Ethics Committee, and written consent was given by all participants.

Participants

In total, 42 suicide attempters and 22 matched controls (psychiatric patients without a history of suicide attempts) participated in a long-term follow-up. Relevant characteristics are summarized in Table 1. All 64 patients had been hospitalized at the same psychiatric hospital between 1986 and 1992. That particular episode of hospitalization was taken to be the index time-point. Suicide attempters had been hospitalized at index because of a suicide attempt, were treated at a research department, and were part of a cohort that has been followed since. Controls had been hospitalized at index for other psychiatric reasons, and had no history of suicide attempts.

Matching. There were 22 matched pairs. Suitable control candidates were identified among 270 reviewed hospital records. Seventy-one candidates had to be contacted to obtain the 22 controls. Controls matched a corresponding suicide attempter

TABLE 1. **Background Variables**

Variable	Controls	Suicide attempters	
		All	**Matched subset**
N	22	42	22
Age at follow-up[††], Mean (SD)	50 (8.5)	51 (10)	49 (8.8)
CPRS at index, Median (IQR)		20 (14–24)	22 (18–27)
CPRS at follow-up[†], Median (IQR)	9 (5–22)	5.5 (3–16)	5.5 (3.1–10)
Sex[‡], n (%)			
Male	9 (41%)	21 (50%)	9 (41%)
Female	13 (59%)	21 (50%)	13 (59%)
Recovered at follow-up[‡], n (%)			
Recovered	7 (32%)	23 (55%)	12 (55%)
Still ill	15 (68%)	19 (45%)	10 (45%)
Repeated suicides, n (%)			
Single		16 (38%)	7 (32%)
Repeated		26 (62%)	15 (68%)
Primary Axis I diagnosis, n at index (and at follow-up)			
Major depressive disorder	8 (3)	14 (7)	8 (4)
Dysthymic disorder	4 (1)	9 (3)	4 (0)
Depressive disorder NOS	2 (0)	3 (0)	2 (0)
Adjustment disorder	4 (0)	8 (1)	4 (1)
Alcohol abuse or dependence[‡]	1 (1)	4 (4)	1 (2)
Psychosis	2 (1)	2 (1)	2 (1)
Bipolar disorder	0 (2)	0 (0)	0 (0)
Generalized Anxiety Disorder	0 (2)	0 (2)	0 (1)
Obsessive compulsive disorder	1 (2)	2 (0)	1 (0)
Axis II disorder at follow-up[‡], n (%)	4 (18%)	10 (24%)	7 (32%)

Note. Background variables of controls, all suicide attempters, and matched suicide attempters (the 22 of 42, who had been matched to controls by age, sex and diagnosis). No significant differences between all suicide attempters and controls, or matched suicide attempters and controls, found, using ([†]) the Wilcoxon two-sample test, ([††]) Students's t-test and ([‡]) χ^2-test.

by year of treatment, primary diagnosis at index, age and sex, and had been treated at the same hospital, but had not attempted suicide. We are aware of no selection bias in how the 22 matched suicide attempters ended up selected from the complete pool of 42 suicide attempters.

Dropouts Among Suicide Attempters. The 42 suicide attempters that participated in the follow-up were a subset of 102 suicide attempters who had been studied at index. Of the 102 patients who had attempted suicide at index, 43 chose not to participate in the follow-up and 17 had died. The causes of death were: natural causes ($n = 5$); confirmed suicide ($n = 11$); suspected suicide ($n = 1$). The reasons for not participating were: unknown (n = 20); feeling well, not wanting to talk about the past ($n = 8$); not feeling well, afraid of deteriorating ($n = 2$); other reasons not directly related to psychiatric health ($n = 13$).

No significant difference was found between participants, those who declined, and dead patients with regard to: gender distribution, CPRS-score at index, primary Axis I diagnosis at index, presence of Axis II diagnosis at index. There was a small difference in age that was approaching significance ($P = 0.08$). The mean (and SD) age at index were: 45 (18) for dead patients; 35 (11) for patients who refrained from participating; and 38 (10) for participants.

Follow-Up Interview

Patients were contacted 10 to 17 years (on average 13 years) after index, to participate in the follow-up. At follow-up, the patients were given a psychiatric re-assessment, and interviewed about negative life events.

Diagnosis. Each patient was assessed by one (of three available) experienced psychiatrists, and a resident in psychiatry, who interviewed the patients, and set a DSM-IV (American Psychiatric Association, 1994) diagnosis by consensus. The three experienced psychiatrists available to the project (author L. T.-B., along with G. R. and A. N. in acknowledgements) never diagnosed their own patients. A series of training sessions were organized before the study, including both residents and the three experienced psychiatrists, to establish inter-rater agreement, both with regard to setting the diagnosis and using rating scales. (Agreement was not quantified.) The Structured Clinical Interview for DSM-IV, Axis II disorders (First, Gibbon, Spitzer et al., 1997) was used to set Axis II diagnoses.

Definition of Recovery. When coding patients as being *still-ill* or *recovered,* we classified patients as recovered if they (a) neither qualified for an axis I nor an axis II disorder at follow-up, or (b) only qualified for a diagnosis of repeated unipolar depressions, but were in full remission.

Residual Morbidity. Psychiatric symptoms were quantified using the Comprehensive Psvchopathological Rating Scale (CPRS; see Asberg, Montgomery, Perris et al., 1978), which had also been used to evaluate the suicide attempters (but not controls) at index. The CPRS score used here is the sum of all items, including self-reported as well as rater-observed variables.

Life-Events Interview: Procedure. At follow-up, the patients were asked about their lives, from birth to the time of the follow-up, by means of a semi-structured interview. The interview was divided chronologically into four sections, always administered in the same order: the period of life between index and follow-up; ages 0–12; ages 13–19; and ages 20 to index. The interview covered a wide range of areas, including negative life events and adversities (inspired by existing scales, e.g., Holmes & Rahe, 1967; Sarason, Johnson, & Siegel et al., 1978), living conditions, suicide attempts and psychiatric morbidity. The interviewer filled in a response sheet during the interview, where most responses were recorded as dichotomous ("yes"/"no") or qualified dichotomous choices (e.g., "no"/"yes, alcohol"/"yes, drugs"/"yes, both" in response to the question of substance abuse). If the patient reported an event, he or she was asked to expand, and additional details from the interview were liberally noted on a sheet of paper, but are not considered here. In this way, the interviewing psychiatrist could clarify ambiguities and correct misunderstandings, in the manner done during a clinical interview, and verify that a reported adversity really qualified as such.

Life Events Interview: Variable Selection and Coding. While the full interview amounted

to 110 specific questions, only a subset of these are considered here. Only adversities reported to have happened before index were considered. Sixteen topics were selected from the full interview as potential risk indicators for suicide. While some of these topics had been explored for all four age categories (e.g., hospitalization) others only applied to selected age categories (e.g., foster-home placement applied to ages 0–12 and 13–19). Gender specific events (e.g., abortions) were not considered, and neither were events that for other reasons clearly only applied to a subset of patients (e.g., divorce only applies to people who are married in the first place). Variables with more than 5% missing values, or no variability (i.e., everyone anwering "yes" or everyone answering "no"), were

also not considered. The variables were, when necessary, recoded and dichotomized, so that a "yes" always reflects the presence of a stressful life event. In the cases when there was uncertainty (e.g., "maybe sexually abused age 0–12"), "no" was selected rather than a missing value.

An overview of adversities considered, and their distribution in the complete material, is shown in Table 2.

5-HTTLPR Polymorphism

Genotyping was done as described in Bah, Lindstrom, Westberg et al. (2008). Patients were characterized as SS, LL or SL based on whether they carried the short allele, long allele or both, respectivley.

