BDNF, impulsiveness and avoidant focused coping in suicide attempters

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LIVIA AMBRUS
DEPARTMENT OF PSYCHIATRY | FACULTY OF MEDICINE | LUND UNIVERSITY

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Livia Ambrus

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Abstract

Brain-derived neurotrophic factor (BDNF) is an important protein for neuroplasticity and neurogenesis. In this thesis the role of BDNF, in suicidal behaviour was investigated with focus on possible risk factors for suicidal behaviour such as avoidant focused coping, dysfuntional personality traits like impulsiveness and hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis.

Paper I: The association between avoidant focused coping and the BDNF Val66Met gene polymorphism in two different cohorts of suicide attempters was investigated. The Met allele of this gene polymorphism was associated with increased use of avoidant focused coping, irrespectively of age and the severity of depressive symptoms.

Paper II: The relationships between BDNF in plasma, clinical symptoms and personality dimensions were studied in recent suicide attempters. BDNF concentrations in plasma were correlated significantly with Solidity but not with symptoms of depression or anxiety.

Paper III: The association between BDNF in plasma and HPA axis activity in recent suicide attempters was investigated. Plasma BDNF concentrations were correlated significantly and negatively with post-dexamethasone cortisol in female but not in male suicide attempters.

Paper IV: The association between avoidant coping strategies, suicide risk measured with the Suicide assessment self-rating scale (SUAS-S) and suicidal ideation was studied in two different cohorts of suicide attempters, and in a cohort of depressed patients without a history of attempted suicide. Regression analyses revealed significant positive correlations between avoidant coping strategies and the total scores of SUAS-S adjusted for age, gender, the severity of depressive symptoms and the co-morbidity with personality disorder in both cohorts of suicide attempters and in depressed patients without a history of attempted suicide. Furthermore, a significant correlation between more severe suicidal ideations and increased use of avoidant focused coping was observed in all three cohorts of patients.

Paper V: The relationship between avoidant focused coping and personality traits in recent suicide attempters and in healthy controls was examined. Avoidant focused coping was correlated significantly with Solidity in suicide attempters. The finding remained significant after controlling for age and gender.

Conclusion: The results indicate that there are associations between BDNF, impulsiveness and HPA axis hyperactivity in suicide attempters. Furthermore, an increased use of avoidant focused coping is suggested as a risk factor for suicidal behaviour in psychatric patients.

Key words Attempted suicide, Braine-derived neurotrophic factor, BDNF, BDNF Val66Met, HPA axis, avoidant focused coping, impulsiveness

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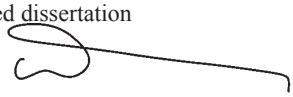
Signature  Date 2016-08-18

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To my loved Andreas and Izabell

Content

Abbreviations

ACTH	Adrenocorticotropic hormone
AD	Adjustment disorder
ANCOVA	Analysis of covariance
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BIS	Barratt Impulsiveness Scale
BMI	Body mass index
BSA	Brief Scale for Anxiety
PD	Personality disorder
COPE	Coping Orientations to Problems Experienced Inventory
CPRS	Comprehensive Psychopathological Rating Scale
CRH	Corticotropin-releasing hormone
CSF	Cerebrospinal fluid
CSQ	Coping Styles Questionnaire
DSM	Diagnostic and Statistical Manual of Mental Disorders
DST	Dexamethasone Suppression Test
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked Immunosorbent Assay
EPQ	Eysenck Personality Questionnaire
HPA	Hypothalamic-pituitary-adrenal
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
MNT	Marke-Nyman Temperament Scale
mRNA	Messenger ribonucleic acid
NEO-FFI	Neuroticism-Extraversion-Openness Five-Factor Inventory
NEO-PI-R	Revised NEO Personality Inventory

PFC	Prefrontal cortex
PTSD	Post-traumatic stress disorder
r_s	Spearman`s Rho correlation´s coefficient
SCID-II	Structured Clinical Interview for DSM-IV-Axis II Disorders
SD	Standard deviation
SNP	Single Nucleotide Polymorphism
SUAS-S	Self-report version of Suicidal Assessment scale
TCI	Temperament and Character Inventory
WHO	World Health Organization

Original papers

This thesis is based on the following publications and manuscripts. The published papers are reprinted with permission of the publishers.

Paper I

Ambrus L, Sunnqvist C, Ekman A, Suchankova P, Träskman-Bendz L, Westrin Å. Associations between avoidant focused coping strategies and polymorphisms in genes coding for brain-derived neurotrophic factor and vascular endothelial growth factor in suicide attempters: a preliminary study. Psychiatry Research, 2014;220:732-3.

Paper II

Ambrus L, Sunnqvist C, Ekman R, Träskman-Bendz L, Westrin Å. Plasma brain-derived neurotrophic factor and psychopathology in attempted suicide. Neuropsychobiology, 2016 Jun 22;73(4):241-248.

Paper III

Ambrus L, Lindqvist D, Träskman-Bendz L, Westrin Å. Hypothalamic-pituitary – adrenal axis hyperactivity is associated with decreased brain-derived neurotrophic factor in female suicide attempters. Nordic Journal of Psychiatry, 2016 May 23:1-7.

Paper IV

Ambrus L, Sunnqvist C, Asp M, Westling S, Westrin Å. Avoidant focused coping and suicide risk in psychiatric patients. Manuscript.

Paper V

Ambrus L, Sunnqvist C, Asp M, Westling S, Westrin Å. Avoidant focused coping and personality dimensions in suicide attempters. Manuscript.

Introduction

Why is suicide research important?

Several lines of evidence point out that suicide is still an issue of paramount importance for researchers. According to data provided by the World Health Organization (WHO), approximately 800 000 people die by suicide every year [1]. In other words, one person completes suicide every 40 seconds somewhere in the world. Moreover, in 2012 suicide was the second leading cause of death globally among 15-29 year olds [1].

High suicide rates are major problems also in Sweden. Approximately 1500 Swedish people complete suicide per year and, similarly to the data presented by WHO, suicide is the second leading cause of death among Swedish younger adults (15-44 years of age) [2]. Another alarming observation that should be considered when studying Swedish suicide rates is that the number of completed suicides has remained approximately the same in recent years [2]. Considering the fact that a significant part of suicide victims has been in contact with health care or mental care before suicide [3-6], the stagnation of suicide rates may indicate that the preventive methods and treatments of persons with high risk of suicide are insufficient.

Another important issue is the strong and often long-lasting negative impact attempted and completed suicides have on family members and friends of the suicidal individual. Furthermore, besides the emotional burden of the near ones, suicide also has socioeconomic consequences affecting the whole community. Specifically, the “direct” costs of suicide including costs of police, ambulance, hospital services and coronial inquiry were estimated at 45-60 million Swedish Kronor (≈ 4.9-6.5 million Euro) according to a report published by the Swedish Rescue Services Agency in 2014 [7]. According to the same report, other costs related to suicide come from the lost productivity by the victims which were estimated at 4.4-9 billion Swedish Kronor (≈ 48-98 million Euro) [7].

Nomenclature for suicidal behaviour used in this thesis

The term suicidal behaviour includes thoughts and plans of suicide, suicide attempts and completed suicide. "Suicidal ideation" refers to suicidal behaviour without action and involves all sorts of suicidal thoughts and plans. Over the years several definitions have been proposed in order to define attempted suicide. In this thesis, a suicide attempt was defined according to Beck and his co-workers as "situations in which a person has performed an actually or seemingly life-threatening behaviour with the intent of jeopardizing his/her life, or to give the appearance of such an intent but which has not resulted in death" [8]. In addition, suicide attempters can be classified according to the number of previous attempts that an individual has made (i.e. suicide repeaters vs non-repeaters). Suicide attempts can also be divided into violent and non-violent types based on the method used. In this thesis, a non-violent suicide attempt was defined as a drug overdose or a single wrist-cut, whereas all other methods (e.g. hanging, use of firearms, or several deep knife cuts) were classified as violent [9]. Finally, suicide is commonly defined as an act of intentionally terminating one's own life [10].

Risk factors for suicidal behaviour

Completed suicide

Several systematic reviews have identified male gender as one of the most robust risk factors for completed suicide [11-18]. Interestingly, this finding has been replicated across diagnostic groups including bipolar disorder [12], schizophrenia [17] and depressive disorder [13]. Furthermore, being male also seems to be a reliable vulnerability factor for completed suicide in non-psychiatric cohorts such as cancer patients [16] or nursing home residents [14].

Another robust risk factor for completed suicide is a history of attempted suicide [17, 19]. In addition, individuals suffering from psychiatric disorders, mainly mood disorders, substance abuse and borderline personality disorder, are at an increased risk for completed suicide [11, 13, 14, 20].

Besides demographic and clinical factors, there are other vulnerability factors for suicide, such as, the experience of stressful/adverse/negative live events [21].

Other possible risk factors for suicide that repeatedly have been identified are impulsivity and aggressiveness [22].

Attempted suicide

As discussed above, individuals with a history of attempted suicide have an increased risk for completed suicide, seemingly irrespectively of clinical diagnosis.

On a group level, there are several well-known risk factors for attempted suicide, including female gender [12, 23]. Another factor that seems to convey an increased risk for attempted suicide is a history of mental illness, including (but not limited to) major depressive disorder (MDD), substance abuse disorders and personality disorders (PD), mainly those belonging to Cluster B [11, 23]. In addition, the experience of adverse life events has been linked to an increased risk for attempted suicide [21]. In light of these findings, it may not be surprising that high levels of anxiety-related traits, associated with low stress-tolerance, have been found to be a candidate risk factor for attempted suicide [24-26]. Specifically, some evidence suggests that suicide attempters are characterised by higher levels of anxiety-related traits (Eysenck Personality Questionnaire (EPQ)-Neuroticism, Temperament and Character Inventory (TCI)-Harm avoidance) compared to healthy controls or psychiatric patients without a history of attempted suicide [24-26]. Furthermore, according to a study comprising 1333 suicide attempters and 589 psychiatric patients without attempted suicide, the association between attempted suicide and anxiety-related personality traits (TCI-Harm avoidance) seems to be independent of clinical diagnoses [25].

Another personality-related risk factor for attempted suicide is impulsiveness [22, 24]. Particularly, it has repeatedly been found that persons who attempt suicide have higher levels of personality traits associated with impulsiveness (EPQ-Impulsiveness, TCI-Novelty seeking) compared to controls [24, 25]. Interestingly, similarly to anxiety-related personality traits, the association between impulsiveness (TCI-Novelty seeking) and attempted suicide seems to be irrespective of Axis I diagnosis [25].

The stress-diathesis model of suicidal behaviour

One of the most prominent theories aiming to explain suicidal behaviour is the stress-diathesis model. This model postulates that suicidal behaviour is the result of an interaction between state-dependent (environmental) stressors and a trait-like vulnerability (diathesis) to suicidal behaviour, independently of psychiatric disorders.

The experience of psychosocial crises has been suggested as a stressor in the model. It is based on the observation that the experience of stressful live events is more common among individuals who complete or attempt suicide, compared to non-suicidal individuals [21, 27]. Other stressors may be ongoing psychiatric disorders. The suffering from a psychiatric illness can indirectly lead to stress via for example the triggering of relationship conflicts.

The diathesis component can be defined as the necessary antecedent condition for the development of a disorder or problem like suicidal behaviour. Several candidate components of the diathesis have been suggested, such as aggression and/or impulsivity, pessimism, hopelessness, deficits in problem-solving or cognitive rigidity [27, 28]. During the last decades, associations between suicidal behavior, neurobiological factors and psychological factors, particularly those related to cognitive functioning have become important areas in suicide research [28-32]. According to results of these works, structural and functional changes in the brain or the impairment of cognitive functioning like impaired decision making have been suggested as the part of the stress-diathesis model of suicidal behaviour [28, 30-32].

Sjöbring`s personality model and attempted suicide

Defining personality and temperament

Personality and temperament are very similar terms and can be defined as characteristic patterns of thoughts, feelings, and behaviours stable over time and across situations. However, there is an important difference between them, such as that temperament often refers to traits reflecting predominantly biological predispositions, while personality traits are influenced by environmental factors.

A general description of Sjöbring`s personality model

Henrik Sjöbring (1879-1956) was a prominent Swedish psychiatrist and researcher who developed a model of personality [33] distinguishing four personality variants labelled Validity, Solidity, Stability and Capacity. Validity is a measure of available and effective energy. High levels of Validity reflect a high level of energy, self-confidence and adaptability, while persons with low scores are anxious and have low energy. Solidity is a measure of organization and integration. Lower scores of Solidity reflect changeability and impulsiveness, while higher scores reflect dependability and rigidity. Stability is a measure of emotional control. Persons with low scores seem to be sociable, warm and naive, while higher scores of Stability reflect a high level of self-control, coolness and sophistication. Finally, Capacity measures intelligence. Persons with low levels of capacity can be described as slow, single-minded and having a low ability to comprehend complicated issues. On the contrary, persons with high levels of such personality variants can be described as open-minded and having the ability to think quickly.

Sjöbring`s and Eysenck`s theory: Is there any relationship?

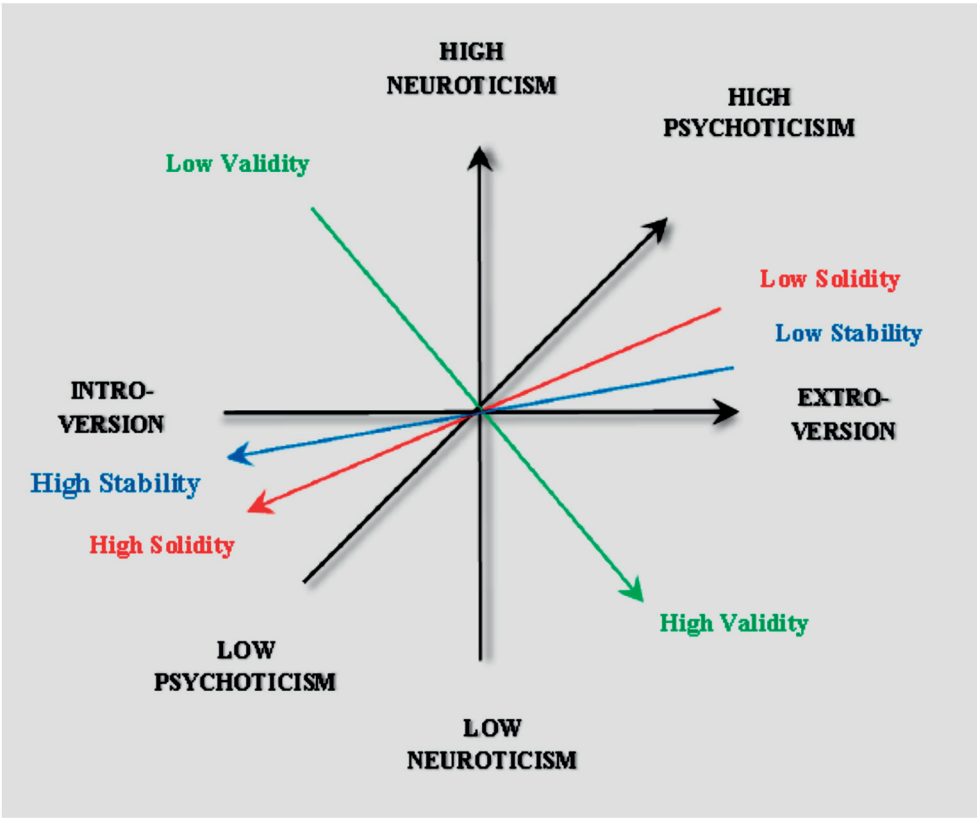
One of the most common personality theories used in clinical research is the theory of the psychologist Hans Eysenck. In his book, Dimensions of personality (1947) [34], he described the two personality dimensions of Extraversion and Neuroticism. Extraversion is characterized by being outgoing, high on positive affect and in need of external stimulation. Neuroticism, according to Eysenck's theory, is based on activation thresholds in the sympathetic nervous system or visceral brain. Persons with low levels of Neuroticism are emotionally stable, calm and collected under pressure. Furthermore, they have high activation thresholds and good emotional control. On the contrary, persons with high levels of Neuroticism have low activation thresholds, and are unable to inhibit or control their emotional reactions under pressor.

