



Department of Child and Adolescent Psychiatry and Psychotherapy

**From Symptom to Diagnostic Entity –
Strengthening Diagnostic Validity of
Non-Suicidal Self-Injury Disorder**

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Rebecca Brown (née Groschwitz)

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Acting dean: Prof. Dr. Frank Kargl

Reviewer: Prof. Dr. Paul L. Plener

Reviewer: Prof. Dr. Christian Schmahl

Reviewer: Prof. Dr. Tina In-Albon

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Abbreviations

5-HT	5-Hydroxytryptamin
5-HTTLPR	serotonin-transporter-linked polymorphic region
ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
APA	American Psychiatric Association
BDI-II	Beck Depression Inventory-Revision
BPD	borderline personality disorder
BSI	Brief Symptom Inventory
CANDI	Clinician-Administered NSSI Disorder Index
CBT	cognitive behavioural psychotherapy
CDRS-R	Children's Depression Rating Scale-Revised
CSF	cerebrospinal fluid
DBT	Dialectical Behavioral Therapy
DBT-A	Dialectical Behavioral Therapy for adolescents
dIPFC	dorsolateral prefrontal cortex
DSH	deliberate self-harm
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
HPA	hypothalamic-pituitary-adrenocortical
IAPS	International Affective Picture System
ICD	International Classification System of Diseases
ISAS	Inventory of Statements about Self-Injury
IQ	intelligence quotient
MBT	Mentalization based treatment
MBT-A	Mentalization based treatment for adolescents
MINI-DIPS	Diagnostic Interview for Mental Disorders – Short version
mPFC	medial prefrontal cortex
NSSI	non-suicidal self-injury
NSSID	non-suicidal self-injury disorder
OFC	orbitofrontal cortex
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
SBD	suicidal behavior disorder
SD	standard deviation
SEYLE	Saving and Empowering Young Lives in Europe
sgACC	subgenual anterior cingulate cortex
SHBQ	Self-Harm-Behavior-Questionnaire
SITBI	Self-Injurious-Thoughts-and-Behaviors-Interview
SITBI-G	Self-Injurious-Thoughts-and-Behaviors-Interview-German

SPM	Statistical Parametric Mapping
TAU	psychiatric treatment as usual
vACC	ventral anterior cingulate cortex
vIPFC	ventrolateral prefrontal cortex
WHO	World Health Organization
WL	wait list

Abstract

Non-suicidal self-injury (NSSI) has been suggested as independent diagnosis in Section three of the DSM-5. Although international research in recent years has been able to further the knowledge about this proposed disorder, there is still an ongoing discussion about its inclusion in classification systems. In 1970, Robins and Guze published guidelines for the validation of disorders. The present thesis includes five publications which follow those guidelines, in order to further the discussion about NSSI disorder (NSSID). The first publication included in this thesis is the first to describe the prevalence of NSSID in a representative sample in the general population of Germany. Although the prevalence of present NSSID shows to be around 0.3%, lifetime prevalence of NSSI is as high as 3% and NSSID is significantly more common in younger age groups. The second publication included in this thesis presents the validation of a structured clinical interview for NSSID. The Self-Injurious-Thoughts-and-Behaviors-Interview-German (SITBI-G) shows good reliability for assessing most diagnostic criteria of NSSID. However, it does not assess criterion E (clinically significant distress caused by NSSI) and is extensive in its use of time. The third study of this thesis investigates differences in neural processing of social exclusion in adolescents with major depression and with or without co-morbid NSSID. Adolescents with NSSID show differential processing in the medial prefrontal cortex and the ventrolateral prefrontal cortex, which could point to a hypersensitivity to social exclusion in adolescents with NSSID. The fourth study included in this thesis distinguishes NSSID from suicidal behavior disorder (SBD). Differences in methods, frequency and functionality of NSSID and SBD were found. The fifth study includes young adults who had engaged in NSSI as adolescents. While 50% of the sample still engaged

in NSSI, 70% met criteria for an axis 1 psychiatric disorder and 50% were diagnosed with borderline personality disorder (BPD).

Overall, results of this thesis show that NSSID is prevalent rather in young adults or adolescents, validated assessment tools for NSSID exist, NSSID can be differentiated from major depression, SBD, and BPD; and that adolescents engaging in NSSI are at high risk for psychological impairment into their young adulthood. Although further research is still needed in order to validate certain criteria of NSSID, results of this thesis point towards the validity of NSSID.

Zusammenfassung

Nicht-suizidales selbstverletzendes Verhalten (NSSV) wurde als eigenständige Diagnose im Klassifikationssystem DSM-5 vorgeschlagen. Obwohl internationale Studien das Wissen über diese vorgeschlagene Diagnose verbessern konnten, besteht eine anhaltende Diskussion darüber, ob NSSV als eigenständige Diagnose in Klassifikationssysteme aufgenommen werden soll. Robins und Guze formulierten 1970 verschiedene Phasen der Validierung einer Diagnose. Die vorliegende Dissertation enthält fünf Publikationen, die die diagnostische Validität der NSSV-Störung (NSSVS) anhand dieser Phasen untersucht. Die erste Publikation dieser Dissertation ist die bisher erste Studie, die die Prävalenz von NSSVS in einer repräsentativen Stichprobe der Allgemeinbevölkerung Deutschlands beschreibt. Obwohl nur 0,3% der Teilnehmer aktuell die Diagnosekriterien der NSSVS erfüllten, lag die Lebenszeitprävalenz von NSSV bei 3%. NSSVS trat zudem signifikant häufiger in jüngeren Altersgruppen auf. Die zweite Publikation dieser Dissertation präsentiert die Validierung eines strukturierten klinischen Interviews für NSSVS. Das Self-Injurious-Thoughts-and-Behaviors-Interview-German (SITBI-G) zeigte gute Reliabilitäten für die meisten Kriterien der NSSVS. Allerdings erfasst es nicht Kriterium E (klinisch signifikante Einschränkungen verursacht durch NSSV) und ist relativ zeitintensiv. Die dritte Studie dieser Dissertation untersuchte Unterschiede in der neuronalen Verarbeitung von sozialem Ausschluss von Jugendlichen mit der Diagnose einer depressiven Episode mit oder ohne komorbider NSSVS. Jugendliche mit NSSVS zeigten eine abweichende Verarbeitung im medialen präfrontalen Kortex und ventrolateralen präfrontalen Kortex, was auf eine erhöhte Sensitivität für sozialen Ausschluss bei Jugendlichen mit NSSVS hinweisen könnte. Die vierte Studie dieser Dissertation grenzt NSSVS von der suizidalen Verhaltensstörung (SVS) ab. Es wurden