TABLE 2. **Overview of Adversities**

	Ages 0–12		Ages 13–19		Age 20 to index	
	Suic./Cntl. "Yes":"No"	OR[†]	Suic./Cntl. "Yes":"No"	OR[†]	Suic./Cntl. "Yes":"No"	OR[†]
Bullied	13:29/7:15	0.81	10:32/4:18	1.1		
Disease	34:8/19:3	0.57	26:16/15: 7	0.67	32:9/18:4	0.67
Psychiatric contact	7:35/0:22	4.3	5:37/0:22	2.9		
Few or no friends	24:18/10:12	1.4	19:23/10:12	0.86		
Foster home	5:37/3:19	0.62	4:38/1:21	1.1		
Hospitalization	20:22/4:18	3.1*	10:32/5:17	0.86	18:23/8:14	1.2
Interpersonal difficulties	23:19/10:12	1.3	22:20/4:17	3.6*	29:12/7:15	4.2*
Neglected	25:17/4:18	5.0*	22:20/5:17	3.0*		
Relocation	20:22/7:15	1.6	21:21/11:11	0.88	34:7/16:6	1.5
Separation or loss	21:21/7:15	1.8	15:27/8:14	0.83	25:16/8:14	2.3
Sexual abuse	7:35/0:22	4.3	5:37/1:21	1.4		
Tried alcohol or drugs	4:38/1:21	1.1				
Criminality			5:37/1:21	1.4	5:36/1:21	1.4
Drug abuse			7:35/1:21	2.0	12:29/6:16	0.91
Psychological problems			21:21/4:18	3.4*		
Financial difficulties					18:23/8:14	1.2

Note. Overview of life events across different ages, considered in the analysis. Counts of "yes" and "no" responses ("yes":"no") for all suicide attempters (Suic.) and all controls (Cntl.). All adversities allegedly happened before index, but were reported at follow-up.
([†]) Odds ratios (OR) based on all 64 participants.
(*)Significant χ^2-test ($P < 0.05$), not adjusting for multiple comparisons.

Statistics

The statistical software *R* (R Development Core Team, 2008) was used for the analysis. Documenatation and further references covering the methods used can be found on the software's web-site (http://www.r-project.org). Add-on packages *MASS* (Venables & Ripley, 2002), *epitools* (Aragon, 2008), *car* (Bates, Firth, Friendly et al., 2008), and *lattice* (Sarkar, 2008) were additionally used.

Odds ratios presented were calculated using the method of normal approximation

with small sample adjustment. Pearson's χ^2-test was used, applying Yate's continuity correction where applicable. When explicitly stated, adjustments were made for multiple comparisons, controlling for false discovery rate. Spearman's rank-order correlation, r_s is exclusively used for correlation, and agreement between binary categories measured with Cohen's κ.

Total Burden of Adversities.   The total burden of adversities was calculated as the ratio of that patients total number of "yes" responses to his/her total number of "no"
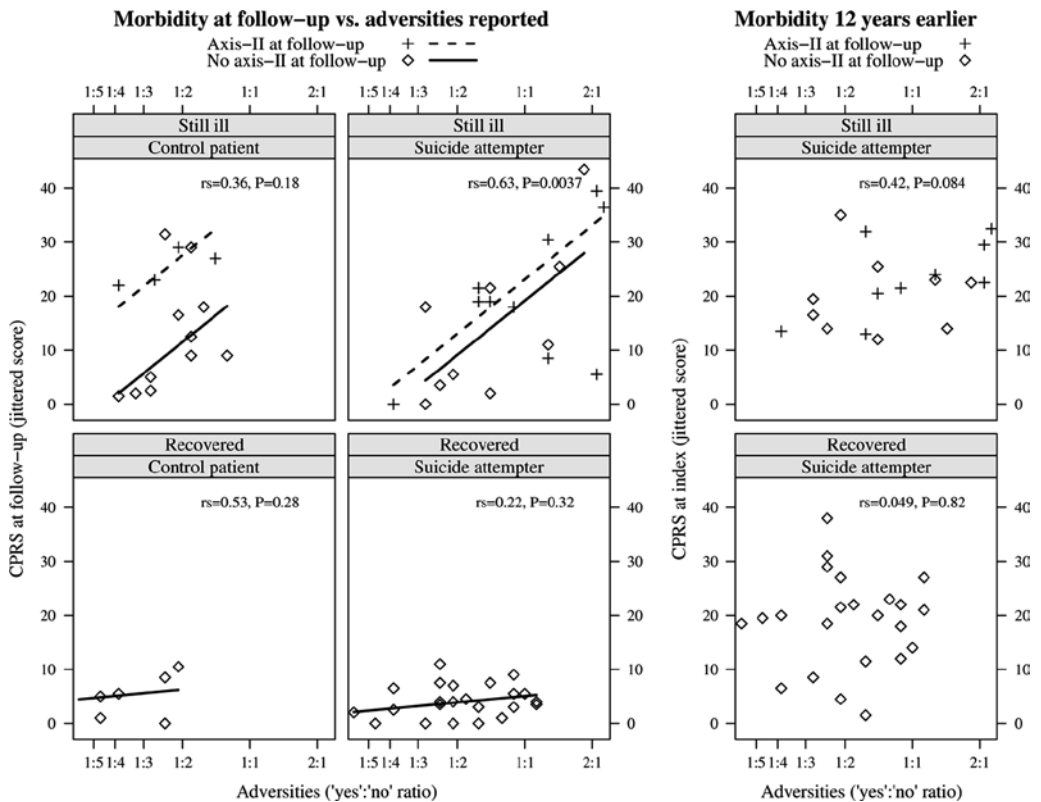
FIGURE 1.   *Past and present morbidity versus adversities. Morbidity (measured with CPRS) at follow-up (left) and index (right) versus adversities. (Adversities are measured as the ratio of "yes, experienced it" to "no, did not experience it" responses when asked about the adversities listed in Table 2, during the follow-up interview. All adversities happened before index, but were reported at follow-up.) Lines show regression model. There is a convincing relationship between adversities and morbidity at follow-up amongst the still ill. However, adversities are not associated with morbidity at the time of the suicide attempt (possibly with the exception of the most chronically ill—see text).*

responses, when asked about whether he/she had experienced the adversities listed in Table 2. Rank-based tests (Wilcoxon's one and two sample tests), medians and quartiles were preferred, for interpretability. (The ranks would be approximately the same whether one uses the number of adversities, the proportion of "yes" responses to questions, or the proportion of "yeses" to "nos," with missing values being the culprit of any slight discrepancies. Using "yesses" to "nos," allows taking the logarithm and interpreting as log-odds in the usual ways, when using mean-based methods.)

Linear Models. Linear models were used to test whether the number of adversities reportedly experienced prior to the suicide attempt was affected by genotype. The logarithm of burden of adversities (i.e., logarithm of "yes":"no" ratio) was taken as the independent variable. Recovery state was known to be important, and was included in the model a priori along with

the intercept. The effect of genotype and its interaction with recovery status were tested sequentially, using the *F*-test. Finding that a six parameter model was needed, it was parametrized using polynomial contrasts for genotype, and sum contrasts for recovery status within each genotype.

A descriptive robust linear model was added to Figure 1, calculated using M-estimators (function *rlm* from package *MASS*), predicting CPRS-score from total burden of adversities, recovery, suicide/control group, and axis II morbidity.

RESULTS

Total Burden of Adversities in Suicide Attempters Versus Matched Controls

The 22 suicide attempters reported a higher burden of adversities than the 22 controls (matched by age, diagnosis, and time of treatment; Wilcoxon's one samples test,

TABLE 3. Life Events Associated with Attempted Suicide

Life event	Suic./Cntl. "Yes":"No"	χ²-test		OR (95% CI)[‡]
		P	**Corr.[†] P**	
Ages 0–12				
Neglected	17:5/4:18	0.00021	0.0071*	10 (3.2–53)
Sexual abuse	6:16/0:22	0.02	0.14	7.8 (0.93–340)
Ages 13–19				
Psychiatric contact	5:17/0:22	0.049	0.23	6.1 (0.73–270)
Interpersonal difficulties	12:10/4:17	0.027	0.15	3.7 (1.2–17)
Neglected	14:8/5:17	0.014	0.13	4.4 (1.5–19)
Psychological problems	14:8/4:18	0.005	0.085	5.6 (1.8–27)
Age 20 to attempt				
Interpersonal difficulties	15:6/7:15	0.015	0.13	4.0 (1.4–17)

Note. "Yes" and "No" responses for suicide attempters (Suic.) and controls (Cntl.). All 34 life-events before index were tested, but only life-events where the χ²-test was significant ($P < 0.05$) are shown in the table.
([†]) The corrected *P* value (Corr. *P*) controls for 34 multiple comparisons.
([‡]) 95% CI not adjusted for multiple comparisons.
(*) Corrected *P*-value significant at $P < 0.05$.