The third dimension, Psychoticism, was added to the model in the late 1970s. This dimension is rooted in the characteristics of toughmindedness, non-conformity, inconsideration, recklessness, hostility, anger and impulsiveness. Low levels of Psychoticism reflect conformity and good impulse control, while high levels of this trait mirror toughmindedness, impulsiveness, or non-conformist behavior. Based on these three personality dimensions, Eysenck has developed the PEN-

model (including three personality dimensions Psychoticism, Extraversion and Neuroticism) (Figure 1).

Interestingly, according to some previous studies, the personality traits of Sjöbring and Eysenck may share similarities [35, 36]. Particularly, Stability has been found to be negatively correlated with Eysenck`s Extraversion scale [35, 36]. Validity seems to be associated inversely with Neuroticism and positively with Extraversion [35, 36]. Furthermore, Solidity has been found to correlate negatively to Eysenck`s Extraversion and Psychoticism [35, 36], as well as to the Eysenck Extraversion impulsivity subscale (items associated with impulsiveness extracted from the Extraversion scale) [37]. Therefore, findings from studies using the EPQ can probably be compared to results obtained from the MNT. Figure 1 depicts the potential inter-relationships between Sjöbring`s traits and Eysenck`s PEN-model [35, 36].

Figure 1. Sjöbring`s personality dimensions and Eysenck`s PEN-model



Sjöbring`s personality traits in attempted suicide

As far as we know, there are three previous studies that have investigated the possible association between attempted suicide and Sjöbring`s personality variants. Specifically, Banki and co-workers [38] showed that suicide attempters were characterised by significantly higher levels of Stability and lower levels of Validity compared to healthy controls. Same results were found in the work of Pendse et al [39]. On the contrary, Ryding et al [40] investigated only Solidity and Validity did not observe any significant differences in these subscales between suicide attempters and controls. However, this might have been due to the small sample size of that study (n=12 suicide attempters and n=12 controls) [40].

Is suicidal behaviour heritable?

Several family, twin, and adoption studies have examined whether suicidal behaviour may be heritable [41-43]. Specifically, twin studies have demonstrated a higher concordance rate for completed suicide in monozygotic compared to dizygotic twins [42, 43]. In addition, according to a meta-analysis including 21 family studies, close relatives of suicidal probands have a 5-fold increased risk for engaging in suicidal behaviour (including completed suicide or serious suicide attempt) compared to relatives of controls, independently of psychiatric disorder [43]. Adoption studies have also reported significantly higher rates of completed suicide in the biological relatives of adoptees who died by suicide, compared with adoptive relatives [44].

Indeed, studies investigating only attempted suicide, have suggested that attempted suicide appears to be heritable too [41, 42]. Furthermore, family studies consistently report higher rates of suicide attempt in relatives of suicide attempters compared with relatives of non-attempters [41, 42]. In addition, whole-genome linkage studies have identified several chromosomes linked to attempted suicide including chromosomes 2, 5, 6, 8, 11, X [42].

Avoidant focused coping

Coping in general

Coping is commonly defined as the attempt to manage problems caused by stressful events appraised as threatening, harmful, challenging, or beyond one's personal resources at that time [45]. Over the years, several distinctions have been developed to describe the structure of coping. One of these focuses on the orientation toward or away from stress and distinguishes approach and avoidance coping. Approach coping involves confronting a problem and taking active steps to resolve it [46]. Examples of approach coping include seeking information, obtaining knowledge, planning a strategy and self-control. Avoidance coping is aimed at escaping the threat or related emotions [46]. Examples of avoidance coping include ignoring, psychological or behavioural distancing oneself from the stressor or denial.

Coping with stress is a dynamic process. Regarding the approach-avoidance distinction, it has been suggested that orientations toward stressful events, can vary across time for an given individual, and both types of coping with stress may be present at any particular time [47]. To define which coping strategies are adaptive or effective is not an easy task. Traditionally, approach coping has been thought as the adaptive way to cope with stress, while avoidance coping has been suggested to be less adaptive and associated with dysfunctional personality traits and generally poorer outcomes [48]. Interestingly, Roth and Cohen (1986) have discussed the effectiveness of approach and avoidance coping in terms of benefits and costs [47]. In their work, they have suggested that both types of coping have benefits i.e. could be effective. For example, avoidance coping can reduce stress or anxiety and may be useful when people need time for assimilation of stressful information or for mobilization of efforts to manage the situation [47]. In addition, the use of approach coping strategies can give the possibility to affect the nature of a stressor and chose appropriate action to deal with the stressful situation [47]. Furthermore, the authors have suggested that the use of avoidant coping may be better than approach coping if the stressful situation is uncontrollable, whereas approach is better if there is potential control [47].

Regarding mental disorders, several researchers have aimed to investigate whether there is an association between coping and psychiatric disorder [49-51]. According to these studies, more avoidance focused coping and less approach coping

strategies have been repeatedly linked to major psychiatric disorders like affective disorders or schizophrenia [49-51]. In other words, the results from these works indicate that individuals with those disorders are more likely to use strategies to avoid the stressor or related emotions when they deal with stress.

The assessment of avoidant focused coping

A wide range of scales assessing coping strategies have been developed. The most frequently used coping scale in research is the Coping Orientation of Problem Experience (COPE) Inventory [52] developed by Carver, Scheier and Weintraub in 1989. In this theoretically based instrument, they have suggested three coping strategies reflecting avoidance [53]. The first of these is Behavioural disengagement addressing strategies which reduce one's effort to deal with the stressor or giving up the attempt to attain goals with which the stressor is interfering. The second is Mental disengagement including activities in order to distract the person from thinking about the situation with which the stressor is interfering. Strategies belonging Mental disengagement include using alternative activities like daydreaming or sleeping. The third one is Denial which can be defined as refusing, pretending or acting as if the problem has not happened. Items belonging to these three subscales are presented in Appendix I (page 82).

Besides Carver and co-workers, several authors have performed factor analysis on subscales of the COPE [54]. These studies have repeatedly found that subscales Mental disengagement, Behaviour disengagement and Denial were loaded on the same factor [55]. As all these subscales include coping strategies reflecting avoidance, this factor has been considered as avoidant focused coping.

Avoidant focused coping and suicidal behaviour

A wide range of studies have investigated the relationship between coping strategies, suicidal behaviour including suicidal ideation, attempted and completed suicide or suicide risk measured by psychometric scales [55-70]. However, as this thesis focuses on the relationship between suicidal behaviour and avoidant focused coping, only works studying avoidant focused coping strategies separately will be discussed.

Suicidal ideation

Several cross-sectional studies have been done in order to investigate the association between suicidal ideation and the use of coping strategies including avoidant focused coping, however with convergent results [56-60, 62, 71] (Table 1). In the study by Khazem et al on US military members, more us of maladaptive coping strategies including avoidant focused coping and substance abuse, were found to be significantly correlated with more severe suicidal ideations, independently of other coping strategies, depression and a range of demographic variables [58]. In line with this study [58], Marty et al [60] found in a cohort of community-dwelling older adults a significant positive correlation between suicidal ideation and maladaptive coping including avoidant focused coping and substance abuse. Similarly to Khazem et al [58], in the study of Marty et al [60] the positive association between maladaptive coping and suicidal ideation was independent of other coping strategies, as well as gender [60]. Furthermore, Tang et al [59], including university students, replicated the positive association between suicidal ideation and avoidant focused coping. Specifically, in this study, students with recent suicidal thoughts were found to be characterised by significant higher scores on subscales measuring avoidant focused coping like cognitive avoidance, compared to those without recent suicidal thoughts [59]. On the contrary, in a study on female subjects with a history of partner abuse, no significant differences in the scores of avoidant coping were observed between females with death wish or with the desire to attempt suicide compared to those without such desire or death wish [71] (Table 1).

There are also studies that have investigated the association between suicidal ideation and avoidant focused coping among patients with somatic diseases (Table 1) [56, 57]. Specifically, in a study on middle-aged or older subjects living with HIV-AIDS, Kalichman et al [56] reported a positive significant association between avoidant focused coping and suicidal ideation (Table 1). However, after controlling for depressive symptoms, this association did not remain significant [56]. Furthermore, in the study of Marusic et al [57] no significant differences in the use of avoidant coping strategies were observed between inpatients at somatic wards with or without death wishes (Table 1).

To the best of our knowledge, there is only one study that has investigated the association between suicidal ideation and avoidant focused coping among psychiatric patients [62]. In this study, D`Zurilla and co-workers [62] including

Table 1. Suicidal ideation and avoidant focused coping

Authors	Participants	n	Coping scales	Assessments of suicidal ideation	Results
Marusic and Goodwin (2006)	Patients at Somatic wards	415	CSQ [72]	EPQ 68th item: "Have you ever wished that you were dead?"	0
Kalichman et al (2000)	Patients with HIV-AIDS	113	WCQ [73]	The BDI item addressing suicidal ideation	0
Hamdan-Mansour et al (2010)	Women with a history of intimate partner abuse	95	WCQ [74]	MSSI [74] items no. 2 and no. 4	0
Woodhead et al (2014)	Community-residing adults	521	CRI [75]	One item extracted from the HDL	+
Khazem et al (2015)	Military members	903	Brief-COPE [76]	The Beck Scale for Suicidal Ideation [77]	+
Tang et al (2015)	University students	5972	CRI [76]	Two questions: (1) ''Did you seriously think about committing suicide in the past 12 months?", and (2) "Did you ever seriously think about committing suicide at any point in your lifetime?"	+
Marty et al (2010)	Community-dwelling older adults	108	COPE [53]	GSIS [78]	+
D`Zurilla et al (1998)	General psychiatric inpatients	100	SPSI-R [79]	SI subscale of SPS [80]	0

Abbreviations: CSQ: Coping Styles Questionnaire; EPQ: Eysenck Personality Questionnaire; WCQ: Ways of coping questionnaire; BDI: Beck Depression Inventory; MSSI: Modified Scale for Suicide Ideation; CRI: Coping Responses Inventory; HDL: Health and Daily Living Form; COPE: Coping Orientation of Problem Experience Inventory; GSIS: Geriatric Suicide Ideation Scale; SPSI-R: Social Problem-Solving Inventory–Revised; SPS: Suicidal Probability Scale.

Results: 0 = no significant association; + = significant positive association; - = significant negative association

general psychiatric inpatients did not find a significant correlation between suicidal ideation and avoidant focused coping (Table 1).

In addition, there is a prospective study that has investigated the association between coping strategies and future suicidal ideation [65]. In that study, Woodhead and co-workers [65] found that the more us of avoidant coping at baseline was associated with future suicidal ideation in community adults (Table 1). Interestingly, in this work there was no significant association between approach coping and future suicidal ideation [65] which indicates that avoidant coping but not approach coping may be a predictor of subsequent suicidal ideation.

To sum up, findings regarding the relationship between suicidal ideation and avoidant focused coping are inconsistent. This may be due to different methods used in studies for example the assessments of coping styles and suicidal ideation or the included populations. Interestingly, as shown in the table 1, there may be similarities among studies that raise some interesting questions. Firstly, most of studies reporting a significant association between suicidal ideation and avoidant focused coping had larger samples sizes like the work of Tang et al [59] or the study of Khazem et al [58] compared to studies reporting the absence of such association such as in studies of D`Zurilla et al or Hamdan-Mansour et al [62, 71]. This may raise the issue whether negative studies were insufficiently powered to detect an association. Secondly, none of works investigating clinical samples has observed a positive relationship between suicidal ideation and avoidant coping, while most of the studies including non-clinical populations have (Table 1). This observation in turn may indicate that the association between suicidal ideation and avoidant coping is limited to non-clinical samples.

Attempted suicide

There is some evidence for the association between attempted suicide and increased use of avoidant focused coping strategies [65, 82]. Kaslow et al [64] studied patients seeking medical or psychiatric care and found that suicide attempters scored significantly higher on the subscale measuring avoidant coping compared to non-attempters. In line with this study, Sunnqvist et al [81] reported that recent suicide attempters were significantly more likely to use avoidant focused coping strategies compared to healthy controls. Furthermore, they also found that recent suicide attempters were characterized by more avoidant coping strategies compared to suicide attempters who were followed up 12 years after a suicide attempt [82].

Table 2. Suicide risk and avoidant focused coping

	Partici-pants	n	Age Mean± SD	Coping scales	Assessments of suicide risk	Results
Cukrowicz et al (2008)	Older patients with both MDD and PD	69	61.32 ±5.22	CSQ [73]	Scores of ASIQ and BHS [82]	Negative correlation between suicide risk and avoidance coping independently of gender and depressive symptoms.
D`Zurilla et al (1998)	University students	283	18.7±-[1]	SPSI-R [80]	SPS [81]	Positive correlation between the SPS scale and avoidant coping strategies.
Gandy et al (2013)	Patients with epilepsy	123	40±17	WOCS-R [74]	the suicidality module of the MINI [83]	Patients with suicide risk had significantly higher scores on the subscale of Escape avoidance compared to those without suicide risk.