Unterschiede hinsichtlich der gewählten Methoden der Selbstverletzung, der Frequenz des Verhaltens und der Funktionalität gefunden. Die fünfte Studie dieser Dissertation untersuchte junge Erwachsene, die sich als Jugendliche selbstverletzt hatten. Während sich 50% der Teilnehmer noch immer selbst verletzten, erfüllten 70% die Kriterien einer Achse I Störung und 50% wurden mit einer Borderline Persönlichkeitsstörung (BPS) diagnostiziert.

Insgesamt zeigen die Ergebnisse dieser Dissertation, dass NSSVS vor allem bei jüngeren Erwachsenen oder Jugendlichen auftritt, ein validiertes Interview zur Diagnostik der NSSVS existiert, dass NSSVS von einer depressiven Episode, einer SBD und einer BPS abgegrenzt werden kann und dass Jugendliche mit NSSV ein hohes Risiko für die Entwicklung psychischer Störungen im Erwachsenenalter haben. Obwohl weitere Studien notwendig sind, um die Kriterien der NSSVS weiterhin zu validieren, deuten die Ergebnisse dieser Dissertation auf die Validität der NSSVS hin.

From Symptom to Diagnostic Entity - Strengthening Diagnostic Validity of Non-Suicidal Self-Injury Disorder

1 General introduction

Non-suicidal self-injury (NSSI) is defined as the intentional, direct, and self-inflicted destruction of body tissue without suicidal intent, that is not socially sanctioned (Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007). The definition of NSSI specifically only includes intentional behaviors (i.e. no accidental self-injury) and direct destruction of body tissue (exclusion of i.e. eating disorders, drug abuse). Most common methods of NSSI are cutting, scratching, banging/hitting, carving, and scraping (Zetterqvist, 2015). Socially sanctioned self-injuries (i.e. tattooing or piercing) are explicitly excluded from this definition. NSSI is a widespread phenomenon in adolescence and has steadily gained interest of international researchers during the course of the past 15 years. Recently, NSSI has been included as independent diagnosis in Section III (*Conditions for Further Study*) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; (American Psychiatric Association, 2013)). Three recent reviews (In-Albon, 2015; Selby, Kranzler, Fehling, & Panza, 2015; Zetterqvist, 2015) report first evidence emerging from literature on NSSI as independent diagnosis in the DSM-5, but call for more research in order to achieve diagnostic validity for NSSI disorder (NSSID). This thesis comprehends an overview of current literature on NSSID and presents five original manuscripts aiming to improve diagnostic validity of NSSID.

1.1 Considering NSSI as diagnostic entity

In the international classification for diseases, 10th edition (World Health Organization, 1992), the diagnostic nomenclature of NSSI is limited to a symptom of Borderline Personality Disorder (BPD), or to 'intentional self-harm (X78)' in Chapter XX 'external causes of morbidity and mortality – intentional self-harm'. However, NSSI does not only occur as symptom of BPD, but is rather co-existent to a number of axis 1 disorders (i.e. depression, anxiety disorders, eating disorders), and can lead to significant functional impairment and negative consequences without any comorbid psychopathology (Andover, 2014; Jacobson & Gould, 2007; Klonsky, 2011; Klonsky, May, & Glenn, 2013; Stanford & Jones, 2009; Turner, Chapman, & Layden, 2012).

Therefore, discussions about including NSSI as a distinct diagnostic entity have been ongoing for several decades. In 1972, Rosenthal and colleagues termed the phenomenon of repeated wrist cutting without suicidal intent *wrist cutting syndrome*. A first proposal for a *deliberate self-harm syndrome* was brought forward in the early 1980s by Kahan and Pattison (Kahan & Pattison, 1984; Pattison & Kahan, 1983). Following this proposal, the inclusion of deliberate self-harm, or NSSI, in diagnostic manuals as separate diagnostic entity has been discussed repeatedly (Favazza & Rosenthal, 1993; Muehlenkamp, 2005). In 2009, Shaffer and Jacobson proposed NSSI disorder criteria to the DSM-5 Childhood Disorder and Mood Disorders work group for inclusion as a disorder (Shaffer & Jacobson, 2009). Shaffer and Jacobson's criteria have been slightly revised and have now been included in section 3, condition for further study, of the DSM-5 (American Psychiatric Association, 2013). Section 3 of the DSM-5 includes suggested diagnostic entities, which are still in need of validation, before being considered fully acknowledged disorders.

The inclusion of NSSI in the DSM-5 has provoked controversial discussions. For example, Kapur and colleagues (2013) and De Leo (2011) raised concerns about considering NSSI and suicidality as two dichotomous criteria (divided by the intent to die). They argue that NSSI and suicide attempts should rather be considered on a continuum of self-harming behaviors, as NSSI has been shown to be a robust risk factor for suicide attempts (for details see chapter 1.5.2). Furthermore, they raise the concern of clinicians possibly underestimating the risk of self-injury, when regarding it as solely non-suicidal, without considering co-existing suicidality. Moreover, classifying a behavior as a distinct disorder, without effective treatments in existence (for details see chapter 5.2) is seen as a major problem. As a further concern, the risk of potentially stigmatizing a large number of adolescents as mentally ill, although the behavior ceases in later adolescence or early adulthood in most affected adolescents, has been brought to mind (De Leo, 2011; Kapur, et al., 2013).