$V = 26$, $n = 22$, $p = 0.002$). The median (and IQR) of the "yes" to "no" ratio was 0.42 (0.27–0.53) for controls, and 0.74 (0.56–1.23) for suicide attempters.

Specific Adversities in Suicide Attempters versus Matched Controls

Since the total number of life events differed between cases and controls, we explored which events were overrepresented in our sample of suicide attempters. *Neglect* ages 0–12 was significantly more often reported by suicide attempters (than by control patients of the same age, sex, diagnosis, and year of hospitalization), even when correcting for multiple comparisons (see Table 3, middle columns).

Markers of Having a High Burden of Adversities

Some types of adversities may be over-represented in suicide attempters, because they identify persons with a high total burden of adversities, which in turn is associated with suicidal behavior. These are shown in Table 4.

Adversities in Relation to Past and Present CPRS Score

Adversities in relation to morbidity is shown in Figure 1.

The rank-order correlation between the total burden of adversities and CPRS at follow-up for all suicide attempters was 0.55

TABLE 4. Adversities that Suggest a High Total Burden of a Adversities

	Question	κ
Items predictive of a suicide attempter reporting more adversities than "normal" (i.e., "Yes":"No" ratio >50% percentile)		
Most predictive item	Interpersonal, Ages 0–12	0.71
2nd-most predictive	Neglected, Ages 0–12	0.70
3rd-most predictive	Neglected, Ages 13–19	0.47
4th-most predictive	Few or no friends, Ages 0–12	0.46
5th-most predictive	Hospitalization, Ages 0–12	0.39
Median κ (all questions)		0.19
Items predictive of a suicide attempter reporting exceptionally many adversities (i.e., "Yes":"No" ratio >90% percentile)		
Most predictive item	Sexual abuse, Ages 13–19	0.77
2nd-most predictive	Bullied, Ages 13–19	0.45
3rd-most predictive	Sexual abuse, Ages 0–12	0.42
4th-most predictive	Foster home, Ages 13–19	0.38
5th-most predictive	Bullied, Ages 0–12	0.33
Median κ (all questions)		0.13

Note. Some particular adversities are associated with high or extremes exposure to adversities in general, affecting the interpretation of our results, and what it means to have a high burden of life-time adversities. The table shows the top-five predictive questions that are indicative of a suicide attempter reporting greater than normal of adversities (above the 50% percentile) or exceptionally high number of adversities (above the 90% percentile). κ measures the agreement between the item (e.g., bullied, "yes" or "no") and the number of adversities (e.g., >50% percentile, "yes" or "no").

($n = 42$, $P < 0.001$). However, the same correlation between adversities and CPRS at index was only 0.29 ($n = 41$, $P = 0.07$). Moreover, this trend was largely due to the suicide attempters with a persisting axis II disorder at follow-up (see legend in Figure 1), who suffered particularly stable, chronic illness. (All but one of them also had an axis II diagnosis at index, and all but one also had an axis I diagnosis at follow-up.) The rank-order correlation between adversities and CPRS at index was 0.65 ($n = 9$, $P = 0.06$) for suicide attempters with an axis II diagnosis at follow-up. For all other suicide attempters (i.e., recovered and still-ill, but without an axis II disorder) the rank-order correlation between the number of adversities and CPRS at index was only 0.11 ($n = 32$, $P = 0.55$).

Adversities in Relation to Recovery and Repetition in Suicide Attempters

Suicide attempters who had recovered or were in remission, reported a lower burden of adversities ($W_{23,19} = 130.5$, $P = 0.03$) than those who were still ill. The median ratio of "yes" to "no" responses (and IQR) was 0.48 (0.42–0.84) for patients who recovered or were in remission, and 0.70 (0.55–1.35) for still-ill patients. No particular adversities were significantly associated with recovery after adjusting for multiple comparisons. There was no significant difference in the burden of adversities reported by suicide attempters with and without repeated suicide attempts ($W_{26,16} = 203$, $P = 0.9$).

TABLE 5. **Genotype and Adversities Preceeding Suicide Attempt**

Model	df	RSS	F-test Comparison	F	P
A. Tests of whether genotype affects adversities reported (alone or in interaction with recovery status)					
1. Recovery $+c$	36	9.90	Known a priori		
2. Genotype $+$Recovery $+c$	38	12.96	Model 1 vs. 2	3.74	0.03*
3. Genotype $\times$ Recovery $+$Genotype $+$Recovery $+c$	40	14.08	Model 2 vs. 3	3.85	0.03*

Coefficient	T-test t	df	P
B. Tests of estimated coefficients (variable levels).			
Recovery (sum contrasts)			
In LL group, recov. $\neq$ still-ill?	-0.43	36	0.7
In SL group, recov. $\neq$ still-ill?	-3.96	36	0.0003*
In SS group, recov. $\neq$ still-ill?	-0.08	36	0.9
Genotype (polynomial contrasts)			
LL$<$SL$<$SS, linear trend?	-2.82	36	0.007*
LL$<$SL$<$SS, quadratic trend?	-1.40	36	0.2
Intercept (c) not shown (assumed non-zero)			

Note. Fewer adversities would be expected to preceed mental illness amonst patients at high risk (SS genotype) than those at low risk (LL genotype). Results using linear models confirm a linear trend, with more adversitites reported before the initial suicide attempt for each additional long allele. The higher number of adversities that we know are reported by recovered than still-ill suicide attempters, is only detectable in the SL-group. (See also Figure 2A for a graphical representation.)
(*) Significant at $P < 0.05$.
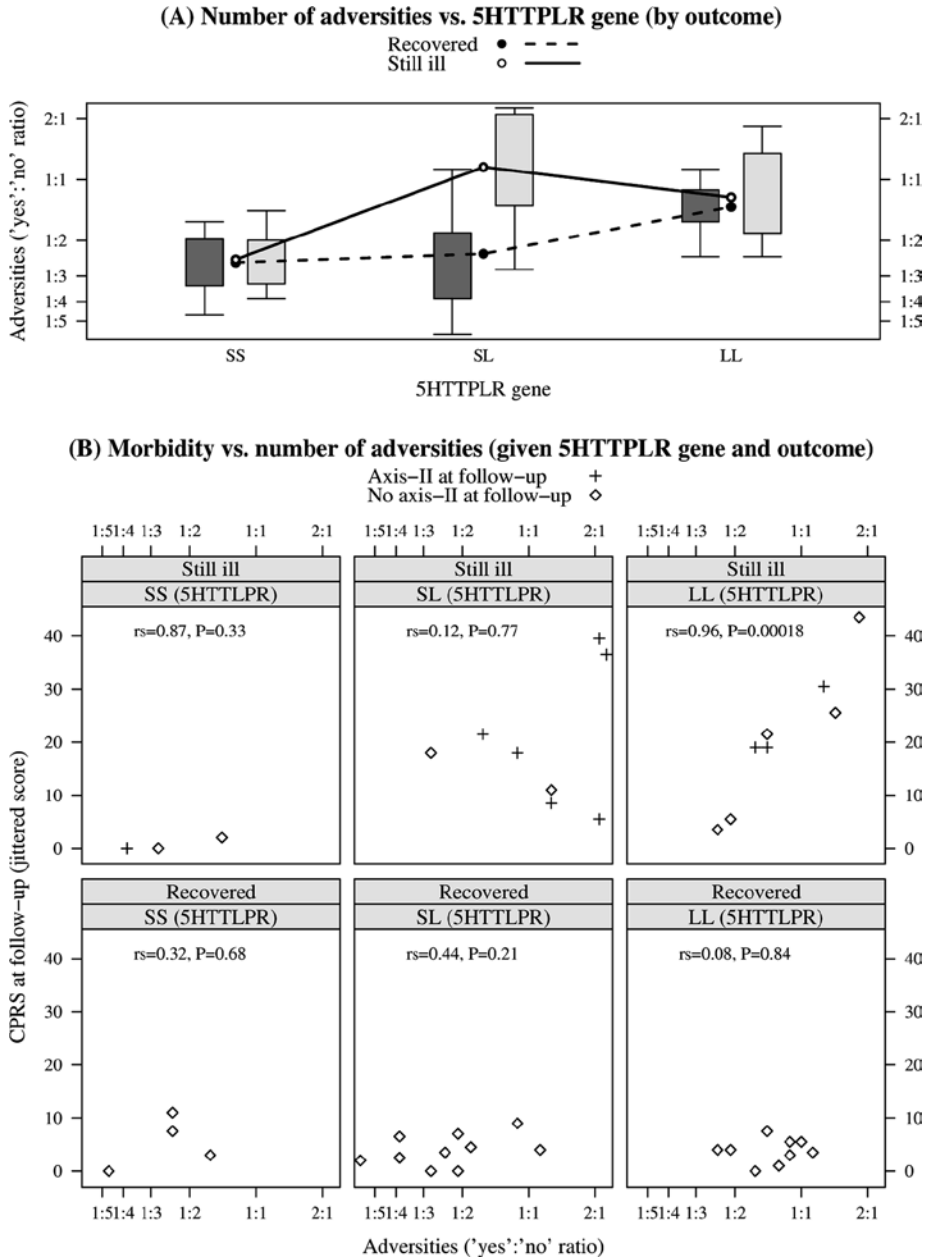
FIGURE 2. *Genes and morbidity at follow-up. (A) The burden of adversities reported by suicide attempters with different geno-
types, for those who recovered at follow-up and those who were still ill (see also Table 5.) More reports of adversities
by the LL genotype is consistent with a protective effect* before *the initial suicide attempt. (B) The relationship
between adversities and morbidity in still-ill and recovered suicide attempters with different genotypes. If the LL
genotype had been "protective", we would have expected proportionately more recovered patients, and a more shallow
slope of the CPRS-versus-adversities line (neither of which is the case).*