Abbreviations: MDD: major depressive disorder; PD: personality disorder; CSQ: Coping Styles Questionnaire; ASIQ: Adult Suicidal Ideation Questionnaire; BHS: Beck Hopelessness Scale; WOCS-R: Ways of coping questionnaire-revised; SPSI-R: Social Problem-Solving Inventory–Revised; SPS: Suicidal Probability Scale; MINI: The Mini-International Neuropsychiatric Interview. [1]Data regarding SD was not presented in the study.

Completed suicide

The association between completed suicide and avoidant coping has also been studied [66, 69]. Specifically, Li and Zhang [69] reported a significant increased use of avoidant coping strategies assessed through interview of family members among rural suicide completers compared to community living controls. Furthermore, in a prospective study, similarly to the work of Woodhead et al [65], Svensson and co-workers [66] found that more use of avoidant coping was associated with future suicide in a middle age and older general population.

Suicide risk

Not only suicidal behaviour but also suicide risk measured by different psychometric scales has been linked to the increased use of avoidant focused coping strategies [55, 62, 82] (Table 2). Specifically, among patients with epilepsy the risk of suicide (assessed by the suicidality module of the Mini-International Neuropsychiatric Interview (MINI)) has been found to be associated with

significant more use of avoidant focused coping [55]. This positive association was independent of employment status and other coping strategies [55]. In line with these results, D`Zurilla et al [62] observed a significant positive correlation between avoidant coping (Avoidance style) and suicide risk, assessed by the Suicidal Probability Scale, among university students.

There is also some evidence for the relationship between suicide risk and avoidant focused coping among psychiatric patients. However, contrary to previous results [55, 62], Cukrowicz et al [82] found that the increased use of avoidant coping strategies were significantly correlated with lower suicide risk measured by the composite of two psychometric scales (Table 2) in elderly subjects with MDD and PD. A possible explanation for the discrepancy between this study and works of D`Zurilla et al [62] and Gandy et al [55] may be the difference in age of the study samples. As it is seen in the Table 2, patients in the study of Cukrowicz et al [82] are much older than in other two works [55, 62]. This may raise the issue that whether there is an inverse relationship between the more use of avoidant focused coping and suicide risk among old people, at least among those with MDD and PD diagnoses.

Conclusion

To sum up, according to results of these studies an association between the more use of avoidance coping strategies and suicidal behaviour, as well as an increased suicide risk is plausible. From population-based studies, there is also evidence for the relationship between avoidant focused coping and future suicidal ideation or completed suicide [65, 66]. However, no studies have investigated whether the increased use of avoidant focused coping may be associated with future suicidal behaviour among psychiatric subjects. Furthermore, as far as we know data regarding the possible relationship between avoidant focused coping and self-reported suicide risk or suicidal ideation is missing in suicide attempters.

Avoidant focused coping strategies and personality traits

Several studies have investigated whether there is a relationship between personality traits and coping strategies including avoidant focused coping among adults [84, 85]. Specifically, Connor-Smith and Flachsbart [84] performed a meta-analysis including studies comprising mainly non-psychiatric cohorts. According to this meta-analysis, higher levels of anxiety-related traits (Neuroticism) were significantly correlated with the increased use of avoidant focused coping [84]. Furthermore, lower levels of Conscientiousness reflecting problems with self-

control, self-regulation and self-discipline were significantly associated with increased use of avoidant focused coping [84].

Despite some evidence suggesting a link between suicidal behaviour, high levels of anxiety-related traits and impulsiveness [24], it is interesting that there are no previous studies (as far as we know) that have studied the potential relationship between these personality traits and avoidant focused coping among persons with suicidal behaviour.

Are avoidant focused coping strategies stable over time?

Considering the results of longitudinal studies including different populations such as patients with panic disorder [86], with multiple sclerosis [87] or adult caregivers of Alzheimer's patients [88], avoidant focused coping has been found to be stable over time, at least 1-5 years. Furthermore, according to these studies, avoidant focused coping has been reported to remain stable despite of changes in clinical symptoms or therapy in non-suicidal subjects [86-90]. In addition, Pollock and his colleagues [91] reported that suicide attempters may use poorer coping strategies compared to psychiatric controls without attempted suicide. Moreover, according their result the poorer coping did not changed despite of improvement in mood after six weeks [91].

In support of the notion that avoidant focused coping may be stable is that avoidant focused coping seem to be heritable and has been linked to several single nucleotid polymorphism (SNP) (will be discussed in details in below).

As discussed above, avoidant coping has been found to correlate with personality traits like anxiety-related traits or traits reflecting impulsiveness [84]. Given that personality traits seem to be stable over time, this could also support the view that avoidant focused may be a stable trait.

Summarising these findings above, it is plausible that that avoidant focused coping may be stable over time. However, as data is missing, it is unclear whether this is true also in the context of suicidal behaviour.

Genetic issues regarding avoidant focused coping

The question whether coping strategies may have heritable component has already become a research issue in early 1990s. Since then relative high numbers of

studies have investigated the possible heritability of coping [92]. Specifically, a meta-analysis including twin-pairs has been suggested that the heritability of coping has been estimated to 0.68-0.76 [92].

In addition, several genetic association studies have investigated whether there is a link between SNPs related to the vulnerability for stress-related psychiatric disorders and coping strategies, such as avoidant focused coping [93-95]. Particularly, Heck and co-workers [95] found that SNPs in the gene coding for angiotensin-converting enzyme may be associated with coping strategies reflecting avoidance, in both healthy subjects and patients with affective disorders. Furthermore, among university students, an association between the BDNF Val66Met gene polymorphism and emotion focused coping, including avoidance, passive resignation, and wishful thinking has been observed [93]. Specifically, it has been found that subjects with the Met allele of this SNP had significantly higher scores on emotion focused coping compared to those with the Val/Val genotype [93]. Similarly to these results, Aizawa et al [94] reported that the Met/Met genotype is associated significantly with the more use of distancing reflecting mental avoidance, compared to the Val/Val genotype in healthy subjects. In the same work, they also reported a significant association between the same coping style and some SNPs in the gene coding for the BDNF receptor TrKB [94].

Brain-derived neurotrophic factor (BDNF)

A general description of BDNF

BDNF is a small dimeric protein that was first isolated from pig brain by Barde and his co-workers in 1982 [96]. It belongs to the neurotrophin family and plays a key role in the development and survival of both peripheral and central neurons [97]. BDNF displays a widespread distribution pattern in the brain, with the highest levels of mRNA and protein in the hippocampus and cerebral cortex [98, 99]. Initially, it was thought that BDNF is produced only in the central nervous system by the nerve cells. However, over the years it has become clear that BDNF is also expressed by several other cells, for example immune cells, muscle cells, vascular endothelial cells [100, 101]. Furthermore, platelets appear to store BDNF without producing it [102].

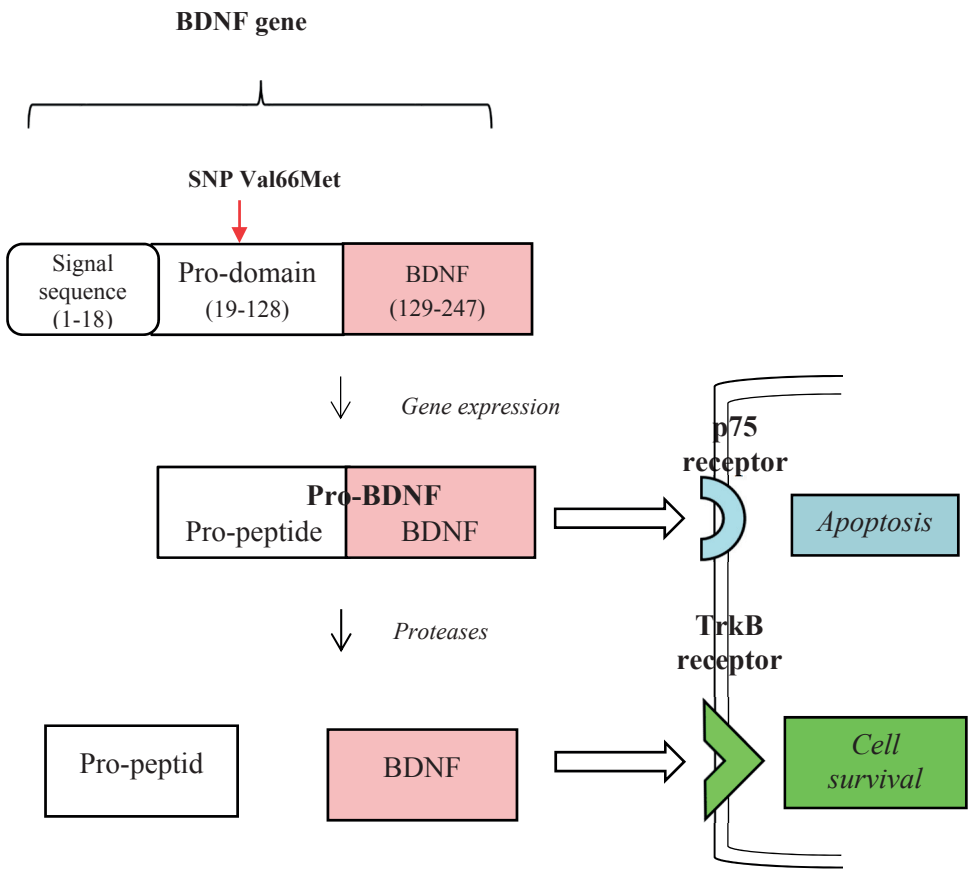


Figure 2. The pro-BDNF is synthesised which is cleaved into the BDNF pro-peptide and BDNF (or mature BDNF) by intra- or extracellular proteases. Pro-BDNF binds to p75 receptor and induces apoptosis, while BDNF binds to TrkB receptor and leads to cell survival. The red arrow shows that the SNP Val66Met is located on the BDNF gene sequence coding of pro-peptide.

BDNF (this term is used in the thesis) or mature BDNF is synthesized as a precursor protein, pro-BDNF which is cleaved into BDNF and a 120 amino acids fragment, the BDNF pro-peptide (Figure 2). BDNF binds preferentially to TrkB receptor and the interaction between BDNF and this receptor promote cell survival (Figure 2). On the contrary, the pro-BDNF acts to the p75 neurotrophin receptor (p75NTR) inducing cell apoptosis [103] (Figure 2). Not only pro-BDNF and BDNF, but also the BDNF pro-peptide affects neurogenesis [104]. However, the underlying mechanism of this process has not yet been clarified.

The gene coding for BDNF is located on the short (p) arm of chromosome 11 at position 13. It is comprised of one main coding exon (exon IX) and nine alternatively spliced promoters to direct site-specific transcription and subcellular localization. The 119 amino acids that constitute the mature BDNF (Figure 2) are identical in pigs, mice, rats and humans [105].

The most commonly studied SNP regarding suicidal behaviour, is the BDNF Val66Met. The Val66Met or even called rs6265 is an exonic single nucleotide polymorphism where adenine and guanine alleles vary, resulting in a variation between valine and methionine at codon 66. The SNP is located in the pro-domain area and results in structural changes in the pro-peptide (Figure 2). In turn, these changes seem to affect the biological action on hippocampal plasticity [104].

Is BDNF a biological marker of suicidal behavior?

BDNF and mRNA of BDNF in the brain: post-mortem studies

As far as we know, five previous post-mortem studies have investigated the possible association between BDNF concentration in brain areas associated with suicidal behaviour and completed suicide. Subjects and results of these studies are summarized in Table 3. Several studies have found significantly lower mRNA and protein levels of BDNF in the prefrontal cortex (PFC) and the hippocampus among suicide victims compared to controls [106-109]. Furthermore, some of these studies have found that mRNA levels of BDNF are significantly correlated with BDNF protein levels in the brain of suicide victims [106, 107]. Taken together, these findings indicate that lower BDNF levels in the brain may be the result of down-regulated gene expression in suicide victims [110]. One study has investigated whether there is a difference in BDNF in the amygdala between suicide victims and controls [111]. However, the authors did not observe a significant alteration between suicide victims and the comparison groups. The absence of any significant differences in BDNF in the amygdala between suicide victims and controls may be due to the small sample size (Table 3) [111]. On the other hand, it is also possible that the absence of difference may be because of the fact that BDNF in the amygdala is less important for the pathophysiology of suicidal behaviour.

Table 3. BDNF in post-mortem studies of suicide victims

Authors	Subjects	Results
Dwivedi et al (2003)	27 suicide victims 21 controls	Significantly lower protein and mRNA levels of BDNF in the hippocampus and the PFC among suicide victims compared to controls. BDNF levels among suicide victims are not associated with the MDD diagnosis.
Karege et al (2005)	30 suicide victims 24 controls	Significantly lower protein BDNF levels in the hippocampus and in the PFC among suicide victims compared to controls. BDNF levels among suicide victims are not associated with the MDD diagnosis.
Banerjee et al (2013)	21 suicide victims 19 controls	Significantly lower protein and mRNA levels of BDNF in the hippocampus among suicide victims compared to controls.
Maheu et al (2013)	12 depressed suicide victims 10 depressed subjects 14 controls	No significant difference in protein levels of BDNF in the amygdala between suicide victims, depressed patients or controls.
Hayley et al (2015)	18 depressed suicide victims 19 controls	Significantly lower BDNF levels in the hippocampus among male suicide victims compared to controls. Significantly lower BDNF levels in the PFC among female suicide victims compared to controls.

Abbreviations: BDNF: brain-derived neurotrophic factor; MDD: major depressive disorder; PFC: prefrontal cortex; mRNA: messenger ribonucleic acid

In addition, some studies reported that suicide victims with or without MDD are comparable regarding BDNF levels in the hippocampus and PFC [106, 107]. This in turn indicates that BDNF-related changes in the suicidal brain may be independent of clinical diagnosis. Interestingly, Hayley and co-workers suggested that there may be gender-related differences in the localisation of observed alterations regarding BDNF between suicide victims and controls [109]. Specifically, they found that female suicide victims were characterized by lower BDNF levels in PFC compared to controls while males had significantly lower BDNF levels in the hippocampus compared to controls [109]. As no other post-

mortem studies on suicide victims have investigated gender differences in BDNF, it is unclear whether the gender difference may be limited to the study of Hayley et al [109] or a general phenomenon in suicide victims. However, in the light of the well-known gender difference in suicidal behaviour [112], as well as in the regulation of BDNF [113] the findings of Hayley and his co-workers [109] are interesting.

Peripheral levels of BDNF in suicide attempters

Several studies have investigated possible associations between peripheral BDNF levels and attempted suicide [114, 115] (Table 4). Studies can be subdivided based on whether BDNF was quantified in plasma, serum or in platelets.

The two studies in which plasma BDNF was analysed reported significantly lower BDNF levels among recent suicide attempters compared to healthy controls or patients with MDD without attempted suicide [116, 117].