On the other hand, advantages of regarding NSSI as independent diagnoses are manifold. A distinctive definition of NSSI would facilitate communication among researchers and clinicians (Muehlenkamp, 2005). Research would be more comparable concerning prevalence rates, etiology, and the longitudinal course of NSSI. Moreover, not distinguishing between NSSI and suicidal behaviors often leads to false case conceptualization and unwarranted hospitalization of patients, if their NSSI is classified as suicidal (Glenn & Klonsky, 2013). Furthermore, by classifying NSSI uniquely as a symptom of BPD, many patients are labeled, and therefore treated, inaccurately (Wilkinson & Goodyer, 2011). The recognition of NSSI as independent disorder would therefore help to encourage the development and evaluation of clinical assessment tools and treatment programs specifically for NSSI. On a last note, considering health insurance

systems in many countries, treatment of NSSI is currently only possible when the comorbidity of an axis 1 or axis 2 disorder is prevalent. Therefore, treatment of patients who are clinically distressed by engaging in NSSI, but do not meet criteria for other psychiatric disorders would be facilitated by the recognition of NSSID (Wilkinson & Goodyer, 2011).

1.2 Methods of establishing diagnostic validity

The question whether a behavioral or psychological syndrome warrants the definition of a psychiatric disorder has been discussed repeatedly throughout the years. In order not to over stigmatize human behavior, Stein and colleagues (2010) propose several features a psychiatric diagnosis should encompass. Besides resulting in clinically significant distress or disability, the behavioral or psychological pattern should also not be an expectable response to stressors or losses, or a culturally accepted behavior (i.e. within a religious ritual). It should also reflect an underlying psychobiological dysfunction, not solely be result of social deviance as well as incorporate diagnostic validity and clinical utility.

In 1970, Eli Robins and Samuel B Guze suggested a method consisting of five phases to achieve diagnostic validity for psychiatric illnesses (Robins & Guze, 1970): (1) clinical description, (2) laboratory study, (3) exclusion of other disorders, (4) follow-up study, and (5) family study. The first phase, *clinical description*, suggests the description of a clinical picture. The clinical picture should not only include symptoms of the proposed disorder, but also epidemiological features like age of onset, differences in race, sex, and precipitating factors of the disorder. The second phase, *laboratory studies*, includes all chemical, physiological, radiological and anatomical (i.e. biopsy or autopsy) studies. In this phase, Robins and Guze also include the use of psychological tests, if they have been

shown to be reliable. The use of structured clinical interviews in order to establish diagnostic validity is strongly recommended by Aboraya et al. (2005). In phase three, *exclusion of other disorders*, exclusion criteria should be defined in order to exclude disorders presenting with similar symptoms to create a homogenous diagnostic entity. To determine the homogeneity of a diagnostic entity, the longitudinal course is to be investigated in phase four, *follow-up study*. Robins and Guze argue that very heterogenic long-term outcomes do not completely contradict the existence of a diagnostic entity, but do challenge the validity of a homogenous diagnosis (as long as etiological and pathological details of the disorder are not known). In addition to naturalistic follow-up studies, (Kendell, 1989) and (Kendler, 1980, 1990) proposed treatment response as a further validity criterion for diagnostic consistency over time. As a last phase, Robins and Guze suggest the utilization of *family studies*, as prevalence of the same diagnosis in close family members would increase diagnostic validity independent of its etiology (hereditary or environmental).

2 Validity of NSSI criteria

The following thesis reviews current literature on NSSI and presents five original studies on NSSI following the five phases of establishing diagnostic validity by Robins and Guze (1970).

2.1 Clinical description of NSSI (Phase 1)

2.1.1 Description of symptoms

As mentioned above, NSSI was added to the DSM-5, section 3 condition for further study, as autonomous diagnostic entity. Table 1 presents the proposed diagnostic criteria.

Table 1: Proposed criteria for Non-suicidal Self-Injury in the DSM-5, section 3 (American Psychiatric Association, 2013, p. 803)

A. In the last year, the individual has, on 5 or more days, engaged in intentional self-inflicted damage to the surface of his or her body of a sort likely to induce bleeding, bruising, or pain (e.g. cutting, burning, stabbing, hitting, excessive rubbing), with the expectation that the injury will lead to only minor or moderate physical harm (i.e., there is no suicidal intent).

Note: The absence of suicidal intent has either been stated by the individual or can be inferred by the individual's repeated engagement in a behavior that the individual knows, or has learned, is not likely to result in death.

B. The individual engages in the self-injurious behavior with one or more of the following expectations:

1. To obtain relief from a negative feeling or cognitive state.
2. To resolve an interpersonal difficulty.
3. To induce a positive feeling state.

Note: The desired relief or response is experienced during or shortly after the self-injury, and the individual may display patterns of behavior suggesting a dependence on repeatedly engaging in it.

C. The intentional self-injury is associated with at least one of the following:

1. Interpersonal difficulties or negative feelings or thoughts, such as depression, anxiety, tension, anger, generalized distress, or self-criticism, occurring in the period immediately prior to the self-injurious act.
2. Prior to engaging in the act, a period of preoccupation with the intended behavior that is difficult to control.
3. Thinking about self-injury that occurs frequently, even when it is not acted upon.

D. The behavior is not socially sanctioned (e.g., body piercing, tattooing, part of a religious or cultural ritual) and is not restricted to picking a scab or nail biting.

E. The behavior or its consequences cause clinically significant distress or interference in interpersonal, academic, or other important areas of functioning.