Effects of Adversities and 5-HTTLPR Genotype in Suicide Attempters

There was a difference in the total burden of adversities reported by suicide attempters with different genotypes: LL patients reported most, SL reported an intermediate amount, and SS reported fewest adversities (see Table 5 and Figure 2A). SL patients who had recovered by follow-up, reported significantly fewer adversities than SL patients who were still ill. In LL patients, there was instead a significant correlation between adversities and morbidity among those who were still ill (see Figure 2B). There was no significant difference in overall recovery rate between suicide attempters with LL, SL, and SS genotypes ($\chi^2 = 0.04$, $df = 2$, $P = 0.98$); 9 of 17 LL-genotype, 10 of 18 SL-genotypes, and 4 of 7 SS-genotype suicide attempters recovered.

DISCUSSION

Impact of Particular Types of Life Events

Exploratory analyses suggested that suicide attempters report more childhood neglect than patients with the same age, sex, and diagnosis. This material does not, however, support the conclusion that childhood neglect is especially likely to lead to suicidal behavior, independently of other adversities. On the contrary, it seems to be the best indicator of being exposed to many adversities of all kinds.

A qualitatively slightly different picture is painted of suicide attempters with many adversities, and those with extremely many adversities. Suicide attempters with many adversities are picked out by questions about neglect, interpersonal difficulties and few friends (i.e., unsatisfying relations to others). Suicide attempters with extremely plentiful reports of adversity are picked out by questions about bullying

and sexual abuse (i.e., aggressive, perhaps violent, transgressions).

These findings are in line with other published findings, where serious efforts are made to adjust for other explanatory variables (e.g., Enns, Cox, Afifi et al., 2006). The role of physical and sexual abuse remains illusive. They are often reported to have a special relationship to suicidal and self-injurious behavior (e.g., Brodsky, Mann, Stanley et al., 2008; Soderberg, Kullgren, & Salander, 2004; Ystgaard, Hestetun, Loebl et al., 2004), but are often found to be related to multiple risk factors and an overall burden of adversities, and do not always remain very important in studies that adjust for this (e.g., Enns, Cox, Afifi et al., 2006; Klonsky & Mover, 2008).

Dose-Response Effect of Adversities on Morbidity

There is a considerable dose-response relationship between adversities and current morbidity among still-ill suicide attempters. (Of course, among recovered patients, there is virtually no morbidity to report, and hence no dose-response relationship to measure. Instead we note that recovered patients reported fewer adversities than those who did not recover.) Other findings to the same effect have been documented, although most authors choose to focus on outcome and not residual morbidity (e.g., Dube, Anda, Felittil et al., 2001).

Effect of Adversities on past versus Present Morbidity. Interestingly, suicide attempters' reports of adversities had no significant correlation with psychiatric morbidity directly after the suicide attempt 13 years earlier, even though we only considered adversities reported to have occured before the suicide attempt. Two interpretations are plausible. One possibility is that people's memory of life events are affected by

factors such as mood and morbidity at the time of the interview. Another interpretation is that the patient was enduring extraordinary circumstances at the time of the suicide attempt, and morbidity at that point reflected state-like (episodic/brief) morbidity, not trait-like (chronic/durable) morbidity. If so, the later interview and psychiatric assessment, that came at a calmer stage, would have captured the impact of adversities on chronic trait-like morbidity. (In evidence of the latter, is the observation that the only convincing trend towards a correlation between morbidity at index and adversities was observed in the group of suicide attempters with the most chronic course.)

Effects of Genotype

The fact that LL patients reported the most, and SS patients the least adversities is consistent with the notion of the long allele being protective of developing mental illness. Since all participants were enrolled by virtue of having developed a psychiatric disorder, we would expect the LL patients to have suffered most adversities, before finally succumbing and becoming eligible for inclusion in this study.

The main surprise is that the 5-HTTLPR LL-genotype does not confer an advantage. It neither improves chances of recovery relative to the SL or SS groups, nor moderates the effect of adversities on morbidity among the still-ill. Being "protected," one would have hypothesized that each additional adversity would only have a small effect on morbidity (i.e., yielding a more shallow slope of the regression line, or a smaller correlation, in the LL-genotype patients). However the opposite seems to be the case (Figure 1). We cautiously speculate that the LL-genotype may not be as beneficial in established chronic illness, as in preventing the never-ill from becoming ill.

Some other findings suggest that the 5-HTTLPR genotype may not alter a psychiatric illness, but may help cope. Cusin, Serreti, Lattuadat et al. (2001) looked at recurring mood disorders, and did not find the time between onsets (a measure of severity of chronic illness) to be affected by 5-HTTLPR genotype. Jacobs, Kenis, Peeters et al. (2006) found that though the SS genotype led to a greater sensitivity to negative events in a community setting, it was largely explained by neuroticism—hence, they recommend focusing on how the 5-HTTLPR genotype relates to our stable trait-like ways of responding and coping with minor adversities. Indeed, Willis-Owen, Turri, Munafo et al. (2005) looked at depression in the extreme tails of neuroticism, and found no effect of 5-HTTLPR genotype on depression despite a very large sample, acknowledging one explanation to be that the effect of the genotype might not be as important at the extremes.

A promising line of inquiry has been delineated by studies of 5-HTTLPR and anxiety (Gonda, Rihmer, Juhasy et al., 2007), increased amygdala activation (reviewed in Munafo, Brown, & Hariri, 2008), and neuroendocrine response to stress (Gotlib, Joormann, Minor et al., 2008). These are all suggestive of the 5-HTTLPR genotype somehow asserting its influence through the fear–anxiety–stress systems of the brain. Following quite a different line of reasoning, it has been suggested that the 5-HTTLPR genotype may affect suicidal behavior by a quite different mechanism: through affecting the ability to learn, and aquire adequate decision-making strategies (Jollant, Buresi, Guillaume et al., 2007).

Merits and Limitations

Our study has several merits, several of which have been purchased at the expense of sample size. Information about life

events is derived from an extensive interview, similar in form to a clinical interview. We believe this gives the study ecological validity, when carrying our results into clinical practice.

The patients have also been followed up after 13 years, which is a comparatively long time. Moreover, the suicide attempters had been treated at a research department. They had been carefully diagnosed, and the some of the same methods could be consistently applied to reassess them. Another interesting feature is that we are studying adversities reported a long time after the initial hospitalization. This allows us to ask about events from childhood, right up to the time of the suicide attempt, but we do so at a quite different time from the event that led to patients being enrolled. This is of particular interest, since it remains unclear how memory of life events is affected by concurrent emotional and psychiatric states.