Studies measuring serum BDNF levels in suicide attempters have produced inconsistent results. Out of seven studies, three found that suicide attempters have lower serum BDNF levels compared to healthy controls or non-suicidal psychiatric patients [115, 118, 119]. The remaining four studies, however, did not report any significant differences in serum BDNF levels between suicide attempters and controls [120-123].

Furthermore, Lee & Kim found lower BDNF concentrations in platelets among MDD patients with a recent suicide attempt compared to healthy controls [124]. In addition, there is some evidence that BDNF stored in platelets may be the source of BDNF levels in plasma [125]. Considering this, the finding in the study by Lee & Kim might be considered in line with the findings of the studies showing lower plasma BDNF in suicide attempters [116, 117].

The amount of time elapsed between the suicide attempt and blood collection may have an impact in the subsequent BDNF analyses. Interestingly, studies collecting blood samples within 24 hours after a suicide attempt, have consistently reported lower BDNF levels in suicide attempters [116, 119, 124]. On the contrary, those studies that investigated associations between BDNF and a history of a suicide attempt, where blood was not collected in conjunction with the attempt, found no association between BDNF and attempted suicide [121-123]. Furthermore, Eisen et al collected blood samples within 3 months after the suicide attempt did not observe any significant differences in BDNF between suicide attempters compared to healthy controls or psychiatric patients without attempted suicide [120].

Table 4. BDNF in suicide attempters

Authors	Participants	Time*	BDNF	Results
Kim et al (2007)	MDD patients: 32 with AS 32 without AS 30 healthy controls	0-24 hours after AS	plasma	Significantly lower BDNF levels in MDD patients with AS compared to healthy controls and MDD patients without AS.
Lee et al (2007)	MDD patients: 28 with AS 49 without AS	unclear	plasma	Significantly lower BDNF in MDD patients with AS than those without AS controlling for BMI.
Deveci et al (2007)	10 with AD and with AS 24 MDD patients 26 healthy controls	0-24 hours after AS	serum	Significantly lower BDNF in suicide attempters compared to healthy controls.
Grah et al (2013)	MDD patients: 26 patients with AS 25 without AS Emotional unstable PD: 33 with AS 26 without AS AD patients: 37 with AS 25 without AS	unclear	serum	Among patients with AD, with PD but not among MDD, patients with AS had significantly lower BDNF levels compared to those without AS independently of age and gender.
Pinheiro et al (2012)	Postpartum women: 12 with AS 178 without AS	Past AS	serum	No association between a history of attempted suicide and BDNF.
Park et al (2013)	MDD patients: 18 with AS 33 without AS	Past AS	serum	No significant difference in BDNF between MDD patients with or without the history of attempted suicide.
Huang and Lee (2006)	Schizophrenic patients: 12 with AS 115 without AS	unclear	serum	No significant difference in BDNF between schizophrenic patients with or without a suicide attempt.
Priya et al (2016)	42 suicide attempters 42 age-gender matched control	unclear	serum	Significant lower BDNF in suicide attempters compared to controls.
Eisen et al (2016)	84 psychiatric patients with AS 93 community controls 104 psychiatric controls without AS	Within three months after AS	serum	No significant association between a recent suicide attempt and BDNF.
Lee and Kim (2009)	MDD patients : 20 with AS 20 without AS 20 healthy controls	0-24 hours after AS	platelet	MDD patients with or without AS had significantly lower BDNF compared to healthy controls. No significant difference in BDNF was observed in MDD patients regarding AS.

Abbreviations: AS: Attempted suicide; BDNF: brain-derived neurotrophic factor; PD: personality disorder; AD: adjustment disorder; MDD: major depressive disorder; BMI: body mass index.
*Time between AS and blood sampling

Conclusion

The observed results regarding concentrations of BDNF (mRNA and protein levels) in the brain of suicide victims are very consistent, in particular BDNF protein and mRNA levels found in the hippocampus. On the contrary, the BDNF findings in the blood of suicide attempters are inconsistent. This may be due to various factors such as differences in samples sizes, method of BDNF analysis, time for blood sampling. There is some evidence that plasma BDNF may reflect BDNF in the hippocampus [126, 127]. If this is the case, studies reporting association between lower BDNF in plasma or platelets (as the possible source of plasma BDNF [125]) and attempted suicide may be in line with post-mortem studies on suicide victims. Furthermore, considering the results from previous studies, it is possible that lower BDNF may rather be associated with a recent suicide attempt than a history of attempted suicide.

BDNF Val66Met and suicidal behaviour

Completed suicide

Several studies have investigated the association between BDNF Val66Met gene polymorphism and suicide, however with inconsistent results. One of the studies reporting an association between this SNP and suicide is the work of Pregelj et al [128]. Among Caucasian subjects, they found that the Met allele was significantly more frequent among female suicide victims than female controls [128]. Furthermore, they found that female suicide completers who used violent methods had more often the Met allele compared to non-violent suicide attempters [128]. On the contrary, Zarrilli et al [129] including Caucasian subjects and Ratta-Apha et al investigating Asian people [130] did not find any association between suicide and the BDNF Val66Met SNP.

Attempted suicide

Interestingly, in contrast with the inconsistent results regarding BDNF Val66Met polymorphism and completed suicide, the association between attempted suicide and this SNP appears to be replicated. Particularly, Zai et al in their meta-analysis including 12 studies, reported a significant association between Met allele, the Met allele-carrying genotypes and a history of attempted suicide [131]. In line with these results, Ratta-Apha et al [130] found that the Met allele tended to be associated with attempted suicide but not with completed suicide. Furthermore, Wang and co-workers reported an association between the Met allele and

attempted suicide in an elderly Asian population [132]. Contrary to these results, González-Castro et al including 139 Mexican subjects with bipolar disorder found an association between a lifetime history of suicidal behaviour and Val/Val genotype [133]. The discrepant result may be due to the differences in ethnicity [133].

Summarizing the results above, the association between the Met allele of the BDNF Val66Met gene polymorphism and a history of attempted suicide is plausible. This in turn indicates that BDNF Val66Met may play a role in the pathophysiology of suicidal behaviour.

BDNF and vulnerability factors for suicidal behaviour

As previously discussed, various vulnerability factors for suicidal behaviour have been identified, for example clinical symptoms of depression, anxiety and certain personality traits.

Clinical symptoms

Many studies have investigated the possible association between BDNF and the severity of depressive symptoms. Specifically, it has repeatedly been found that lower BDNF concentration is linked to more severe depressive symptoms in patients with mood disorders including MDD and bipolar disorder [134, 135]. Other evidence that BDNF may be a state marker of depression comes from clinical trials investigating how BDNF levels are related to antidepressant treatment response [134]. A meta-analysis reported a significant increase in BDNF levels after treatment with antidepressant drugs, as well as a significant negative correlation between BDNF levels and depressive symptoms in patients with MDD [134]. In addition, significant negative associations between peripheral BDNF concentrations and depressive symptoms have also been observed in healthy subjects [136] and in patients with fibromyalgia [137]. Only one study to date has studied the relationship between peripheral BDNF levels and depressive symptoms in suicide attempters. In this study no significant correlation was found between BDNF in plasma and the severity of depressive symptom [116].

There is also evidence for an association between lower BDNF levels and more severe anxiety symptoms. Specifically, in patients with MDD, a significant negative association was observed between BDNF and the severity of anxiety symptoms [138]. Furthermore, among healthy subjects, plasma BDNF levels were

Table 5. Peripheral BDNF and personality traits

Authors	Participants	n	BDNF	Persona-lity scales	Results
Lang et al (2004)	Healthy persons	118	serum	NEO-FFI	Significant negative correlation between BDNF and Neuroticism.
Minelli et al. (2010)	Healthy persons	217	serum	TCI	Significant negative correlation between BDNF and Harm avoidance.
Terracciano et al (2011)	Healthy persons	391	plasma	NEO-PI-R	Significant positive correlation between BDNF and Neuroticism among males.
Terracciano et al (2010)	Community based cohort	2099	serum	NEO-PI-R	Significant negative correlation between BDNF and Neuroticism.
Okuno et al (2011)	Healthy persons	269	plasma	NEO-FFI	Significant positive correlation between BDNF and Extraversion
Bhang et al (2012)	Healthy persons	111	plasma serum	TCI	No significant correlation between BDNF and personality traits.
Yasui-Furukori et al (2013)	Healthy persons	178	plasma	TCI	Significant negative correlation between BDNF and Harm avoidance Significant positive correlation between BDNF and Self-Directedness
Nomoto et al (2015)	patients with MDD	125	serum	TCI	Negative correlation between BDNF and Self-Directedness adjusted for age, sex, BMI, dose of antidepressant, and severity of depression.
Martinotti et al (2015)	patients with PTSD subjects persons to trauma but without PTSD	23 19	serum	BIS	Positive correlation between BDNF and BIS in patients with PTSD but not among persons exposed to trauma.

Abbreviations: BDNF: brain-derived neurotrophic factor; NEO-FFI: Neuroticism-Extraversion-Openness Five-Factor Inventory; NEO-PI-R: Revised NEO Personality Inventory; TCI: The Temperament Character Inventory; MDD: major depressive disorder; PTSD: Post-traumatic stress disorder; BIS: Barratt Impulsiveness Scale.

found to correlate negatively to anxiety symptoms [136]. However, whether there is a relationship between BDNF and anxiety symptoms in suicidal individuals has not yet investigated.

Personality dimensions

In several studies, peripheral BDNF has been found to be associated with various personality traits [136, 139-146]. The results of these studies are presented in Table 5. As evident from the table, findings have been inconsistent which may be due the differences in methodology, such as choice of the personality inventory based on different theoretical backgrounds, statistical analysis, or the use of different BDNF assays. However four studies have suggested that peripheral BDNF concentrations were significantly and negatively correlated with anxiety-related personality traits [139, 140, 142, 144] including Neuroticism (NEO-FFI) and Harm avoidance (TCI) in healthy subjects.

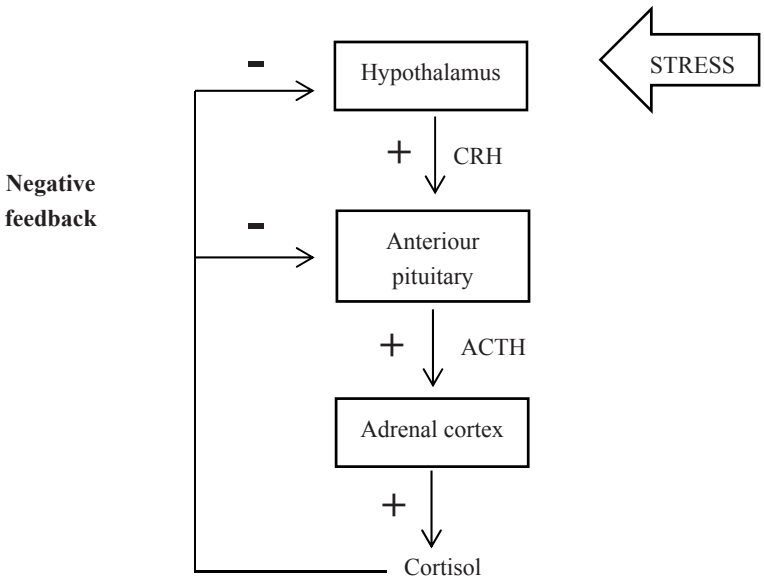
BDNF and the HPA axis

HPA axis

The hypothalamic–pituitary–adrenal (HPA) axis is a neuroendocrine system with an important role in the regulation of the body`s response to stress. The axis involves the hypothalamus, the pituitary gland, and the adrenal gland (Figure 3). In response to stress, Corticotropin-releasing hormone (CRF) is released into hypophysial portal vessels that access the anterior pituitary gland. Binding of CRF to its receptor on pituitary corticotropes induces the release of adrenocorticotropic hormone (ACTH) into the systemic circulation. The main target for circulating ACTH is the adrenal cortex, where it stimulates cortisol synthesis and secretion (Figure 3). Cortisol will be released for several hours after the stress response. However, at a certain blood concentration, cortisol exerts negative feedback at the level of the hypothalamus and the pituitary gland, thus reducing the cortisol output in order to achieve homeostasis.

One commonly used method for the investigation of HPA axis activity within suicide research is the Dexamethasone suppression test (DST). Dexamethasone is an exogenous steroid that provides negative feedback to the pituitary gland through the suppression of ACTH secretion. This, in turn, leads to a decrease in cortisol. Among persons with normal HPA axis a one-time treatment with dexamethasone results in a decrease of cortisol levels. On the contrary, individuals with an overactive HPA axis do not suppress endogenous cortisol levels following

Figure 3. HPA axis function



dexamethasone administration, indicating impaired HPA-axis negative feedback [147]. The cortisol concentration can be measured in saliva or in serum.

HPA axis and attempted suicide

An increasing number of studies have investigated whether there may be a relationship between HPA axis dysregulation and suicidal behaviour, however with inconsistent results [148-153]. As the thesis is focusing on suicide attempters, only works investigating the association between suicide attempters and HPA axis function will be discussed here.

It has repeatedly been suggested that recent suicide attempters may display significantly higher cortisol levels in urine, saliva, blood and cerebrospinal fluid compared to psychiatric patients without a suicide attempt or healthy controls [148-150, 154]. Our group reported higher serum cortisol levels before and after a DST, in recent suicide attempters as compared to healthy controls [154]. We also reported that non-suppression of cortisol is associated with high scores of the

Suicide Assessment Scale (SUAS) in recent suicide attempters, indicating an elevated suicide risk in these patients [155]. Indeed, according to some studies, non-suppression of cortisol after the DST has been found to be significantly associated with future completed suicide in suicide attempters [152, 156].

On the contrary, others have suggested decreased cortisol in suicide attempters [157, 158] and there are also some studies that have reported no significant differences in cortisol between patients with or without attempted suicide [154]. Thus there may be both high and low cortisol levels in suicide attempters. Our group reported the lowest DST cortisol levels in patients with cluster B personality disorders [159] and low cortisol levels in suicide attempters twelve years after an index suicide attempt in comparison to patients who never had attempted suicide [157]. Interestingly, according to a recent meta-analysis, the positive association between cortisol levels and attempted suicide may be limited to patients, less than 40 years old [160] and that there may be a negative association between cortisol levels and attempted suicide among patients older than 40 years [160].

Relationship between BDNF and HPA axis

Preclinical studies have suggested that elevated levels of circulating glucocorticoids, as a result of exogenous administration, may led to down-regulation in BDNF gene expression in cortical and hippocampal brain regions [161]. Furthermore, a significant and negative correlation between corticosterone and BDNF, both peripherally and in the prefrontal cortex, have been observed in rats [162]. In line with these results, a post-mortem study on schizophrenic subjects and controls revealed a significant negative association between cortisol and BDNF in the prefrontal cortex, as well as in CSF [162]. Taken together, these results may indicate an inverse relationship between HPA axis activity and BDNF.