F. The behavior does not occur exclusively during psychotic episodes, delirium, substance intoxication, or substance withdrawal. In individuals with a neurodevelopmental disorder, the behavior is not part of a pattern of repetitive stereotypies. The behavior is not better explained by another mental disorder or medical condition (e.g., psychotic disorder, autism spectrum disorder, intellectual disability, Lesch-Nyhan syndrome, stereotypic movement disorder with self-injury, trichotillomania, excoriation disorder).

As DSM-5 criteria have only been proposed recently, only a limited number of studies have investigated the validity of NSSID thus far. In a recent review of the literature, Maria Zetterqvist (2015) found 16 empirical studies using criteria of NSSID. However, only four of those studies used the final DSM-5 criteria, while the other studies used the original criteria of Shaffer and Jacobson (2009). Of all studies, only five had assessed all criteria

of NSSID. Therefore, conclusions about the validity of NSSID are still indefinite. Overall, most studies found good evidence for criterion A, with some studies suggesting a different figure for the frequency of NSSI (i.e. 11 times within the last year; (Zetterqvist, Lundh, & Svedin, 2013b) being discussed. Washburn et al. (2015) also mentioned a possible overestimation of criterion A, as some instruments assess methods of NSSI that may not lead to bleeding, bruising, or pain, and therefore suggest an exclusion of such methods from validated instruments (i.e. hair pulling). Criterion B (expected effect of NSSI) and C (antecedent of NSSI) were very commonly endorsed in all studies. Washburn et al. (2015) questioned the necessity of separate criteria B and C, as criterion B cannot occur without criterion C. They therefore suggest a merge of both criteria. Interestingly, most often criteria B1 and correspondingly C1 (relief from negative feelings after NSSI and interpersonal distress and/or negative feelings or thoughts prior to NSSI) were met, while criteria B2, B3, C2, and C3 were less common (Andover, 2014; Zetterqvist, et al., 2013b). Taking it a step further, Brausch, Muehlenkamp and Washburn (2016) called the clinical utility of criterion B into question. In two samples of individuals who had engaged in NSSI within the last year, 99.4% and 98.5%, respectively, reported at least one function of NSSI. The presence of functions in general did not separate groups of participants who met criterion A (at least 5 times of NSSI within the past 12 months) or did not (1-4 times NSSI). However, participants who met criterion A, rated intrapersonal functions to be significantly more relevant and reported more functions in total than those participants not meeting criterion A. Therefore, the authors suggest including more specific functions to criterion B (i.e. affect regulation or self-punishment), but also strongly suggest further research in order to validate criterion B further. This is in line with Selby (2015), who suggested a more

detailed validation of social and automatic positive functions to be included or excluded from NSSID criteria in future studies.

Another criterion which is discussed in a number of studies, is criterion E (the behavior causing significant distress). Especially in adolescent samples, NSSI was often viewed as helpful in order to reduce distress, rather than evoking it. However, Gratz et al. (2015) found criterion E to be the most valid distinguishing criterion between participants engaging in NSSI, but not meeting all criteria for NSSI disorder. In this clinical sample of 107 self-injuring adolescents, 37% met all criteria for NSSI disorder. While most participants (77-91%) met criteria A, B, C, D, and F, only 41% met criterion E. One other study investigating all criteria of NSSID was conducted in a sample of female adolescent inpatients (N=73) (In-Albon, Ruf, & Schmid, 2013b). Overall, results of this study support the usefulness and necessity of the classification of NSSI as distinct disorder. The authors conclude that NSSI seems to be a highly impairing behavior and that participants with NSSI showed high levels of comorbidity with other psychiatric disorders. However, 29% of participants engaging in NSSI did not meet criterion E by denying impairment or distress caused by NSSI. The authors stress that impairment or distress is not easy to operationalize objectively, as also stated by Plener and Fegert (2012). Interestingly, when the authors asked whether participants thought they required help for their NSSI, 80% of the total sample (and 30% of those not reporting distress/impairment from NSSI) reported a need for help to deal with NSSI.

In a different approach, Lengel and Mullins-Sweatt (2013) investigated the validity of NSSI criteria by asking researchers who had published at least one paper concerning NSSI/self-harm and practicing clinicians (N=119) on their opinion about NSSID criteria. However, criterion E was criticized, as the cause of significant distress was not rated to be

prototypical for NSSI. A low participation rate of around 10% has to be considered, when interpreting results of this study. In total, participants rated NSSI criteria as feasible and valid.

Regarding results of those studies, criterion E seems to be important for the validity of the disorder, but might have to be operationalized differently in studies and clinical practice (i.e. by including reports from parents or other caregivers or considering objective measures of psycho-social functioning like school performance or participation in social activities). In summary, criteria of NSSID seem to be mostly valid. Some discussion remains about the frequency threshold of NSSID, the validity of social functions and positive automatic functions, the necessity of having both, criteria B and C, and the assessment of criterion E (Selby, et al., 2015; Zetterqvist, 2015).

2.1.2 Prevalence of NSSI

To date, only a few studies report prevalence rates of NSSID. In her systematic review, Maria Zetterqvist (2015) found prevalence rates for NSSID ranging from 1.5 to 6.7% in child and adolescent community samples. In adolescent and young adult samples of psychiatric patients, 37-50% met criteria for NSSID. Across all studies, 46-78% of those adolescents with a history of NSSI met criteria for NSSID. Most studies reported more girls than boys meeting NSSID criteria and the average age of onset was consistent across all studies (mean age of onset = 12.52-13.05 years, (Zetterqvist, 2015)). No geographical differences were found when comparing two studies (one from the US, one from Germany) using NSSID definition (Glenn & Klonsky, 2013; Kaess et al., 2013). Both studies found prevalence rates of around 50% in clinical samples. In an online sample of

the general adult population (N=548), Andover (2014) found a prevalence of 3% for NSSID. Of those with a history of NSSI, 11% currently met NSSID criteria.