Validity of Reports. The fact that the number of adversities correlates better with present CPRS than with past CPRS, possibly because of memory bias, raises questions about the validity of the information obtained in a clinical interview.

Some researchers would advocate the use of a more structured scale to elicit a measure of negative life events, and this might indeed improve historical accuracy. Various scales have been designed to aid in uncovering life events and adversities—for example, the Life Experiences Survey (Sarason, Johnson, & Siegel, 1978), or the Social Readjustment Rating Scale (Holmes & Rahe, 1967). However, even when using a structured questionnaire, recall is imperfect, and may be biased by concurrent morbidity (Southwick, Morgan, Nicolaou et al., 1997; see also discussion in Dohrenwend, 2006). Furthermore, if the scales are used in the form of self-assessment questionnaires, the comparability to the clinical interview is lost.

Limitations. The cost of doing such a long-term follow-up is a rather low sample size and rather high drop-out rate. Many speculations can be made about how the drop-out rate may have affected the results. The major concerns pertain to the loss of patients who either feel well and do not wish to talk about past troubles, or who feel particularly unwell, and the loss of patients who later successfully committed suicide. Although we are not aware of any systematic bias in the matching, only a subset of suicide attempters were matched to controls. Other limitations include the risk of memory bias when reporting life events (discussed above), and multiple testing.

CONCLUSION

We conclude three things: (1) More adversities are reported by suicide attempters than by matched contols, and by still-ill suicide attempters than those who recovered. Certain specific types of adversities were reported more often in a clinically representative sample of suicide attempters, but also indicate a high total burden of adversities. (2) There was a dose-response effect of adversities on morbidity, which was either (a) dominated by memory bias, or (b) limited to explaining *chronic* morbidity (but not the morbidity more generally seen in the turmoil surrounding a suicide attempt). (3) In this sample, the 5-HTTLPR genotype may have affected the likelihood of developing a mental illness in response to life time adversities, but not the chances of recovery, and the "protective" LL genotype did not reduce the impact of adversities on morbidity in still-ill patients.

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Paper IV: Basal ganglia, temperament and serotonin transporter

Brief report

Size of basal ganglia in suicide attempters, and its association with temperament and serotonin transporter density

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ABSTRACT

Magnetic resonance imaging was used to compare subcortical volumes of seven suicide attempters with those of six healthy controls. Suicide attempters had 10% smaller right caudate nucleus and 19% bilaterally smaller globus pallidus. In suicide attempters, volumes of the globus pallidus correlated negatively with previously reported measures of *solidity* (non-impulsive temperament) and serotonin transporter binding potential.

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1. Introduction

Subcortical brain structure has been examined in illnesses in which suicide is a common occurrence, but only rarely in suicidal behaviour specifically. A recent post-mortem study found depression, genotype (homozygote short 5HTTLPR allele), and suicide to be independently associated with over-all enlargement of the thalamus (Young et al., 2008). Based on magnetic resonance imaging (MRI), depressed women who had attempted suicide at least once were found to have larger right amygdalae than non-suicidal depressed women (Monkul et al., 2007). Periventricular white matter hyper-intensities (Pompili et al., 2008) and grey matter hyperintensities in the basal ganglia (Ahearn et al., 2001) may be associated with attempted suicide.

We previously found a positive correlation between serotonin transporter (5HTT) binding potential and the temperament dimension *solidity*, and a negative correlation between dopamine transporter (DAT) binding potential and the dimension *validity* in suicide attempters (Ryding et al., 2006). The finding was most pronounced in the basal ganglia.

The purpose of this study was to measure subcortical structures in suicide attempters and controls, and to determine if any apparent

differences were related to our previous findings of a temperament–monoamine transporter link.

2. Methods

2.1. Subjects

The patients were recruited from the internal medicine emergency ward, after a suicide attempt that involved a high intent to die. They had not been exposed to antidepressant or antpsychotic medicines for at least 6 months prior to that. The patients were diagnosed by a consultant psychiatrist with several years' experience in DSM diagnostics, supported by DSM-IV based checklists, repeated clinical interviews, observation, and staff reports at a psychiatric in-patient ward.

The healthy controls were matched by age and sex, and were screened to exclude past and present psychiatric disease, and psychotropic medication. One control had a first degree relative with a history indicative of psychiatric illness, and one control knew of a first degree relative who had attempted suicide. Patient character-istics are listed in Supplementary Table 1. Further details can be found in Ryding et al. (2006).

2.2. Measures of temperament

The subjects had completed the Marke–Nyman Temperament (MNT) scale. Low solidity is characterized by changing friendships, opinions and interests; seeking excitement; informal style; and impulsiveness. Low *validity* is characterized by being easily stressed

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Table 1
Volumes of subcortical structures.

Structure	Mean volume, %ICV ($\pm$S.D.)		t-test			
	Suicide att. ($n=7$)	Control ($n=6$)	d	t	d.f.	Sig.
Amygdala						
Left	0.10 ($\pm$0.015)	0.099 ($\pm$0.009)	0.1	0.20	10.0	0.85
Right	0.094 ($\pm$0.0019)	0.096 ($\pm$0.009)	−0.1	−0.18	8.67	0.86
Hippocampus						
Left	0.24 ($\pm$0.021)	0.23 ($\pm$0.026)	0.3	0.50	9.62	0.63
Right	0.25 ($\pm$0.026)	0.24 ($\pm$0.033)	0.2	0.32	9.34	0.75
Globus pallidus						
Left	0.099 ($\pm$0.011)	0.12 ($\pm$0.013)	−1.6	−2.88	10.0	0.016 *
Right	0.094 ($\pm$0.017)	0.12 ($\pm$0.010)	−1.8	−3.25	9.9	0.0088 *
Caudate						
Left	0.22 ($\pm$0.034)	0.23 ($\pm$0.010)	−0.5	−0.93	7.29	0.38
Right	0.20 ($\pm$0.014)	0.22 ($\pm$0.015)	−1.6	−2.83	10.2	0.017 *
Accumbens						
Left	0.032 ($\pm$0.0055)	0.030 ($\pm$0.0063)	0.4	0.68	10.1	0.51
Right	0.034 ($\pm$0.0063)	0.028 ($\pm$0.0035)	1.1	2.03	9.6	0.071
Putamen						
Left	0.30 ($\pm$0.048)	0.31 ($\pm$0.037)	−0.2	−0.36	10.9	0.73
Right	0.30 ($\pm$0.044)	0.31 ($\pm$0.037)	−0.2	−0.41	11.0	0.69

Volumes of subcortical structures of interest as a percentage of intracranial volume. Effect size measured with Cohen's d and differences tested using Welch's t-test. (*) $P<0.05$.

or tired; dislike of disruptions, quick decisions and change; and anxiety about the future.

2.3. Measures of serotonin and dopamine transporter binding

Monoamine transporter binding potential was measured using 123-I-beta-CIT, a cocaine analogue that binds to 5HTT and DAT. By administering a selective serotonin reuptake inhibitor between repeated scans, it is possible to study 5HTT and DAT binding separately. Lower binding potentials can be due to lower transporter affinity for 123-I-beta-CIT; fewer transporters; or competitive binding inhibition by higher concentrations of the relevant neurotransmitter. The whole-brain binding potentials reported previously (Ryding et al., 2006) were used.

2.4. Volumetric analysis and statistics

The 13 most recently acquired MR scans from the 24 participants in the original study (Ryding et al., 2006), remained stored in the hospital's radiological database and were reanalyzed. These images came from seven suicide attempters and six of their corresponding matched controls, and are not to our knowledge a biased selection. Images were acquired using MPRAGE on a 1.5 T Siemens Magnetom scanner with $0.9 \times 0.9 \times 1.3$ mm resolution. *FreeSurfer* was used to automatically segment the scans, and estimate the volume of anatomical structures (Fischl et al., 2002). *R* (http://www.r-project.org) was used for statistics.

3. Results

Volumes of the subcortical structures are shown in Table 1. Solidity and validity did not jointly explain any significant bilateral size differences in the caudate nucleus ($F(2,9)=2.58$, $P=0.1$), putamen ($F(2,9)=1.81, P=0.2$), or nucleus accumbens ($F(2,9)=1.79, P=0.2$), but did explain size differences in the globus pallidus ($F(2,9)=5.30$, $P=0.03$), using linear models.