Aims

General aim

The general aim of this thesis was to increase the understanding of the pathophysiology of attempted suicide with focus on BDNF and avoidant focused coping.

Specific aims

Paper I

Background: BDNF Val66Met gene polymorphism has been suggested to be associated with attempted suicide [131]. In addition, the association between the Met allele and avoidant coping (identified as a risk factor for suicidal behaviour) has also been reported in healthy subjects [93, 94]. However, the relationship between the BDNF Val66Met and avoidant coping strategies in suicide attempters has not yet been studied.

Aim: to study whether the *BDNF* Val66Met gene polymorphism may be associated with avoidant focused coping in subjects with attempted suicide.

Paper II

***Background*:** Peripheral BDNF concentrations have been linked to several vulnerability factors for suicidal behaviour including severity of clinical symptoms [134, 135] and personality dimensions (Table 5). However, the association between BDNF and these vulnerability factors in suicide attempters has not been well studied.

Aim: to investigate whether there is a relationship between peripheral BDNF, clinical symptoms and personality dimension in recent suicide attempters.

Paper III

Background: Both decreased levels of BDNF and HPA-axis dysregulation have been suggested to be involved in the pathophysiology of suicidal behaviour [110, 163]. Preclinical and clinical studies have shown interactions between HPA-axis activity and BDNF, but this has not been studied in suicidal subjects.

Aim: To study the association between BDNF and HPA-axis activity in psychiatric patients with attempted suicide, and to test the relationship between these biological systems and cognitive symptoms in suicide attempters.

Paper IV

Background: Increased use of avoidant coping strategies has repeatedly been linked to suicidal ideation (Table 1) as well as to suicide risk (Table 2) in non-psychiatric and psychiatric populations. In addition, suicide attempters have been found to be use significant more avoidant focused coping compared to healthy controls or non-suicidal psychiatric patients [65, 75]. However, whether there is an association between avoidant focused coping and suicide risk in suicide attempters is unclear.

Aim: To investigate whether suicide risk is associated with the use of avoidant coping strategies in suicide attempters.

Paper V

Background: Avoidant focused coping has been identified as a risk factor for suicidal behaviour (Table 1 and 2). Interestingly, positive associations between avoidant focused coping and dysfunctional personality dimensions linked to suicidality have been observed in non-clinical populations and psychiatric patients [84, 85]. However, whether there is an association between the use of avoidant focused coping and personality dimensions among suicide attempters is unclear.

Aim: To investigate the possible association between personality dimensions and avoidant focused coping strategies in psychiatric patients with a recent suicide attempt.

Material and method

Participants

The participants included in the papers were recruited from five different studies. In some case, the same participants were included in different papers. The recruitment process is described in Figure 4.

The first cohort of recent suicide attempters: This study started in 1986 and lasted until 2001. During these years, patients were recruited from the medical intensive care unit or from a general psychiatric ward at the psychiatric clinic in Lund, shortly after a suicide attempt. Overall, three-hundred patients were recruited. More information regarding the study can be found in Paper II and III.

Follow-up study: This study started in 1999 and lasted until 2002 and 42 individuals participated. The patients were recruited from the first cohort of suicide attempters. They were followed-up approximately 12 years after a suicide attempt. More information regarding this study can be found in the thesis of Sunnqvist (2009) [164] which is available online [165].

The second cohort of recent suicide attempters: This study started in 2006 and lasted until 2008. During these years, a total of 56 patients were recruited from the medical intensive care unit or from a general psychiatric ward at the psychiatric clinic in Lund, shortly after a suicide attempt.

The cohort of depressed patients: Depressed patients were included from an ongoing study started 2012. The study includes in- or outpatients at the Division of psychiatry, Region Skåne Sweden with current depression, referred by their psychiatrist due to treatment difficulties. Inclusion criteria are an ongoing clinical depression. At the time of the study presented in Paper IV, one hundred-thirty patients had been recruited.

Healthy controls: Healthy controls were randomly selected from the municipal population register in Lund.

The process of inclusion into the different papers

Paper I: As depicted in Figure 4, the subjects in Paper I were recruited from the follow-up study and the second cohort of recent suicide attempters. Because of missing data regarding BDNF Val66Met gene polymorphism six patients were excluded.

Paper II-III: In these studies, patients were recruited from the first cohort of recent suicide attempters. As at the time of these studies, only patients with available plasma could be involved (Paper II n=90 and Paper III n=95). Additional exclusion criteria for both studies were treatment with steroid medication, substance abuse disorder, and extremely high levels of BDNF (outliers). The definition of outliers can be found at page 54.

Figure 4. The recruitment process

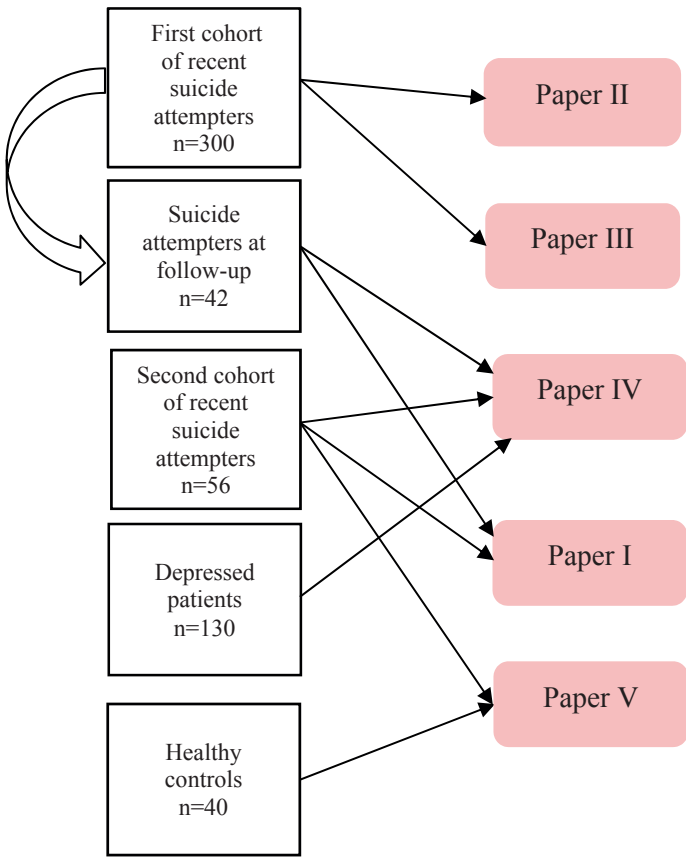


Table 6. The demographic and clinical characteristic of the participants in the different papers

Papers	n	Age Mean±SD	Females/ Males	Axis I diagnosis Yes/no	PD Yes/no
Paper I[1]					
Pooled sample	92	43.8±13.8	49/43	76/16	36/56
Paper II					
Recent suicide attempters	61	35.4±12.4	35/26	61/0	38/22[2]
Paper III					
Recent suicide attempters	75	36.5±12.8	41/34	71/4	47/24[3]
Paper IV					
Recent suicide attempters	55	39.3 ±14.1	30/25	55/0	31/24
Suicide attempters at follow-up	38	51.0±10.1	19/19	25/13	8/30
Depressed patients	72	41.1±13.4	44/28	72/0	25/47
Paper V					
Recent suicide attempters	55	39.3 ±14.1	30/25	55/0	31/24
Healthy controls	36	39.8 ±13.8	21/15	-	0/36

Abbreviations: SD: Standard deviation; MDD: major depressive disorder; PD: personality disorder.
[1] Data of only patients involved in the investigation regarding BDNF and avoidant focused coping are presented. [2] Data of Axis II diagnosis was missing in one patient. [3] Data of Axis II diagnosis was missing in four patients.

Paper IV: This study included subjects from three studies (Figure 4). *Depressed patients:* From the original study (ongoing study recruiting depressed patients) only patients without attempted suicide were included. The information about attempted suicide was based on the suicidality module of the MINI [83] from which the question no. C9 "In your lifetime: Did you ever make a suicide attempt?" was extracted. According to the response to this question, seventy-five patients had never attempted suicide. In three patients data regarding COPE were missing. Therefore, these patients were excluded. *Follow-up study:* from the original forty-two patients thirty-eight were included into the paper IV as we had data of both COPE and SUAS-S of these patients. *Cohort 2 of recent suicide attempters:* from the original fifty-six patients, fifty-five were included in this paper, as these patients had data on both COPE and SUAS-S.

Paper V: The second cohort of recent suicide attempters: as we had data of both COPE and MNT in all patients, they were included in Paper V. *Healthy controls:* only persons who had data on both MNT and COPE (n=36) were included.

The demographic and clinical data of participants in the different paper are presented in Table 6, while the used psychometric scales, interviews or biological analyses are shown in Table 8.

Instruments for data collection

Psychometric scales and interviews

MINI

MINI is a short structured diagnostic interview, developed by psychiatrists and clinicians from the DSM-IV and ICD-10 [83]. The interview takes approximately 20-25 minutes to perform.

Structured Clinical Interview for DSM-IV-Axis II Disorders (SCID-II)

The SCID-II is a diagnostic interview used to determine personality disorders according to the DSM-IV. It was published in 1997 [166].

The Montgomery-Åsberg Depression Rating Scale (MADRS)

To measure the severity of depressive symptom, the MADRS which was extracted from the CPRS was used [167]. The MADRS is widely used in research, as well as clinical settings for assessing the severity of depressive symptoms [168]. The scale consists of 10 items rated from zero to six points. Many studies have investigated the validity of MADRS and found that it has a good discriminating power to detect depression in various groups of patients such as patients with MDD or bipolar I disorder [169, 170], patients with Parkinson disease [171, 172], patients with severe obesity [173], patients at memory clinic [174], geriatric patients [175] and patients with coronary artery disease [176].

The Brief Scale for Anxiety (BSA)

To measure the severity of anxiety symptoms, the BSA was used [177]. Similarly to the MADRS, this scale was also extracted from CPRS [177]. The BSA consists of 10 items and all items are rated from zero to six.

The self-report version of Suicide Assessment Scale (SUAS-S)

To assess suicide risk the self-rating version of The Suicide Assessment Scale was used [178]. The SUAS-S is a 20-item self-report rating scale measuring the patient's attitude towards suicide, suicide-related behaviours and suicidal ideation on the day of reporting and during the previous seven days. Each item is scored in the range of 0–4 on a Likert-type scale and resulting in a scale sum score with a range of 0–80. The scale is designed to measure levels of suicidality and to be sensitive to temporal changes in suicide-related symptoms. The original SUAS-S scale has been found to possess good concurrent validity compared with the interview version [178].

COPE

To evaluate avoidant focused coping, COPE Inventory was used. This scale is commonly used in research to assess coping strategies [52]. All items are scored on a five-point scale ranging from 0 (not at all) to 5 (a lot). COPE was translated from English into Swedish by the support from the Lund University Department of Languages. As we wanted to investigate avoidant-oriented coping we used only Factor III in this thesis (Appendix I).

MNT

In order to investigate personality dimensions, the MNT was used. The MNT scale is a self-administered questionnaire based on the personality theory by Sjöbring [179]. It measures three of the dimensions suggested by Sjöbring, denoted Validity, Stability and Solidity. Each of these dimensions is represented by 20 items with a response of "yes" or "no" (score range 0–20).

Biochemical and genetic analyses

BDNF genotyping

Human genomic DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The genotyping of DNA samples from patients was performed at KBiosciences (Hoddesdon, UK).

BDNF analysis in plasma

After the wash-out period and a night of fasting and bed rest, venous blood samples from antecubital vein were collected at 8 a.m. in tubes containing EDTA. The samples were immediately placed on ice, and centrifuged at 4°C and 3000g for 10 min in order to separate plasma from cellular components within 1 hour of collection. Plasma was stored -80° C until analysis of BDNF. The storing-time of the samples ranged from 7 to 20 years. The plasma content of BDNF was measured using the ChemiKine sandwich ELISA kit (Chemicon International, USA). This kit has been suggested to provide valid measurements of BDNF [180]. A microplate reader (Milenia, kinetic analyzer, DPC, USA) was used to determine plasma-BDNF values, according to the manufacturer's instructions. Intra- and interassay levels of variation were less than 15 %. The detection limits were 50 and 3750 pg/ml.

Critical comments: Firstly, BDNF levels in plasma seem to be affected by demographic and clinical factors which could result in several pitfalls. In Table 7, such factors and recommended solutions in order to avoid pitfalls are presented. Secondly, according to a previous study, the ChemiKine sandwich ELISA kit which we used for BDNF analysis, has been showed approximately 50% cross-reactivity for pro-BDNF [181]. This indicates that this kit is not specific for the mature BDNF. Another critical issue regarding BDNF analysis is that the used blood samples have been stored during a long period. However, the use of tube containing EDTA which reduces the activity of proteases and the fact that plasma was stored -80° C until analysis of BDNF may allow us to think that BDNF was stable until the time of the analyses. Furthermore, a previous study has recommended that BDNF in plasma is intrinsically more stable than in serum [182]. The final caveat is that we analysed peripheral BDNF levels, and we do not know how these reflect BDNF function in the brain. However, several studies have suggested that BDNF in plasma may reflect central BDNF concentrations [126, 127, 183, 184].

Table 7. Analysis of plasma BDNF in clinical researches: pitfalls and solutions

Confounders	Authors	Pitfalls	Solution(s)
Gender	Lommatzsch et al [185]; Terracciano et al [141]	Gender difference in plasma BDNF	1. use gender as a covariate 2. subgroup subjects according to gender
Age	Lommatzsch et al [185]	BDNF decreases with increasing age	1. use age as a covariate 2. divide subgroups according to age
BMI/Weight	Lommatzsch et al [185]	BDNF decreases with increasing weight	1. use BMI/weight as a covariate 2. use subgroups for example overweight normal weight
Diurnal variation	Pluchino et al [186]; Choi et al [187]	Diurnal variation in BDNF	1. blood sampling at the same time in all subjects
Antidepressant medication	Brunoni et al [134]	Antidepressants affect BDNF	1. use wash-out period 2. use medication as a covariate
Drug/alcohol withdrawal	Zhang et al; Ren et al; Huang et al; Corominas et al [188-191]	Early and soon withdrawal increase peripheral BDNF levels	1. exclude or study separately patients with withdrawal 2. control statistical analysis for withdrawal
Physical activity	Huang et al [192]	Both acute and chronic exercise affect plasma BDNF concentration	*Acute effect*: rest before blood sample *Chronic effect*: use homogenous sample

Abbreviations: BDNF: Brain-derived neurotrophic factor; BMI: Body mass index

DST

The DST was performed after the blood sampling for BDNF analysis. One milligram dexamethasone was given at 10:00 p.m., and serum samples were drawn at 8:00 a.m. and 3:00 p.m. the following day for analysis of cortisol. The samples were immediately placed on ice, centrifuged at 4 °C and 3000 × g for 10 min within 1 h of collection. If cortisol was not analysed 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 7nmol/l and the intra- and inter-assay coefficients of variation were below 5 and 7%, respectively.