When not applying NSSID-criteria, prevalence rates of NSSI are highly heterogeneous across studies. This seems to be mainly due to methodological differences, which account for around half of the differences in prevalence rates across studies (Swannell, Martin, Page, Hasking, & St John, 2014). Higher prevalence rates were associated with a checklist listing different methods, a greater number of specified methods, incentives for participation, anonymity, questionnaires, and if the research focus was specifically on NSSI (Swannell, et al., 2014). In a systematic review, meta-analysis, and meta-regression controlling for methodological differences, Swannell et al. (2014) found average lifetime prevalence rates of 17.2% among adolescents (10-17years), 13.4% among young adults (18-24years) and 5.5% among adults (<25years). Interestingly, after controlling for methodological differences, prevalence rates had not increased over time between 1993 and 2012 (time-span of studies included in the review). Additionally, no gender differences and no differences with regards to ethnicity or country of origin were found. The prevalence rate of 17.2% among adolescents is comparable to an average prevalence rate of 18% (SD=7.3) found in a systematic review by Muehlenkamp et al. (2012a). Interestingly, no significant differences in prevalence rates between studies defining NSSI, or studies using the definition of deliberate self-harm (DSH) were found. One large European study (SEYLE study, (Brunner et al., 2014), N=12086, mean age: 14.9, SD=0.89) compared prevalence rates of deliberate self-injury (not excluding self-injury with suicidal intent) between 11 European countries. Following France (38.5%), the second highest prevalence rates of deliberate self-injury were reported from Germany (35.1%), with an average prevalence of 27.6% across all countries.

In general adult populations, lifetime-prevalence rates range from 2.2% – 5.9% (Bebbington et al., 2010; Klonsky, 2011; McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009; Swannell, et al., 2014). Interestingly, lifetime-prevalence rates seem to decline with increasing age. For example, McManus et al. (2009) reported lower prevalence rates of self-harm in the age group of 75+ year olds (0.5%) than in the age group of 16 to 24 year olds (12.4%). This is somewhat puzzling, as the risk to engage in a behavior should naturally increase over a life span. One possible explanation is that NSSI represents a trend which was not prevalent when most adults today were adolescents. However, several studies have shown steady prevalence rates over the last 10 years (Muehlenkamp, Williams, Gutierrez, & Claes, 2009; Swannell, et al., 2014). On the other hand, as first large general population-based studies were only conducted in the late 1990s to early 2000s, little is known about the prevalence of NSSI in the general population of adults and adolescents before that time. For example, the first study on the prevalence of NSSI in a school-based population was published in 2002 (Ross & Heath, 2002). A second explanation would be a so-called recall-bias (Coughlin, 1990), where past behavior is not reported accurately by an individual due to re-attribution or simply not remembering facts correctly. Supporting this notion, Nock et al. (2008) reported a recall-bias for suicide attempts in an adult population.

2.1.3 Precipitating factors

As criterion C1 of NSSI disorder states, NSSI is typically precipitated by interpersonal difficulties, negative feelings, or negative thoughts. A large body of research has found those factors to be the most common preceptors of NSSI (Claes, Klonsky, Muehlenkamp,

Kuppens, & Vandereycken, 2010; In-Albon, Burli, Ruf, & Schmid, 2013a; Klonsky, 2009; Zetterqvist, Lundh, Dahlstrom, & Svedin, 2013a). In a real-time ecological assessment study of adolescents and young adults, worrying, bad memories, feeling pressure, or feeling sad/worthless or overwhelmed were the most common immediate preceptors of NSSI. Furthermore, individuals were more likely to engage in NSSI, when they perceived feelings of being rejected, or when being alone (Nock, 2009a). In their four-function model of NSSI, Nock and Prinstein (Nock & Prinstein, 2004, 2005) describe automatic positive reinforcement (i.e. feeling something), automatic negative reinforcement (i.e. relief from negative feelings), social positive reinforcement (i.e. getting attention), and social negative reinforcement (i.e. avoiding social situations) to be the four functions of NSSI. Apart from finding strongest evidence for an emotional regulative function of NSSI, in a review of the literature, Klonsky (2007) found strong evidence for a self-punishment function, and more modest support for interpersonal influence, anti-suicidal, interpersonal boundaries, and sensation seeking functions.

In his 'Integrated theoretical model of the development and maintenance of self-injury, Nock (Nock, 2009b, 2010), see figure 1) describes distal risk factors (i.e. genetic predisposition for high emotional reactivity, childhood abuse/maltreatment, familial hostility/criticism) to be moderated by intrapersonal (i.e. intense aversive emotions / poor distress tolerance) and interpersonal (i.e. poor social problem-solving skills) factors and then leading to over- or under-arousal following stressful events. If an individual also presents with NSSI specific vulnerability factors (i.e. NSSI as socially learned behavior, or abnormalities in the neurological reaction to pain), the individual is likely to engage in NSSI. In turn, NSSI serves the function of regulation emotional experiences or social situations.