There was a significant rank-order correlation between solidity and globus pallidus volume for suicide attemtpers ($r_s=-0.8$, $P=0.03$), but not controls ($r_s=-0.3$, $P=0.5$). There was also a significant rank-order correlation between 5HTT binding and globus pallidus volume for suicide attempters ($r_s=-0.9$, $P=0.008$), but not controls ($r_s=-0.6$, $P=0.2$). This is shown graphically in Supplementary Fig. 1.

4. Discussion

In a recent review, Konarski et al. (2008) found 25 studies (of 140 included) that looked at the basal ganglia, and concluded that some evidence existed for bigger striatum in bipolar disorder, and smaller striatum in depression. We note, however, that the four patients diagnosed with major depressive disorder in our study had marginally larger globus pallidus, and marginally smaller caudate volumes on average than the three suicide attempters with other diagnoses.

The most direct interpretation is that the globus pallidus somehow contributes to abnormal temperament. This is made plausible by the anatomical links between parts of the globus pallidus and the reward circuits of the ventral striatum (recently reviewed in Haber and Knutson, 2010).

It may seem counterintuitive that suicide attempters had smaller globus pallidus on average, and yet a negative correlation emerged between globus pallidus size and *solidity* (low solidity being associated with impulsiveness). However, not all suicides are impulsive, although some may be. Also, in our sample, there is almost no variability in suicidality as every patient had made a suicide attempt with a high intent to die. It follows that individual differences in solidity would not account for variability in suicidality. Instead, we believe they account for differences in underlying pathology.

Limitations include the small sample size, suggesting cautious interpretation. The heterogeneity of the sample with respect to age and sex may also inflate anatomical variability. Segmentation with *FreeSurfer* is ideally done with one or more 3 T scans. Our findings need to be confirmed using larger samples, and using clinical controls.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2010.05.007.

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SUPPLEMENTARY TABLE 1: Patient characteristics.

| Code | Age | Sex | Diagnosis†† | | Method of suic. attempt | Repeated attempts |
			Axis I	Axis II		
A†	36	Female	AD	No	Medicines	No
B	36	Female	AD	No	Medicines	No
C	30	Male	MDD	No	Medicines	No
D	35	Male	MDD	Mixed	Hanging	Yes
E	54	Male	None	NOS	Medicines	No
F	23	Male	MDD	No	Hanging	No
G	53	Male	MDD‡	No	Gas‡‡ + Hang.	No

Characteristics of the 7 patients. Controls were matched by age and sex. (†) Matched control for patient A not available. (††) Primary diagnosis of adjustment disorder (AD) or major depressive disorder (MDD), and axis II disorder, according to DSM-IV. (‡) Also alcohol abuse (‡‡) Carbon monoxide poisoning.

SUPPLEMENTARY FIGURE 1:

Globus pallidus volume versus solidity and 5HTT binding potential.
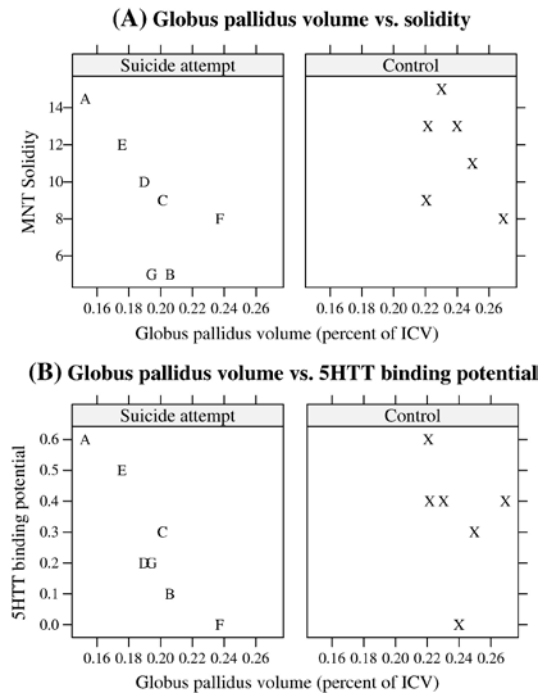
Total corrected volume of globus pallidus ($\frac{volume}{ICV} \times 100\%$) in relation to (A) solidity (non-impulsive temperament) and (B) 5HTT binding potential. Letters in panels indicate patient (A -- G, referenced in Supplementary Table 1) or healthy control (X).

Paper V: Dichotic listening and suicidality

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Appendix I: How to measure adversities

There are some important differences between commonly used methods of eliciting information about adversities. This appendix briefly reviews some common alternatives, to illustrate key conceptual differences.

Types of questions and questionnaires

Many self-report questionnaires come in the shape of check-lists, where the respondent has to mark which events have occurred during some given time-frame. For instance, the Social Readjustment Rating Scale (SRRS, [251]) asks about 43 stressful events, such as: marital separation; death of a spouse; jail term; loss of job; retirement; foreclosure of a large loan; or trouble with in-laws.

Certain life-events are more potent stressors than others. To address this, some scales assign a different number of points to different events. For instance, the SRRS assigns 100 life-change units to the death of a spouse, 40 for pregnancy, and 12 for surviving Christmas.

Note that the SRRS scale attempts to measure how much the respondent's life has been shook up in the bygone year, "regardless of desirability"[251], with potentially positive events like Christmas or marriage contributing to the score along with unequivocally negative experiences like sexual difficulties and imprisonment. Nonetheless, there is a bias towards asking about negative events in the SRRS, evident on immediate inspection. Other questionnaire designs may include or exclude events with a particular valency (e.g. choosing to focus only on negative life events, like the LTE-Q, [252]) or may try to assign scores in a way that reflects their negative impact.

The same event may be experienced as traumatic by one person, but not another, and even as positive by a third (e.g. a divorce can be traumatic to one but an outright relief to another). Hence some questionnaires or interviews also ask about the subjective impact of the event on the participant. For instance the Life Event Questionnaire

(LEQ, [253]) lists 79 events, allowing additional blank lines for "other recent experiences...[with] impact on your life", and asks the respondent to rate the effect of each experience as "good" or "bad", and its impact on a $0 - 3$ point Likert scale (from "no effect" to "great effect").

Some instruments go as far as to dispense with the checklist of events, and only ask about perceived stress. The Perceived Stress Scale (PSS, [254]) asks whether the participant during the last month has has felt: upset over unexpected events; loss of control; nervous and stressed; unable to handle personal problems; things are going his way; unable to cope with things that needed doing; unable to control irritations; not on top of things; angered over things being beyond control; difficulties are piling up and becoming un-overcomable. Unfortunately, perceived stress (in this sense) can just as well be the reaction to stress, as the symptoms of psychiatric illness (e.g. depression), or an aspect of personality.

Other instruments focus on more limited aspects of adverse events. The Childhood Trauma Questionnaire (CTQ) assesses childhood trauma retrospectively in terms of physical abuse (e.g. asking about having been hit hard enough to leave bruises; hit with belt or cord), emotional neglect (e.g. feeling loved; family members looking out for each other; family being a source of support), emotional abuse (e.g. being called names or told hurtful things by family members; feeling hated by someone in family or unwanted by parents), physical neglect (e.g. dirty clothes; parents too drunk to take care of family; not enough food), and sexual abuse (e.g. being molested; performing sexual acts under threat). Of the 24 questions, three ask directly whether the participant believe himself/herself to have been sexually, physically or emotionally abused.

Whereas some of the questions in the CTQ probe concrete facts (e.g. ever being hit with a belt or hard enough to be taken to see a doctor), other questions demand subjective judgement. Some questions implicitly require the

respondent to judge excessive or toxic exposure to some stressor. (E.g. everyone has tried being called names by a family member, but was it out of the ordinary, or unusually distressing?). Like the PSS, some questions may reflect personality or psychiatric symptoms in the respondent (e.g. not feeling loved). Such questions may work as they are supposed to in a normative sample, but may be misleading when administered to patients, or people with unusual personalities. At the same time, in our study, some of the strongest associations between suicide attempts and childhood adversities were mediated by questions that largely reflect the patients own over-all assessment (for instance about interpersonal difficulties or neglect).