A subject who did not suppress cortisol to a value < 140nmol/l at either 8:00 a.m. or 3:00 p.m. or both after dexamethasone was classified as a non-suppressor of cortisol (DST non-suppressor). A subject with levels ≤ 140nmol/l was classified as a suppressor (DST suppressor).

Analysis of the permeability of the blood-brain barrier (BBB)

The analysis of the BBB permeability has previously been described in details in the work of Bayard-Burfield and co-workers (1996) [193]. Increased permeability of the blood-brain barrier was defined according to reference limits of CSF/serum albumin ratios derived from a group of healthy controls as described previously [194].

Table 8. The used methods in the five papers

Papers	MINI	SCID II	CPRS		SUAS-S	MNT	COPE	BDNF genotyping	BDNF analysis	DST
			MADRS	BSA						
I			x				x	x		
II		x	x	X		x			x	
III		x							x	x
IV		x	x		x		x			
V	x	x				x	x			

Abbreviations: MINI: Mini-International Neuropsychiatric Interview; SCID-II: Structured Clinical Interview for DSM-IV-Axis II Disorders; CPRS: Comprehensive Psychopathological Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; BSA: Brief Scale for Anxiety; SUAS-S: Self-report version of Suicidal Assessment scale; MNT: Marke-Nyman Temperament Scale; BDNF: brain-derived neurotrophic factor; DST : Dexamethasone Suppression Test.

Statistics

Softwares and programmes

All statistical analyses were conducted using SPSS statistical software version 21.0. In order to estimate haplotype frequencies and to check whether the genotyped BDNF Val66Met may deviate from the Hardy-Weinberg equilibrium the Haploview bioinformatics software was used.

Statistical significance

The level of statistical significance was set commonly to $p < 0.05$. However, in paper I, II and III in order to reduce the chances of obtaining false-positive results Bonferroni correction [195] was applied.

One- or two-tailed level of significance

The chose of level of significance depends on the hypothesis [196]. When the hypothesis states the direction of the difference or relationship, then one-tailed probability could be used. That was the case in paper I and paper III therefore in these papers to test the priori hypotheses one-tailed level of significance was used. Remaining statistical analyses were tested for two-tailed level of significance.

Parametric and non-parametric tests

The distribution of data was assessed by visual inspection and Shapiro-Wilk test as previously suggested [197]. In the case data were not normally distributed logarithmic transformations were carried out (like in paper VI or V) or we excluded outliers (like in paper IV). Outliers were defined as data which fall more than 1.5 times the interquartile range above the third quartile or below the first quartile.

If the data were normally distributed parametric tests were used. To compare interval data between groups (e.g. comparing avoidant focused coping between Met allele vs Val/Val carriers in paper I) ANCOVA was used. This statistical test gives the possibility to control the comparison for covariates such as age and MADRS scores as was done in paper I. To investigate the correlation between two continuous variables with possibility to control for covariates (such as in paper V) partial correlations were performed. Furthermore regression analysis was performed in paper IV in order to study the association between avoidant focused coping, total scores of SUAS-S and covariates.

In the case of non-normally distributed data, non-parametric test (paper II, III as well as partly in paper IV and V) were used. Specifically, the Mann-Whitney U Test was used to investigate differences in interval data between dichotomous groups. To evaluate correlation between interval data the Spearman's rank correlation was used.

More information regarding the used statistical analyses in papers can be found in the original papers and manuscripts.

Results and comments

Paper I

Genotype distributions of BDNF Val66Met are shown in Table 9. Because of limited space, this information was not presented in the published paper. As shown in Table 9, our findings are similar to observed genotype distributions among Caucasian suicide attempters [198], victims [128] or controls [128] in previous works.

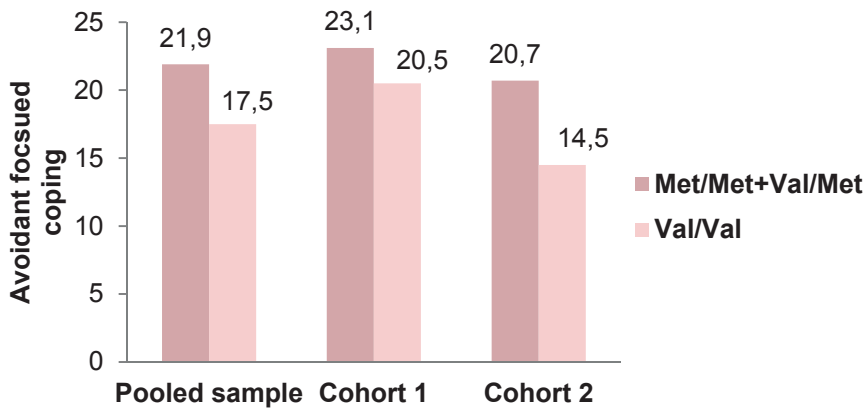
Table 9. The BDNF Val66Met distribution in our and previous samples

	Met/Met	Val/Val	Val/Met
Pregelj et al (2011)			
Suicide victims	4.7%	34.2%	61.0%
Controls	4.3%	32.1%	63.6%
Zarrilli et al (2009)			
Suicide victims	4.5%	34.3%	61.0%
Controls	3.6%	34.4%	62.0%
Perroud et al (2008)			
Suicide attempters	4.9%	33.0%	62.1%
Our results			
Suicide attempters	3.3%	33.3%	63.4%

The two-way ANCOVA (with independent variables: 1. the presence or absence of the Met allele and 2. cohorts) including age and the severity of depressive symptoms (MADRS) as covariates revealed that suicide attempters carrying the Met allele were significantly more likely to use avoidant focused coping strategies

compared to those carrying the Val/Val genotype in the pooled sample (p=0.026, one-tailed) (Figure 5). Furthermore, according to the same statistical analysis, there was no significant cohort effect on the association between the gene polymorphism and the use of avoidant focused coping controlling for the same covariates (p=0.429).

Figure 5. The means of avoidant focused coping in the subgroups regarding the presence of Met allele in the pooled samples and in cohorts



Cohort 1: recent suicide attempters
Cohort 2: suicide attempters at follow-up

Paper II

The Mean ± SD of plasma BDNF concentrations among all suicide attempters, as well as suicide attempters with MDD diagnosis in our sample are shown in Table 10. As shown in this table, mean levels of plasma BDNF observed in our study is higher compared to the work of Lee et al [117] or Kim et al [116]. These discrepancies could be explained by differences in the used methods for BDNF analysis. In addition, as shown in Table 10, the mean of BDNF concentrations in our sample was much lower compared to the mean of plasma BDNF levels in non-

suicidal depressed patients or in healthy controls reported in a meta-analysis of Brunoni et al [134].

Table 10. Plasma BDNF concentrations (pg/ml) in our sample and previous studies

Study	Suicide attempters with mixed diagnoses	MDD patients with a recent suicide attempt	MDD patients	Healthy controls
Paper II	690.8 ± 718.2	563.1 ± 672.6	-	-
Kim et al [116]	-	430.5 ± 397.0	875.8 ± 663.0	889.4 ± 611.3
Lee et al [117]	-	386.6 ± 362.4	689.7 ± 404.7	819.2 ± 347.1
Brunoni et al [134]	-	-	1444 ± 1117[1]	2318 ± 2145[1]

Abbreviations: BDNF: Brain-derived neurotrophic factor; MDD: major depressive disorder. Data presented as Mean ± SD (standard deviation). [1] No data regarding SD was presented in the study.

No significant correlations were observed between BDNF concentrations and MADRS scores (r_s=-0.058, p=0.661) or BSA scores (r_s=-0.164 p=0.210). As far as we know, there is only one previous work that has studied the possible correlation between plasma BDNF concentrations and depressive symptoms among recent suicide attempters. In that study, Kim and his colleagues [116], similarly to our findings, did not find a significant correlation between plasma BDNF levels and the severity of depressive symptoms, measured by the Hamilton's Depression Rating scale, among suicide attempters [116].

In addition, the Spearman`s rank correlation analysis revealed a significant correlation between plasma BDNF and Solidity (r_s=0.355, p<0.006).

Subgroup analyses within suicide attempters showed no significant differences in BDNF levels. Firstly, there was no significant difference in BDNF concentration between suicide attempters with or without MDD (p=0.323). Secondly, BDNF concentrations in plasma were comparable between repeaters and non-repeaters (p=0.357). Thirdly, suicide attempters who used violent method did not differ

from those who used a non-violent method (p=0.354). Finally, there was no significant difference in BDNF concentrations between male and female suicide attempters (p=0.789).

Paper III

The main finding of this paper is the significant negative correlation between BDNF in plasma and post-DST cortisol levels at 8 a.m. among female suicide attempters (r_s=-0.437, p=0.003; one-tailed, Bonferroni-adjusted level of significance p<0.0125). In addition, among female suicide attempters, we found that DST non-suppressors had significantly lower BDNF compared to DST suppressors (p=0.022, one-tailed; Bonferroni adjusted level of significance p<0.025).

Paper IV

The regression analyses including avoidant focused coping as the dependent variable, as well as the total scores of SUAS-S, age, gender, the severity of depression and the comorbidity with personality disorders as independent variables revealed significant positive correlations between avoidant coping strategies and the total scores of SUAS-S adjusted for other variables in both cohorts of suicide attempters and in depressed patients (Table 11).

Furthermore, we found positive correlations between avoidant coping strategies and SUAS-S items addressing recent suicidal ideations in all three cohorts of patients (Table 12). Also, avoidant coping strategies were significantly and positively associated with the SUAS-S item addressing recent suicidal plans (Table 12). As we could not perform any covariate analyses because of the not normally distributed data regarding the investigated items in these cases, it is unclear whether the correlations are independent of clinical and demographic confounders.

Table 11. Beta values of the regression analyses in different cohorts

Avoidant focused coping	n	SUAS-S[1]	Age	Gender	MADRS sub-groups	PD
Recent suicide attempters	55	**0.374**	0.008	-0.070	0.087	0.302*
Suicide attempters at follow-up	38	**0.486**	0.089	0.094	0.150	-0.089
Depressed patients	72	**0.553**	0.038	-0.358*	-0.170	0.328*

Abbreviations: SUAS-S: Self-report version of the Suicidal Assessment Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; PD: personality disorder.
The Bonferroni-corrected p-value was set < 0.0166 for the main hypothesis and significant values are highlighted in bold. For other results, p-value was set < 0.05 and significant results are marked with *. One-tailed level of significance was used regarding the main hypothesis (Paper IV).

Table 12. Spearman`s rho correlation between avoidant focused coping and SUAS-S items

	Avoidant focused coping strategies	
	r_s	p
Recent suicide attempters (n=55)		
Suicidal thoughts	**0.433**	**0.001**
Suicidal plans	0.283	0.036
Suicide attempters at follow-up (n=38)		
Suicidal thoughts	**0.490**	**0.002**
Suicidal plans	0.381	0.018
Depressed patients (n=72)		
Suicidal thoughts	**0.374**	**0.001**
Suicidal plans	**0.346**	**0.003**

Abbreviations: SUAS-S: Self-report version of the Suicidal Assessment Scale, r_s: Spearman`s rho correlation coefficient. Significant values are highlighted in bold. Bonferroni corrected p-value < 0.0055.

Another interesting finding is the gender difference (males had significant higher scores on avoidant focused coping compared to females) in the use of avoidant coping strategies among depressed patients irrespectively of age, the severity of depressive symptoms and comorbidity with personality disorders ($p<0.001$) (Table 11). On the contrary, gender was not associated with avoidant focused coping among suicide attempters ($p>0.05$) (Table 11).

Paper V

The main finding of Paper V is that avoidant focused coping was significantly correlated with Solidity ($p=0.007$) in suicide attempters (Table 13). Furthermore, the negative significant correlation between avoidant focused coping and Solidity remained significant among suicide attempters after controlling for age and gender ($r=-0.385$, $p=0.004$). However, on the contrary, no significant correlation was observed between avoidant focused coping and Solidity among healthy subjects (Table 13).

Table 13. Spearman`s rank correlations between avoidant focused coping and MNT subscales

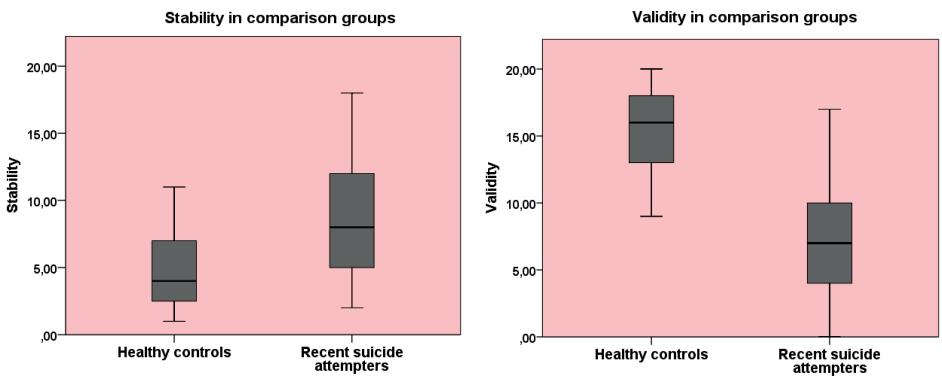
	Recent suicide attempters n=56		**Healthy controls n=36**	
	r_s	p	r_s	p
Stability	0.146	0.285	0.077	0.654
Validity	-0.266	0.0496	0.056	0.746
Solidity	**-0.360**	**0.007**	0.103	0.548

Abbreviation: MNT: Marke-Nyman Temperament Scale.
Significant values are highlighted in bold.

In addition, there are other important results in this paper. We found that suicide attempters had significantly lower scores on Validity ($p<0.001$), as well as significantly higher scores on Stability ($p<0.001$) and avoidant focused coping ($p<0.001$) compared to healthy controls (Figure 6). However, no significant difference in Solidity was observed ($p=0.266$) between suicide attempters and healthy controls.

Similarly to our results, Pendse et al [39], and Banki et al [38] showed that suicide attempters had significantly higher scores on the subscale Stability and significantly lower scores on the subscale Validity compared to healthy controls. On the contrary, in their study, Ryding et al did not observe any significant differences in the investigated MNT subscales Validity and Solidity between suicide attempters compared to controls [40]. However, it might be due to the small sample size of that study (n=12 suicide attempters and n=12 controls) [40].