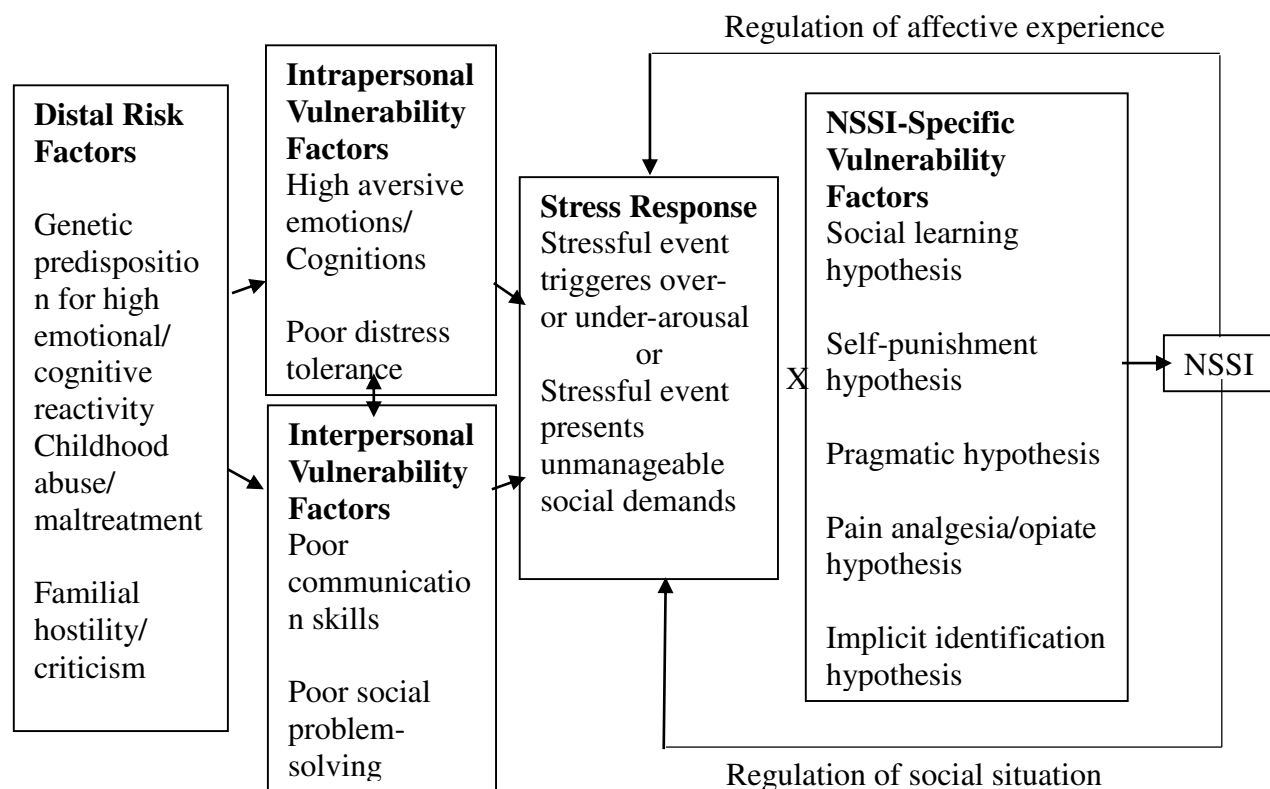


Figure 1: Integrated model of the development and maintenance of self-injury (Nock (2009b), p.79)

To the best of my knowledge, only three studies have so far investigated genetic influences on NSSI. Those three studies have shown some evidence for genetic predisposition explaining a certain percentage of the variance in the occurrence of NSSI (for details see chapter 6 – family studies). When regarding studies on childhood abuse or childhood maltreatment, effects on NSSI seem to be moderate and rather unspecific, and most likely moderated by other factors (Klonsky & Moyer, 2008; Maniglio, 2011) . Several studies have shown familial hostility or criticism to be a rather specific risk factor

for NSSI. In a longitudinal study, Tatnell et al. (2014) found decreasing family support to be a risk factor for NSSI and increasing family support to be protective of NSSI over time. In line with these findings, Tschan, Schmid, and In-Albon (2015) found less perceived maternal support and warmth to be significantly related to adolescents engaging in NSSI. Three studies found parental criticism or antipathy to be significantly associated with NSSI (Kaess, et al., 2013; Wedig & Nock, 2007; Yates, Carlson, & Egeland, 2008). Furthermore, Bowes et al. (2014) found being bullied by siblings to be a significant risk factor for engaging in NSSI.

In line with insufficient social skills and stressful events presenting as unmanageable social demands in Nock's model (Nock, 2009b, 2010), several studies have found bullying to be significantly associated with a higher risk for engaging in NSSI. In two longitudinal studies, being bullied in childhood or early adolescence was a significant predictor for engaging in NSSI in adolescence (Fisher et al., 2012; Lereya et al., 2013). Lereya and colleagues (2015) found being bullied by peers in childhood and early adolescence to be a greater risk for self-harm in adulthood than being maltreated by parents in two large longitudinal samples (Avon Longitudinal Study of Parents and Children in the UK (ALSPAC) and Great Smoky Mountains Study in the US (GSMS)). A large European study (N=12,068 adolescents from 11 countries) found bullying to be highly associated with engaging in self-harming behaviors (Brunstein Klomek et al., 2016). On the same note, belonging to an alternative youth culture (i.e. Goth, Punk) was found to be significantly associated with engaging in NSSI (Bowes et al., 2015; Young, Sproeber, Groschwitz, Preiss, & Plener, 2014; Young, Sweeting, & West, 2006).

In a systematic review of longitudinal studies, Plener et al. (2015) found female gender, depressive symptoms, previous NSSI, and psychological distress to be the most

prominent risk factors for future NSSI across all studies. In the same line previous NSSI, cluster B personality disorders, hopelessness, prior suicidal thoughts and behaviors, exposure to peer NSSI, and depression diagnosis, were reported as increasing the risk of NSSI in a meta-analysis (Fox et al., 2015). However, longitudinal studies systematically assessing risk factors of NSSID, using DSM-5 criteria do not yet exist.

2.2 Laboratory studies (Phase 2)

2.2.1 Psychological tests

The use of psychological tests and structured clinical interviews (if shown to be valid and reliable), is recommended by Robins and Guze (1970) and Aboraya et al. (2005) in order to achieve diagnostic validity. In a systematic review on diagnostic instruments in German language specifically designed for the assessment of NSSI, Groschwitz et al. (2014) found five validated questionnaires and one structured interview (which had not been validated in German language at that time, but has been meanwhile). None of the questionnaires were designed to specifically assess NSSID criteria and all were used predominantly in research, rather than in clinical settings. The structured interview (Self-Injurious Thoughts and Behaviors Interview (SITBI)) was constructed and first validated by Nock and colleagues (2007). It assesses six different types of non-suicidal and suicidal thoughts and behaviors (suicidal ideation, suicide plans, suicide attempts, suicide gestures, thought about NSSI, and NSSI). Frequencies, methods, medical severity, reasons and functions about each thought and behavior are assessed in detail. Using the SITBI, enough information can be obtained to diagnose NSSI disorder (except for criterion E). In an adolescent sample in the US, the SITBI showed good test-retest-reliability ($k=.70$), good inter-rater reliability ($k=.99$) and good construct validity ($k=.54-.87$).