Interviews

The Life Events and Difficulties Schedule (LEDS, [255]) is one interview based system for assessing stressful life events. A very curious feature of LEDS and some related instruments, is that the interviewer probes for information about the circumstances surrounding each reported adversity, and the resulting narrative can then be presented to a completely different person for scoring. Ultimately, the choice of information presented to the rater becomes as important as the criteria for rating the narratives. A related instrument, the Structured Event Probe and Narrative Method (SEPRATE, [256]) extends this, allowing information to be edited before being presented to raters to allow information to either be taken into account or ignored. (E.g. the raters may be rendered blind to ethnicity, or systematically aware of it.)

Using the narratives elicited during interviews, it is possible to rate aspects like magnitude or fatefulness of adversities. Fateful events (e.g. death of a close relative) cannot be affected by the respondent, but non-fateful events (e.g. loss of job, incarceration) can be [49].

When using the life history calendar (as used by Caspi 2003) events are probed by the interviewer and the informant participates in entering the data onto a calendar-like sheet (which also serves to facilitate recall) [257]. This provides information about when things happened, for how long, and how many times (although the data is often recoded to just reflect the number of events).

Self-report questionnaire or interview?

Self-report questionnaires are very popular in the research literature, probably because they have the advantage of being cheap, allowing large samples. Perhaps their availability for quick scrutiny (a copy of the common instruments can usually be found in someone's office, or on the internet) also helps to explain their wide dissemination. However, evidence suggests serious shortcomings in validity, and in a number of respects questionnaires seem not nearly as good as interviews.

Studies where participants both fill in a check-list and allow themselves to be interviewed, suggest that many questionnaire items are not understood as intended. Perhaps half of the events elicited by life-event check-lists would be discarded as invalid in an interview, and only a third of serious life events reported during an interview would be detected by check-lists [48]. Also, agreement between observers (e.g. two siblings) has been found to be good using interviews and poor using check-lists [49].

Appendix II: SUAS-S

This is the English translatio of SUAS-S published in Nimeus A, Hjalmarsson F, Sunnqvist C, Stanley B, Träskman-Bendz L. (2006) *Evaluation of a modified interview version and of a self-rating version of the Suicide Assessment Scale.* European Psychiatry.

1

0. I can feel both joy and sadness, according to the circumstances.

1. I am mostly positive and cheerful, but sometimes I have periods of despair.

2. I am often depressed, but can have bright periods.

3. I almost always feel depressed and miserable; better moments are rare.

4. My life is totally destroyed by the deepest despair and distress.

2

0. I seldom feel irritable.

1. I feel angry and irritable more than is usual for me.

2. I often feel angry and irritable without any real reason.

3. I almost always feel irritated and sometimes really angry without any real reason.

4. I always feel very angry and irritable without any immediate cause.

3

0. I am able to do my everyday duties without unusually getting tired.

1. I manage my daily activities, but often get tired.

2. Sometimes I have difficulty doing my everyday duties, and often I must take a break and rest.

3. I am almost always very tired and worn out and often I cannot do my everyday duties.

4. Due to extreme tiredness, I am totally unable to do anything.

4

0. I am not sensitive to being told off or criticized.

1. Occasionally, I might feel rejected or take things personally when someone tells me off or criticizes me.

2. I feel rejected or humiliated more easily than usual when I am told off or criticized.

3. I very often feel deeply hurt and offended when I am told off or criticized.

4. People around me deliberately try to hurt me by telling me off and criticizing me.

5

0. I keep in close and regular contact with my friends and family.

1. I keep good contact with my friends and family but less often than before.

2. Currently, I keep contact with only a few of my closest friends and family members.

3. I only talk with one or two friends from time to time.

4. I cannot stand contact with other people and I live totally on my own.

6

0. I am able to cope with emotional problems adequately.

1. Occasionally I have difficulties in handling emotional problems.

2. I have a limited ability to see how I can solve my emotional problems.

3. I seldom or never see how to overcome my emotional problems.

4. I am unable even to think about emotional problems.

7

0. I trust myself and my decisions.

1. I am sometimes uncertain about my ability to cope with my problems.

2. I am more often at the mercy of fate or those around me than to my own ability to cope with things.

3. I very seldom make my own decisions; on the contrary, I am at the mercy of fate or those around me.

4. I am totally controlled by faith or my surroundings and do not have any control over my own life.

8

0. I feel relaxed.

1. It is more difficult for me to relax than usual.

2. My whole body is often unpleasantly tense.

3. I am hardly ever relaxed. I feel much muscular tension and other physical discomforts.

4. I am never relaxed but suffer all the time from severe and painful muscular tension.

9

0. I feel calm and without worries.

1. I get worried more easily than usual.

2. I easily get worried and anxious and exaggerate my worries. However, calm moments predominate.

3. I seldom feel calm, but worries and fear about what will happen today and in the future make me anxious.

4. I constantly suffer from severe anxiety and feelings of uneasiness and I am overwhelmed by fear.

10

0. I feel physically healthy.

1. Sometimes I have worries about being physically ill. However, I can easily overcome these concerns.

2. I often think and worry about my physical health. Sometimes other people have to help me by reassuring me.

3. I am fairly convinced that I am physically ill.

4. I am convinced that I have a serious physical illness but people do not believe me. In spite of having mentioned this to other people, nobody cares.

11

0. I satisfy my wishes and needs but only after full consideration of the consequences.

1. Occasionally, I act without considering the consequences.

2. I often have difficulty in stopping acting on impulse. However, the thought of possible consequences might stop me.

3. I nearly always act according to wishes and needs, mostly without thinking of the possible consequences.

4. All I do occur on the spur of the moment and I do not care about the consequences.

12

0. I am very self-confident.

1. Occasionally I lack confidence but am usually able to overcome this.

2. In spite of mostly being confident, I often have a sense of failure or feel uncertain about my abilities.

3. I almost always feel worthless, and I am doubtful that things will change for the better.

4. I am good for nothing and I cannot see anything improving.

13

0. My future looks bright.

1. Occasionally I feel pessimistic about the future.

2. I often feel pessimistic about the future, and rarely have positive thoughts.

3. I always have dark and pessimistic thoughts about my future. I hardly ever have positive thoughts.

4. I feel totally hopeless and despondent and feel that anything negative can happen to me.

14

0. I am interested and involved in things going on around me.

1. Sometimes I find it difficult to be interested in those around me.

2. I often find it very difficult to take an interest in those around me.

3. Most of the time I feel totally indifferent and uninterested even concerning my close friends and family members.

4. I am tormented by my total lack of interest in other people, even those closest to me.

15

0. I only get annoyed or frustrated for a very good reason.

1. Very occasionally, I become irritated or frustrated for minor reasons.

2. I have quite often been annoyed and frustrated for minor reasons.

3. I very often get irritated or frustrated and often without any good reason.

4. I am always annoyed or frustrated without any reason whatsoever.

16

0. I have quite a lot of reasons for living.

1. Sometimes I have negative thoughts about the meaning of life but I am convinced that I will continue to live.

2. Repeatedly I am unsure of my wish to live. However, reasons for living are more predominant.

3. My reasons for continuing to live are few and uncertain, and I feel pessimistic about the future.

4. I see no reason for continuing to live.

17

0. I have no wish to die.

1. I occasionally think about dying but my wish to live is strong.

2. I sometimes think about dying and feel it would be a relief.

3. To me, death means something positive, and my will to live is weak.

4. I long for death and wish I were dead.

18

0. I have no suicidal thoughts.

1. I have occasionally thoughts of suicide.

2. On several occasions I have experienced suicidal thoughts.

3. Very frequently I have thoughts of suicide.

4. I constantly think about suicide.

19

0. I have no suicidal ideation.

1. If I committed suicide, it would be a revenge for old injustices. However, I have better solutions.

2. Supposing I commit suicide it should make a great stir among people.

3. If I committed suicide it would solve serious problems where no better alternatives are available.

4. A suicide means a long-desired relief and rest for both myself and my surroundings.

20

0. I neither think about or plan for suicide.

1. Sometimes I have thoughts of suicide.

2. Sometimes I have thought about different methods of committing suicide, but I have no carefully prepared plans.

3. I have well thought-out plans of killing myself but I have not made any immediate preparations.

4. I am ready to kill myself and I am only waiting for the right opportunity.

Appendix III: SIS and CPRS

The Suicide Intent Scale (SIS) contains 15 items with anchors, each contributing 0 – 2 points. The items are summarized in Table 12. The Comprehensive Psychopathological Rating Scale (CPRS) contains 67 items, summarized in Table 13. They are scored 0 – 3 points, and relatively specific anchors are provided. (E.g. "Less than two or three hours' sleep"; "No appetite. Food is tasteless. Need to force oneself to eat.") Mostly, the anchors have been chosen so that: 0 = symptom entirely absent; 1 = present, but not clinically significant; 2 = clinically significant; 3 = severe, even in the psychiatric setting. Both are interview-beased.