Figure 6. The comparison of Stability and Validity between recent suicide attempters and healthy controls



Discussion and conclusion

BDNF and attempted suicide

Plasma BDNF may reflect impulsiveness

The result of paper II suggests an inverse relationship between plasma BDNF and Solidity in recent suicide attempters. Low Solidity reflects changeability and impulsiveness. Furthermore, the Solidity scale has been suggested to be an inverse impulsiveness scale [37]. Therefore, this result could be interpreted as an association between lower plasma BDNF concentrations and higher levels of impulsiveness in recent suicide attempters.

Several previous studies have investigated the possible relationship between peripheral BDNF levels and personality dimensions in healthy subjects and patients with psychiatric disorders such as MDD or PTSD (Table 5). In contrary to our study, Martinotti and co-workers reported a significant positive correlation between BDNF levels in serum and BIS-scores in patients with PTSD [146]. However, they did not find any significant association between BDNF and BIS-scores in control subjects [146]. Furthermore, none of the remaining studies found any significant correlation between peripheral BDNF levels and impulsiveness as measured by the Impulsivity facet of the NEO-PI-R or the Impulsiveness subscale of the TCI (Table 5). The discrepancies between our and these studies may be due to differences in methodology. Specifically, the personality inventories used in the different studies are based on slightly different theoretical backgrounds (Table 5), the statistical analyses and BDNF assays differ. However, it is also possible that the negative association between plasma BDNF levels and impulsiveness may be limited to suicide attempters.

Suicidal behaviour has been suggested to be associated with higher levels of impulsiveness [22], and lower BDNF levels in brain areas such as the hippocampus and PFC or in blood (Table 3 and 4). In addition, some preclinical

studies have reported inverse association between BDNF concentration in the hippocampus and impulsiveness in rats [199, 200]. Furthermore, plasma BDNF levels have been found to correlate positively to hippocampal BDNF in rats [126]. Taken together, the results from our clinical study, along with some animal data, may support the notion that low BDNF levels are associated with impulsive behaviour although this need to be replicated in future large-scale studies.

Inverse relationship between HPA axis and BDNF in female suicide attempters

In paper III, we found low BDNF levels to be associated with HPA axis hyperactivity in female suicide attempters. In line with our results, a recently published study by Ma et al reported that poorer cortisol suppression in response to dexamethasone administration, were associated with lower levels of BDNF among healthy females [201]. Furthermore, similarly to our findings and the finding of Ma et al [201] Issa et al have observed negative correlations between glucocorticoids (corticosterone in animals and cortisol in humans) and BDNF in the hippocampus and CSF in rodents, as well as in humans [162]. As they have not investigated the relationship between glucocorticoids and BDNF separately in males and females, it is unclear whether there was a gender-related difference in the correlation. Although the correlation analysis does not confirm a causal relationship between the HPA axis and BDNF, the biological interaction between the HPA axis and BDNF may exist. It has repeatedly been suggested that elevated glucocorticoid levels, induced by medication, may cause a downregulation of BDNF gene expression in cortical and hippocampal brain regions [161]. Furthermore, preclinical studies investigating the effect of various type of stress in animals have suggested that the stress-induced increase in glucocorticoids may be responsible for the BDNF down-regulation in the hippocampus [161]. This is interesting in the light of the fact that the experience of adverse life events has been repeatedly linked to attempted suicide [21]. In conclusion, these results indicate that the observed decrease in BDNF in attempted suicide might be associated with the stress-induced increase in HPA axis activity.

In search for an explanation for why our findings were limited to female suicide attempters, we note that previous reports have suggested that gender may have an impact on the regulation of the HPA axis and on BDNF [113, 202, 203]. In addition, there is also evidence that the physiological response to stress may be

different between males and females [202]. Particularly, females appear to have a more rapid HPA axis response and produce larger output of stress hormones, as compared to males [202]. Furthermore, gender differences regarding stress-induced changes in BDNF and in the HPA axis have also been observed [204]. Specifically, one animal study reported that restrained stress led to higher corticosterone levels and decreased BDNF expression in the hippocampus among female mice compared to male mice [205]. Finally, similarly to our findings, Ma et al [201] have observed that the relationship between HPA axis activity and BDNF was limited to females. To sum up, in light of these findings, a gender-related association between HPA axis and BDNF might be plausible.

No association between BDNF, clinical and demographic variables in suicide attempters

Beside the prior investigation in paper II, there are other findings that deserve attention in that study. First of all, we did not find a significant difference in BDNF levels between suicide attempters with or without MDD diagnosis. This result is in line with post-mortem studies reporting no significant BDNF differences in the hippocampus between suicide victims with MDD and suicide victims with other psychiatric diagnosis than MDD [106, 107] (Table 3). This may indicate that BDNF is not associated with MDD in relation to suicidal behaviour.

Similarly to previous studies [106, 116] reporting no differences in BDNF levels in the brain or in the blood between violent and non-violent completed or attempted suicide, we did not find any difference in BDNF between violent and non-violent suicide attempters. This in turn indicates that BDNF may not be related to the use of violent or non-violent suicide methods.

Finally, there was no significant difference in BDNF levels between male and female suicide attempters in our study. This is surprising in the light of evidence suggesting a gender-related impact on vulnerability for suicidal behaviour [11, 12, 14, 112, 206], as well as on plasma BDNF concentrations [113, 141, 185, 207]. As previous studies did not compare plasma BDNF between male and female suicide attempters [116, 117], it is unclear whether the absence of gender-related difference in plasma is a general phenomenon in attempted suicide.

Met allele and the increased use of avoidant focused coping

In paper I, we investigated the possible association between BDNF Val66Met and avoidant focused coping strategies in clinical cohorts of suicide attempters. Our results suggest that suicide attempters carrying the Met allele use more avoidant focused coping strategies to deal with stress, compared to those with the genotype Val/Val independently of age, the symptom severity of depression or the time of the suicide attempt.

Previously, among university students, it has been found that students with the Met allele of the BDNF Val66Met had significantly higher scores on emotion focused coping, including among others avoidance, passive resignation, and wishful thinking compared to those with the Val/Val genotype [93]. In addition, another study also including non-psychiatric subjects reported that the Val/Met genotype was associated with higher levels of rumination compared to the Val/Val genotype [208]. This is interesting, as rumination and avoidance have been suggested to be similar phenomenon [209, 210]. However, in that study there was no significant difference in rumination between the Met/Met and Val/Val genotypes [208].

As was previously discussed in Introduction, the Val66Met gene polymorphism may be linked to suicidal behaviour [131]. Specifically, the Met allele appears to be associated with the history of attempted suicide in psychiatric patients [131]. In the light of that, our result raises the question whether the Met allele may contribute to the vulnerability to suicide through its association with decreased ability to deal with stress.

A possible explanation for the association between the Met allele and avoidant coping may come from genetic studies investigating the relationship between cognitive functioning and the SNP BDNF Val66Met. Specifically, the Met allele of this SNP has been associated with poorer performance during declarative memory and episodic memory tests [211]. This is very interesting in the light of that both avoidant coping strategies and attempted suicide have been linked to impairment in working and episodic memory including autobiographical memory [32]. Furthermore, a link between avoidant coping and impaired autobiographical recall has also been suggested [212]. Taken together, these findings raise the possibility that the Met allele may influence coping strategies indirectly via cognitive functions and deficits of autobiographical memory which in turn may

lead to the more frequent use of avoidant coping strategies. However, this remains a speculation and more research needs to be done to clarify this.

To sum up, our results may indicate that the involvement of the Val66Met in suicidal behaviour and the use of avoidant focused coping strategies are biologically plausible and worthy of further investigation. However, more studies are needed in order to replicate these findings.

Avoidant focused coping and suicidal behaviour

Avoidant focused coping, self-reported suicide risk and suicidal ideation

We found in paper IV that more use of avoidant focused coping was associated with more severe suicidal ideation, planning and the higher scores on the self-report instrument SUAS-S in both cohorts of suicide attempters, as well as in depressed patients. The significant positive correlations between avoidant coping strategies and total SUAS-S scores seemed to be independent of age, gender, the severity of depressive symptoms and comorbidity with personality disorder in all three cohorts. Furthermore, a significant correlation was observed between the increased use of avoidant focused coping and more severe suicidal ideation in all three cohorts. However, it is unclear whether the positive association between suicidal ideation and avoidant focused coping is irrespective of the above mentioned covariates. These findings indicates that psychiatric patients who use more avoidant focused coping may have higher suicide risk (measured by a self-report scale) and suicidal ideation independently of a history of attempted suicide which is in line with previous reports [55, 56, 59, 62-64, 70].

Association between Solidity and avoidant focused coping in attempted suicide

In paper V, we found a negative association between Solidity and avoidant focused coping in recent suicide attempters independently of age and gender but not among healthy controls. Low Solidity reflects changeability and impulsiveness. Furthermore, lower scores on Solidity have been found to be correlated with higher levels of personality traits associated with extraversion,

impulsiveness, aggressiveness and low impulse control [35, 36]. Considering these facts, our findings are in line with the results of a previous meta-analysis [84]. Specifically, the meta-analysis has suggested that low levels of personality traits reflecting problems with impulse control, self-discipline and self-control (Conscientiousness) were associated with more use of avoidant focused coping [84]. As this meta-analysis included mainly studies comprising non-psychiatric cohorts, the question is why the correlation between Solidity and avoidant-focused coping was limited to suicide attempters in our study. A possible explanation could be that the sample size of the control group was too small (smaller than suicide attempters) to detect any significant correlation. On the other hand, it is also possible that the association between avoidant focused coping and Solidity may be specific for suicide attempters.

Summarising, these results indicate that more use of avoidant focused coping is associated with lower levels of Solidity reflecting changeability and impulsiveness among suicide attempters.

Gender and avoidant focused coping in suicide attempters

Some evidence suggest that female and male patients with suicidal behaviour differ from each other in several vulnerability factors for suicide [112]. Interestingly, some studies suggest that gender may affect the way how to deal with stress [213]. Specifically, regarding avoidant focused coping, it has been found that males are more likely to use avoidant focused coping compared to females [213]. Considering these findings, a gender difference in avoidant focused coping could be expected in paper IV among suicide attempters. However, in the regression analyses including avoidant coping strategies as a dependent variable and age, gender, subgroups according to depression severity and comorbidity with PD as independent variables showed that gender was only significantly associated with avoidant focused coping in depressed patients but not in the cohorts of suicide attempters (Table 8). These results may indicate that gender has no importance for avoidant focused coping in suicide attempters.

Marke-Nyman Temperament scale

Is MNT of interest for suicide research?

In Paper V, similarly to the findings from two previous studies [38, 39], recent suicide attempters were characterized by significantly higher levels of Stability and lower levels of Validity, compared to healthy controls. As discussed in the Introduction, Sjöbring`s dimension shares theoretical similarities with Eysenck`s dimensions. Correlations between the subscales of MNT and EPQ`s have also been reported [35, 36]. Particularly, Validity has been found to be associated inversely with Eysenck`s Neuroticism scale [35, 36]. Furthermore, a negative correlation between Stability and the Extraversion of EPQ has been suggested [35, 36]. In light of these correlations, our results could be interpreted as suicide attempters are characterized by higher levels of neuroticism (low Validity) and more introversion (high Stability). In that case, these findings are in line with results of some previous studies that have used EPQ in order to assess personality dimensions [26, 214]. In these studies, suicide attempters have been reported to have significantly higher scores on the EPQ scale Neuroticism and lower scores on Extraversion scale, compared to those without attempted suicide [26, 214]. This in turn indicates that MNT may give similar results than EPQ in comparison studies of suicide attempters.

In conclusion, our study replicated previous results such as the association between attempted suicide, lower levels of Validity and higher levels of Stability. However, because of the small sample size in all studies including ours, it is not possible to draw any reliable conclusion. Therefore, the use of MNT in clinical practice is not recommended before the replication of these results in larger studies.

Limitations

This thesis has several limitations and most of these can be found in the papers. Here only some general limitations of the thesis will be discussed.

The most important limitation is that the thesis included mainly psychiatric patients who were admitted to a psychiatric ward following a suicide attempt

(recently or in the past). Therefore, the results cannot be generalised to all types of suicidal behaviour, for example to suicide attempters who never seek help or suicide victims. On the other hand, this limitation could also be considered a strength, as this group of patients belong to those with highest risk for future suicide. Therefore, our findings are highly important for both clinical use and suicide research.

Another important limitation is the overall small sample size. However, it must be mentioned that subjects who are admitted to psychiatric ward because of a recent suicide attempts represent a relative small group of psychiatric patients. Therefore, the recruitment takes time. For example, the recruitment of 300 suicide attempters (the first cohort of suicide attempters) has been taken approximately fourteen years. These numbers reflect well how difficult is to collect research data from this group of patients.

Future outlook

As discussed in the Introduction, suicidal behaviour is a global public health problem. Despite many years of research, the underlying pathophysiology of suicidal behaviour is still unclear.

Although the findings of this thesis cannot be immediately applied for clinical use they may have some important implications for suicide research. In Figure 9 the main results of the thesis, their relationship as well their indication for future use are presented.

Several suggestions are based on the results of paper IV, i.e. that the more frequent use of avoidant focused coping seems to be associated with higher suicide risk in psychiatric patients, independently of other vulnerability traits for suicidal behaviour. Interestingly, in non-psychiatric samples, avoidant focused strategies have been found to be associated with future suicide or suicidal ideation [65, 66]. These findings may raise the issue of whether the assessment of avoidant focused coping could be used to assess the risk of future suicide in psychiatric samples. Therefore, it would be of interest to perform longitudinal clinical studies in order to test whether avoidant focused coping predict future suicide in psychiatric patients. Furthermore, it would also be of interest to investigate whether psychotherapy with focus on reducing the use of avoidant focused coping strategies or replacing avoidant focused coping with alternative/adaptive strategies may reduce suicide risk among high-risk patients. Finally, the fact that avoidant coping may be a general vulnerability factor of suicidal behaviour (i.e. independent of clinical diagnosis or other suicide risk factors for example attempted suicide or gender) may strengthen the suggestion for the use of avoidant coping as a candidate intermediary phenotype for genetic association studies in suicide research.