In English language, Gratz et al. (2015) validated a questionnaire and semi-structured interview, which reliably and validly assesses all criteria of NSSI disorder, called the Clinician-Administered NSSI Disorder Index (CANDI). In a community sample of young adults (N=107), who all engaged in NSSI (at least once within the last year), 37% met criteria for NSSI disorder administered with the CANDI. The authors conclude that the CANDI is a feasible instrument which distinguishes well between individuals who engage in NSSI but meet or do not meet NSSI disorder criteria.

2.2.2 Physiological laboratory studies

In a systematic review on studies concerning neurobiological factors of NSSI, Groschwitz & Plener (2012) reported on first evidence in the fields of physiological reactivity, reactivity to physical pain, levels of neurotransmitters, and neural processing of varied stimuli. Unfortunately, most studies were conducted in adults with BPD, or inconsistent definitions of NSSI were used.

2.2.2.1 *Physiological reactivity to stress*

Evidence on altered physiological response (i.e. heart rate, skin conductance) in reaction to stressful events is still scarce and rather inconsistent. While one study (Nock & Mendes, 2008) found increased skin conductance in response to a distressing task in 62 adolescents engaging in NSSI compared to 30 healthy controls, opposing results were found in two studies. Crowell et al. (2005) found no elevated heart rate or skin conductance during a distressing task in 23 female adolescents with 'parasuicidal' behaviors compared to 23 healthy controls. Furthermore, using the well-established Trier-Social-Stress-Test, Kaess et al. (2012) did not find alterations in heart rate in 14 adolescents engaging in NSSI compared to healthy controls. On the other hand, two studies found a decrease in heart rate and skin conductance after imagining an act of self-

injury in individuals with self-harming behaviors (Brain, Haines, & Williams, 1998; Haines, Williams, Brain, & Wilson, 1995). In participants with BPD, Welch et al. (2008) did not find a decrease in physiological reactivity immediately during imagery of NSSI, but seconds after the imagined incident of self-injury.

While there is mixed evidence on a higher physiological reactivity to stressful situations in individuals engaging in NSSI, the effect of imagery of NSSI resulting in lower physiological arousal has been shown repeatedly.

2.2.2.2 Reactivity to physical pain

Several studies have shown a higher pain threshold in adolescents with NSSI (Glenn, Michel, Franklin, Hooley, & Nock, 2014) and individuals with BPD compared to healthy controls (Bungert et al., 2015; Ludascher et al., 2015; Schmahl et al., 2006; Schmahl et al., 2004), for review see Koenig et al (2016). In addition, Ludäscher et al. (2009) found highest pain thresholds in BPD patients with current NSSI (N=13), followed by BPD patients with no current NSSI (n=11), and followed by 24 healthy controls, suggesting a habitualized hypalgesia in subjects with NSSI.

Interestingly, in a study on young adults engaging in NSSI (n=13) vs. matched clinical controls (n=15), no differences in pain thresholds were found (Osuch, Ford, Wrath, Bartha, & Neufeld, 2014). However, participants with NSSI reported significantly higher relief after self-administered pain compared to matched controls and compared to externally administered pain.

To date, it is still unclear whether NSSI alone leads to an elevated pain threshold, or if this effect only holds true for individuals with comorbid psychopathology, as most studies were

conducted with BPD patients. Interestingly, relief from pain and the active initiation of pain seem to play an important role in the processing of physical pain in individuals with NSSI.

2.2.2.3 Neurotransmitters

As described above, NSSI is often associated with experiences of chronic (psychosocial) stress, perceived negative emotions and changes in physiological reactivity to distress. The hypothalamic-pituitary-adrenocortical axis (HPA-axis) is engaged in coordinating behavioral and physiological responses to stress, as well as coping with, and recovering from stressful events (Nater et al., 2010). Heim et al. (2000) found changes in the HPA-axis in chronically stressed or traumatized individuals, which were similar to findings in patients with BPD (Carrasco et al., 2007; Nater, et al., 2010) and NSSI (Powers & McArdle, 2003). In detail, decreased basal cortisol levels and a blunted cortisol stress response during acute events of stress were found. These results are in line with a study by Kaess et al. (2012), showing a lowered stress response in adolescents with NSSI with regards to cortisol, which the authors interpreted as a decreased responsiveness of the HPA-axis to acute stress.

Regarding other neurotransmitters like serotonin and dopamine, rather inconsistent evidence was found (Groschwitz & Plener, 2012; Stanley et al., 2010). There is first evidence from animal studies of an association of self-injurious behaviors (like self-biting) and a decreased function of the 5-HT system (Tiefenbacher, Novak, Lutz, & Meyer, 2005). However, the relationship of pain-perception and endogenous opioids is well established (Fields, 2004; Urban & Gebhart, 1999). In line with altered responses to physical pain in individuals with NSSI (and BPD as described above), Stanley et al. (2010) found lowered cerebrospinal fluid (CSF)-levels of β -endorphin and met-enkephaline in patients with

NSSI compared to matched control patients without NSSI. In their homeostasis model of NSSI, Stanley et al. (2010) argue that chronic stress (such as childhood neglect) may have led to a chronic deficiency state of endogenous opioids. In the event of an acute stressor, this deficiency may lead to an opioid response deficiency and homeostasis might be restored by engaging in NSSI, as the injury would lead to increasing endogenous opioid-levels. Considering all current studies on endogenous opioids, there is some evidence on lowered baseline levels of endogenous opioids, and some evidence of NSSI heightening those levels (for details see (Bresin & Gordon, 2013)). However, most studies were conducted in animal models, individuals with developmental disabilities, individuals with BPD, and generally in small samples.