Table 13. Summary of the Comprehensive Psychopathological Rating Scale

CPRS, items 1 – 40 (based on the patient's own report during a clinical interview)

Sadness; Elation; Inner tension; Hostile feelings; Inability to feel; Pessimistic thoughts; Suicidal thoughts; Hypochondriasis; Worrying over trifles; Compulsive thoughts; Phobias; Rituals; Indecision; Lassitude; Fatiguability; Concentration difficulties; Failing memory; Reduced appetite; Reduced sleep; Increased sleep; Reduced sexual interest; Increased sexual interest; Autonomic disturbances; Aches and pains; Muscular tension; Loss of sensation or movement; Derealisation; Depersonalization; Feeling controlled; Disrupted thoughts; Ideas of persecution; Ideas of grandeur; Delusional mood; Ecstatic experiences; Morbid jealousy; Other delusions; Commenting voices; Other auditory hallucinations; Visual hallucinations; Other hallucinations

CPRS, items 41 – 65 (based on the clinician's observations)

Apparent sadness; Elated mood; Hostility; Labile emotional responses; Lack of appropriate emotion; Autonomic disturbances; Sleepiness; Distractability; Withdrawal; Perplexity; Blank spells; Disorientation; Pressure of speech; Reduced speech; Specific speech defects; Flight of ideas; Incoherent speech; Perseveration; Overactivity; Slowness of movement; Agitation; Involuntary movements; Muscular tension; Mannerisms and postures; Hallucinatory behaviour

CPRS, items 66 – 67 (based on the clinician's over-all opinion)

Global rating of illness; Assessment of reliability of rating.

Table 12. Summary of the Suicide Intent Scale

Objective circumstances surrounding the suicide attempt (8 items)

Being alone at the time of the suicide attempt;
choosing a time to avoid intervention;
taking precautions to avoid intervention;
not seeking rescue;
having acted as if death was anticipated (e.g. changing the will);
active preparations (e.g. purchasing equipment needed for suicide);
suicide note;
stating intent to end life to someone before attempt.

Patient's subjective perception of suicide attempt (7 items)

Patient's expectation to die;
patient's perceived lethality of method;
patient's view of whether it was a serious attempt to end life;
if the patient wanted to die;
if the patient considered medical rescue possible;
if the attempt was premeditated (> 3 hours giving three points).

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Swedish summary

Söker man efter bilder om "självmord" eller "suicide" på internet, upptäcker man två populära stereotyper: unga vackra kvinnor som tar sina liv i glamoröst isensatta situationer, eller ansiktslösa okontaktbara personer som tittar hopplöst ned. Bilderna visar vad ordet självmord leder många människors tankar till: "emo", unga kvinnor, uppmärksamhetssökande, nedstämdhet och hopplöshet. Men även om där finns en gnutta sanning i detta, förvränger det verkligheten man ser inom psykiatrin. De flesta som dör av självmord är män, långt ifrån alla är deprimerade, och att söka uppmärksamhet eller iscensätta sig själv är inte de vanligaste motiven. Men, framför allt, upptäcker man snabbt att personer som försöker begå självmord är mycket olika varandra.

Det är mycket svårt att förutse självmordsförsök, och ännu svårare att förutse faktiska självmord. En orsak är just att personer som försöker begå självmord är så olika varandra. En annan viktig orsak är att de flesta människor som mår dåligt psykiskt eller som tänker på självmord faktiskt inte tar sina liv. En tredje orsak är att även om vi kan känna igen vissa högrisk patienter (t.ex. patienter som nyligen gjort ett alvarligt självmordsförsök), är de flesta personer som dör av självmord inte sådana.

Skulle man kunna hitta gemensamma nämnare för människor som faktiskt försöker ta sina liv, skulle man förmodligen också bli bättre på att hitta dem som allra mest behöver hjälp, och kanske till och med välja bättre behandling. Antagligen kommer vi aldrig att hitta en gemensam nämnare för alla som försöker begå självmord. Men vi kan kanske hitta tecken som visar på hög risk inom särskilda patientgrupper, eller hitta grupper av patienter som har en bestämd typ av sårbarhet.

Man skulle kunna ställa frågan: vad skall man fråga en person för att veta om han eller hon är självmordsbenägen? Skall man bara fråga om självmordstankar, -planer, och -handlingar, eller skall man också tänka på hur personen mår (t.ex. nedstämdhet, ilska, hopplöshet, osv)? Denna fråga undersöktes med hjälp av ett frågeformulär som patienterna fick fylla i. Svaret verkade vara att under vissa omständigheter är det nog bäst att bara hålla sig till direkta frågor om självmord.

Man skulle också kunna ställa frågan: vad får vissa människor att gå från tankar till handling, och faktiskt genomföra ett självmordsförsök? Kanske man kan hitta biologiska orsaker till att normala spärrar försvinner. Vissa hjärnskador gör till

exempel att människor blir impulsiva, och handlar utan hänsyn till konsekvenserna. Andra gissningar är att hjärnans förmåga att uppleva belöning, eller hur snabbt man vänjer sig vid skrämmande tankar (som att hoppa framför ett tåg eller skjuta sig själv) kan vara påverkade.

Vi undersökte hormonet kortisol, som produceras när en person stressas kroppsligt eller psykiskt. Detta hormon utsöndras I förhöjda mängder hos många deprimerade, och man menar även at det kan påverka hur hjärnan processerar rädsla. Deprimerade patienter som hade låga värden hade gjort de allvarligaste självmordsförsöken, med störst risk att faktiskt dö.

Serotonin är ett ämne som frisätts av vissa nervceller för att skicka nervsignaler vidare, och tros påverka humör, aggressivitet och impulsivitet. Serotonin transportören samlar upp serotonin som har frisatts, och återför ämnet till nervcellen. Flera framgångsrika läkemedel mot depression och ångest verkar just på serotonin transportören. Tidigare undersökningar hade visat att tillgängligheten av serotonintransportörer i hjärnan var kopplad till personlighetsprofil hos människor som gjort allvarliga självmordsförsök, men inte hos friska kontroller. Därför undersökte vi om dessa två saker (personlighet och serotonintransportörer) även var kopplade till anatomiska förändringar i hjärnan. Vi fann kopplingar till storleken av en struktur, globus pallidus, djupt inne i hjärnan. Även om denna struktur är mäst känd för sin funktion i att styra rörelser, vet vi att den också har andra funktioner. Till exempel finns rapporter om människor som skadat denna del, eller fått den stimulerad med elektroder, och blivit påverkade i humöret – till och med suicidala.

Vi undersökte även om generna som styr hur många serotonin transportörer som bildas påverkade prognosen efter ett självmordsförsök. Även om genetiken verkade påverka insjuknande, verkade det inte påverka långtidsprognosen.

När frontalloberna skadas, blir folk ofta antingen mycket impulsiva eller passiva. De undersökningar som gjorts på människor som försökt begå självmord har ofta tidigare visat förändringar i frontalloberna, som man ännu inte riktigt förstår. Till sist undersökte vi därför hjärnans förmåga att filtrera ljud, och lyssna bara på ena örat, som sätter krav på frontalloberna. Förmågan att filtrera ljud var kopplad till livslust hos personer som försökt ta sina liv.

Figure 22. Images found for "suicide" by Google

We regret that this figure is only available in the printed version of the document, due to more restrictive copyright laws governing electronic publication.

Representative selection of the first thumbnails returned by Google, when searching for suicide. (Representativt utplock av de första miniaturbilder som Google hittar på sökorden "suicide" och "självmord".)