The next suggestion is related to the findings indicating the inverse relationship between the HPA axis hyperactivity and BDNF among female suicide attempters. Although speculative, the inhibition of HPA axis activity might be a target in order to modulate BDNF levels in suicide attempters. Interestingly, several studies have

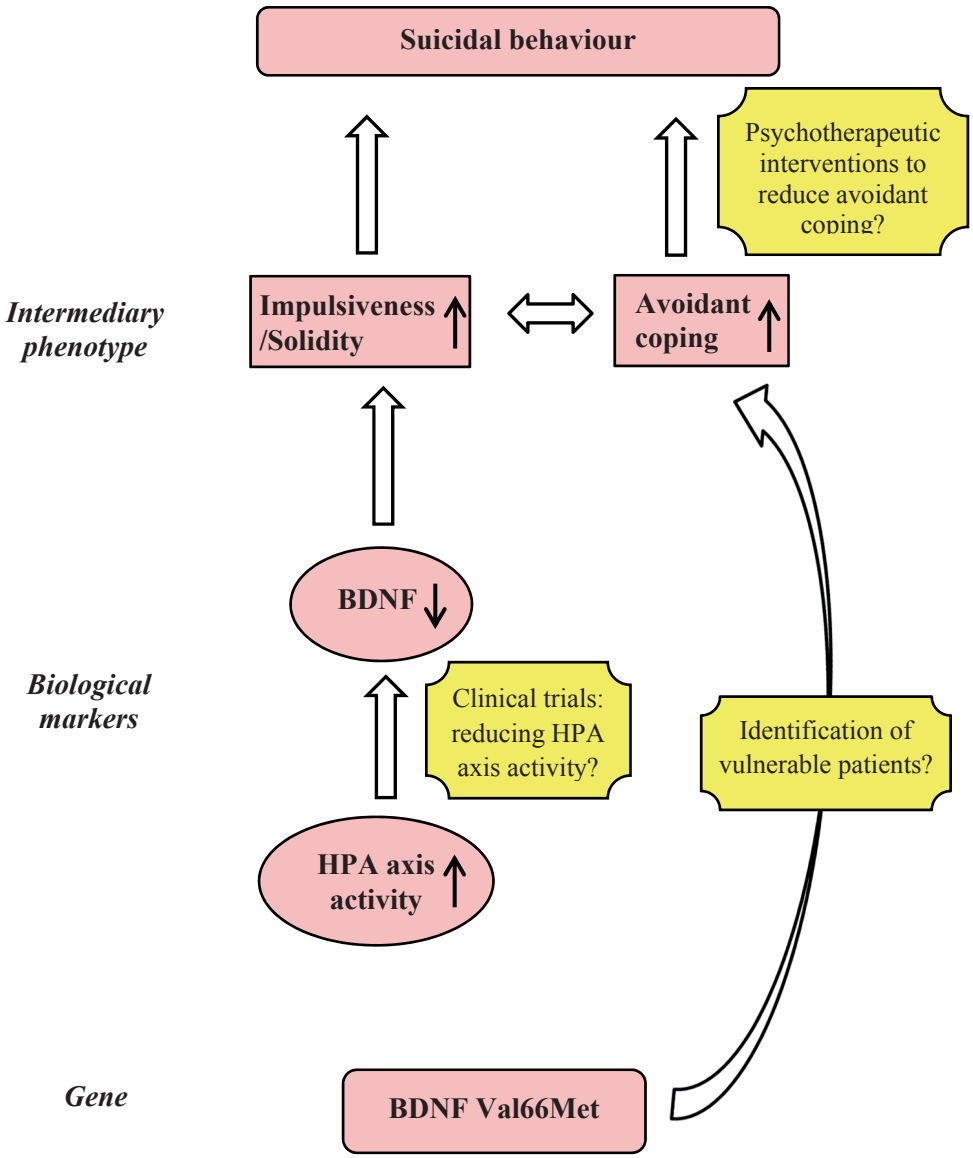
suggested that curcumin a polyphenol from the rhizome of turmeric (Curcuma longa L.) has anti-inflammatory, antioxidant and neuroprotective effect [215]. Furthermore, it has also been thought that the neuroprotective effect of curcumin may occur through the regulation of corticosterone [216-218]. Particularly, curcumin has been found to ameliorate the stress-induced reduction of BDNF in animal (including rats and pigs) brain [216, 217], possibly through the inhibition of stress-induced corticosterone increase [216, 218]. Considering the results of a previous epidemiology study, curcumin appears to have a positive effect on cognition [219]. Furthermore, findings from clinical studies may suggest that medication with curcumin improved the mood in healthy older population [220] or reduced depressive symptoms in depressed patients [215, 221]. In addition, the treatment with curcumin in depressed patients has been associated with cortisol reduction [222]. Considering evidence in reference to our results, an interesting research issue could be whether curcumin might reduce the suicide risk in female suicide attempters through affecting BDNF and HPA axis regulation.

The genetic approach of suicidal behaviour is a relatively new issue in suicide research. As genetic information does not change over time, the use of genetic marker(s) in order to identify vulnerable persons regarding suicide could be a promising method. In the light of that, the result of the first paper may have importance for future genetic association studies.

In addition, there are some suggestions that are not directly linked to the findings of the thesis but are highly relevant for future research. As it is discussed in the Introduction, the results of studies investigating the possible association between BDNF and attempted suicide are inconsistent (Table 2). Furthermore, these inconsistencies may be due to the methodological differences between the studies. This in turn leads to what we actually miss, that is, a method that eventually could be useful to identify patients with high suicide risk. Therefore, it is time we should come to a consensus to use the same method regarding BDNF analysis. Furthermore, not only BDNF (mature BDNF) appears to be biological active but also the pro-BDNF and BDNF pro-peptide (Figure 2) [104]. Interestingly, alterations in both pro-BDNF and BDNF (mature) have been suggested to be linked to psychiatric disorders known as risk factors for suicidal behaviour [223, 224]. Therefore, it would be of interest to investigate whether there may be alterations regarding pro-BDNF in suicidal behaviour.
Moreover, the fact that female suicide attempters may differ from male suicide attempters in pathophysiology strengthens the gender paradox in suicidal

behaviour. This in turn indicates that suicide research must also focus on male and female suicidal behaviour separately.

Figure 7. Summary of results and future indications



Populärvetenskaplig sammanfattning på svenska

Introduktion

I Sverige dör varje år cirka 1500 personer på grund av självmord och ca 10 gånger fler försöker ta sina liv. Hos svenska unga vuxna är självmord den andra vanligaste dödsorsaken. Trots mångårig forskning är orsakerna bakom självmord inte tillräckligt utredda.

Psykisk sjukdom är en betydande riskfaktor för självmord, inte minst bland dem som har gjort ett självmordförsök. Av den andledningen är psykiatriska patienter som tidigare gjort självmordsförsök en särskilt viktig grupp att studera för att förstå olika orsaker bakom självmord.

Det finns redan en hel del kunskap om dessa patienter. Till exempel har tidigare forskning visat att det är vanligare att patienter som gjort självmordsförsök skiljer sig från patienter som aldrig gjort något självmordsförsök i flera psykologiska faktorer. Bland annat, patienter som har gjort ett självmordsförsök karakteriseras av impulsivt temperament jämfört med patienter som aldrig gjort något självmordsförsök. Dessutom finns det flera studier som har visat att patienter som nyligen gjort ett självmordsförsök i större utsträckning än andra använder sig av undvikande copingstrategier när de ska hantera svåra/stressfulla situationer. Det finns även fler välkända biologiska faktorer som sannolikt ökar en persons sårbarhet och som därmed kan öka risken att hen tar sitt liv.

Av särskilt intresse är hjärnans strukturella funktion och nervcellernas förmåga till överlevnad. Brain-derived neurotrophic factor (BDNF) är ett protein som tillhör gruppen tillväxtfaktorer. Det är ämnen som har betydelse för hjärnans funktion och utveckling. BDNF samverkar också med biologiska system som har satts i förbindelse med till självmordsrisk till exempel hypotalamus-hypofys-binjurebarks axeln den sk HPA-axeln. Låga nivåer av BDNF i plasma har tidigare kopplats till både självmordrisk och självmordsförsök. Det finns också bevis för ett samband mellan en särskildvariant av den gen som kodar för BDNF (BDNF Val66Met) och självmordsförsök.

Avsikten med den här avhandlingen var att fördjupa kunskaperna om samband mellan BDNF, HPA-axeln, och riskfaktorer för självmord hos patienter som gjort självmordförsök. I avhandlingen undersöktes även om undvikande coping-strategier kan kopplas till högre suicid risk, suicidtankar eller personlighetsdrag med betydelse för självmordsrisk. Avhandlingen består av fem olika delarbete med följande specifika frågeställningar:

Arbete 1

Att undersöka om genvarianter med Met allelen av BDNF Val66Met kan förknippas med undvikande problemlösning strategier hos patienter som gjort självmordsförsök.

Arbete 2

Att undersöka om det finns samband mellan BDNF mätt i plasma, kliniska symptom och personlighetsdrag hos patienter som gjort självmordsförsök.

Arbete 3

Att undersöka om det finns ett samband mellan BDNF och HPA-axeln hos patienter som nyligen gjort ett självmordsförsök.

Arbete 4

Att undersöka om självmordsrisk har samband med användandet av undvikande copingstrategier hos patienter som har gjort självmordsförsök.

Arbete 5

Att undersöka om det finns ett samband mellan personlighetsdimensioner och undvikande copingstrategier hos psykiatriska patienter som nyligen har gjort ett självmordsförsök.

Material och metoder

Arbete 1

BDNF Val66Met gene polymorfismen analyserades i två olika grupper av patienter med självmordsförsök: en grupp med ett nyligt självmordsförsök och en grupp som har följts upp 12 år efter ett självmordsförsök. Copingstrategier undersöktes med hjälp av Coping Orientations to Problems Experienced scale (COPE).

Arbete 2

BDNF i plasma analyserades hos 61 drogfria patienter som nyligen gjort ett självmordsförsök. Kliniska symptom undersöktes med hjälp av Comprehensive Psychopathological Rating Scale (CPRS). Personlighetsdragen har undersökt med hjälp av Marke-Nyman Temperament Skala (MNT).

Arbete 3

BDNF i plasma och HPA-axel aktiviteten undersöktes hos patienter som nyligen gjort ett självmordförsök. Aktiviteten i HPA-axeln hos de enskilda individerna utreddes med hjälp av det sk Dexametason Suppressions Testet (DST). Det är ett test på individens förmåga att bromsa kortisolnivåerna i blodet. De individer som har höga kortisolnivåer i samband med undersökningen kallas ”nonsuppressorer” och bedöms ha en onormalt hög HPA-axelaktivitet.

Arbete 4

Tre kohorter av psykiatriska patienter involverades: 55 patienter med nyligt självmordförsök, 72 patienter med långvarig depression utan självmordförsök och 36 patienter som har följts upp 12 år efter ett självmordsförsök. Patienterna undersöktes med hjälp av COPE, den svenska versionen av Suicide Assesment Scale (SUAS-S) och CPRS.

Arbete 5

56 patienter med ett nyligt självmordsförsök och 36 friska kontroller har involverats. Personlighetsdragen undersöktes med hjälp av MNT. För att undersöka copingstrategier användes den COPE.

Resultat

Arbete 1

De patienter som någonsin gjort ett självmordsförsök och bär på Met allelen i BDNF Val66Met genen använder sig i högre grad av undvikande copingstrategier jämfört med andra, oberoende av ålder och depressiva symptom.

Arbete 2

BDNF-nivåerna i plasma korrelerade signifikant med personlighetsdrag som speglar impulsivitet men inte med symptom på depression eller ångest hos patienter som nyligen gjort ett självmordsförsök.

Arbete 3

I arbete 3 fann jag samband mellan hyperaktivitet av HPA-axeln och lägre BDNF nivåer hos kvinnor som nyligen har gjort ett självmordförsök men inte hos män.

Arbete 4

I arbete 4 hittade jag att psykiatriska patienter som använder flera undvikande problemlösningsstrategier skattar högre på en skala som mäter självmordsrisk samt har högre poäng på enskilda frågor om självmord och självmordsplaner. Detta verkade vara oberoende av andra risk faktorer för självmord såsom depressiva symptom, kön, ålder och personlighetsstörning.

Arbete 5

Hos patienterna som nyligen har gjort ett självmordförsök korrelerade undvikande copingstrategier signifikant med personlighetsdrag som karakteriseras av högre grad av impulsivitet och dålig självkontroll. Denna korrelation fanns inte hos friska kontroller.

Diskussion

Fynden i avhandlingen talar för att hos psykiatriska patienter finns det samband mellan en disposition till användning av undvikande copingstrategier och självmordsbenägenhet, oberoende av en del andra riskfaktorer för självmord. Det stämmer överens med vad man sett i tidigare studier. Helt nya fynd är att patienter som har en viss variant av *BDNF* genen kan tänkas ha en benägenhet att använda sig av mer undvikande copingstrategier i samband med stress samt att undvikande copingstrategier tycks ha samband med personlighetsdrag som speglar impulsivitet. Det är särskilt intressant då impulsivitet är en välkänd riskfaktor för suicid.

Ett annat intressant fynd i avhandlingen är att bland patienterna som har gjort självmordsförsök var lägre BDNF nivåer kopplade till högre grad av impulsivitet. Det kan därmed tänkas personer vars reglering av BDNF inte fungerar optimalt i större utsträckning är impulsiva varför BDNF skulle kunna ha betydelse för självmordsrelaterat beteende. Fyndet i avhandlingen angående sambandet mellan BDNF och HPA-axel hos kvinnliga patienter som nyligen har gjort självmordförsök talar för att samverkan mellan BDNF och HPA-axeln skulle kunna ha betydelse för dessa patienter. Att vi hittade sambandet mellan BDNF och HPA-axel enbart hos kvinnor väcker också frågan om kvinnor skiljer sig från män vad gäller de biologiska processer som medför sårbarhet för självmordsrelaterat beteende.

Sammantaget innebär avhandlingens resultat kunskap som i framtiden kan leda till förbättrade metoder vad gäller bedömning av självmordsbenägenhet och nya behandlingar med syftet att minska en persons självmordrisk. Exempelvis skulle skattning av en persons undvikande copingstrategier och kanske testning av olika genvarianter av *BDNF* gen i framtiden kunna bli en del i den kliniska utredningen av personer som gjort ett självmordsförsök. Det finns skäl att tro att psykoterapi med fokus på att förbättra patienternas copingstrategier skulle kunna leda till minskad självmordrisk. För att veta det behövs studier designade för att finna svar på den typen av frågeställningar.

Appendix

Appendix I: COPE items reflecting avoidant focused coping

Here the COPE [53] items belonging to avoidant focused coping are presented.

Mental disengagement

I turn to work or other substitute activities to take my mind off things.
I daydream about things other than this.
I sleep more than usual.
I go to movies or watch TV, to think about it less.

Behavioural disengagement

I admit to myself that I can't deal with it, and quit trying.
I just give up trying to reach my goal.
I give up the attempt to get what I want.
I reduce the amount of effort I'm putting into solving the problem.

Denial

I say to myself "this isn't real."
I refuse to believe that it has happened.
I pretend that it hasn't really happened.
I act as though it hasn't even happened.

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Paper I

Paper II

Paper III

Paper IV

Paper V