Overall, there is little, but consistent evidence of endogenous opioids, some evidence for cortisol and no significant evidence in humans considering serotonin or dopamine to be involved in the neurobiology of NSSI.

2.2.2.4 Neural processing

Most neuroimaging studies on individuals with NSSI have been conducted in adult patients with BPD. However, one study by Plener et al. (2012), compared ten adolescents with NSSI to nine healthy controls. They found a divergent neural processing of emotional pictures of the International Affective Picture System (IAPS) and of pictures showing contents of NSSI (i.e. razor blades). Adolescents with NSSI showed elevated activation in the amygdala (bilaterally), the anterior cingulate cortex (ACC), the hippocampus, the right cerebellum and the left superior parietal cortex. Interestingly, this altered pattern of activation was prevalent independently of the valence ratings of the pictures (positive, negative or neutral). The authors interpreted these results as an insufficient effort to

control emotional reactivity (Plener, et al., 2012). With regards to NSSI-related pictures, adolescents with NSSI showed enhanced activation in the middle orbit, the prefrontal, inferior and middle frontal cortex, as well as the inferior parietal cortex. These findings were interpreted as adolescents with NSSI possibly paying more attention to cues related to NSSI. However, due to the small sample size, results have to be interpreted with care. Nevertheless, results are in line with studies on the neural processing of emotions in adult patients with BPD, showing altered activation in the amygdala and ACC in adults with BPD and NSSI (Schmahl, et al., 2006). Another study directly concerning the effect of NSSI in adult BPD-patients (Kraus et al., 2010) showed increased activation in the dorsolateral prefrontal cortex (dlPFC) during stress induction and decreased activation in the ACC while imagining an act of NSSI, compared to healthy controls.

Several studies have investigated the neural processing of pain, and have found differentiated processing in patients with NSSI. However, except for one study by Osuch et al. (2014), all research was conducted in adults with BPD. Osuch et al. (2014) found generally higher activation in brain regions associate with the dopamine system (i.e. right midbrain and pons) and the opiate system (orbitofrontal cortex; OFC) in youth (aged 16-24 years) with NSSI (n=13, with n=9 being diagnosed with BPD) compared to 15 matched clinical controls (n=9 being diagnosed with BPD, but not engaging in NSSI). During relief from pain, youth with NSSI showed higher activation in the thalamus, dorsal striatum and anterior precuneus; areas which are associated with reward and addiction (Osuch, et al., 2014).

In a study combining negative emotions and warm and painful stimuli, Niedtfeld et al. (2010) found higher activation in the ACC and amygdala in adult BPD patients during negative and neutral emotional stimuli, which was no longer present after the induction of

warm or painful stimuli. Bonenberger et al. (2015) found similarly modulated activation in the posterior insula in adults with and without a history of NSSI according to stimulus intensity. This might point towards a similar processing of somatic aspects of unpleasant stimuli. However, while activation in the anterior insula was modulated in adults without a history of NSSI according to stimulus intensity, no such modulation was found in adults with a history of NSSI. As the anterior insula is associated with affective processing of physical pain, these results could point towards an altered processing of affective aspects of physical pain.

Given that social exclusion has been shown to be a risk factor for NSSI and plays an important role in the symptomatology of BPD patients, the investigation of the neural processing of social rejection has gained increasing interest. However, only studies on adult patients with BPD have so far been conducted. Using functional near-infrared spectroscopy (fNIRS), Ruocco et al., (2010) found enhanced activation in the dlPFC during social exclusion in adults with BPD compared to healthy controls. Interestingly, Domsalla et al. (2014) found enhanced activation in the dACC, the medial prefrontal cortex (mPFC) in BPD patients compared to healthy controls during all conditions (neutral, inclusion and exclusion). Results can be interpreted as BPD patients' hypermentalizing during social situations, and situations of social exclusion being more salient for BPD patients than healthy controls.

Overall, results from a limited number of fMRI and fNIRS studies suggest deficits in neural emotional control, and altered processing of physical pain with a prominent effect of relief from pain in individuals with NSSI. However, most studies were conducted in small samples and studies on social exclusion have only been conducted in adult BPD-patients.

2.3 Exclusion of other disorders (phase 3)

NSSI is a symptom of Borderline Personality disorder and would therefore have to occur in absence of BPD, in order to be considered as independent diagnoses. Furthermore, NSSI is often associated with suicidality, which has also been proposed as separate diagnostic entity in the DSM-5 (American Psychiatric Association, 2013). NSSI also often occurs co-morbid to depression, eating disorders and substance use disorders. The occurrence of self-injurious behaviors which are better explained by psychotic disorder, autism spectrum disorder, intellectual disability, Lesch-Nyhan syndrome, stereotypic movement disorder with self-injury, trichotillomania or excoriation disorder, are specifically excluded from DSM-5 NSSID criteria and will therefore not be part of this chapter.

2.3.1 NSSI disorder and Borderline Personality Disorder

Several studies have found NSSI disorder to occur independently of BPD in adult, as well as adolescent samples. For example, in a sample of female adolescents, In-Albon, Ruf, & Schmid (2013b) found NSSI to be independent of BPD, with only 20.5% of adolescents meeting NSSID criteria also meeting BPD criteria. Comparably, Odelius and Ramklint (2014) did not find differences in the prevalence of BPD in patients meeting NSSI disorder criteria (22%) and those not meeting NSSI disorder criteria (24%). In an adult sample, 54% of participants with BPD also reported NSSI. Of those individuals engaging in NSSI, around 17% also met BPD-criteria (Selby, Bender, Gordon, Nock, & Joiner, 2012). Glenn and Klonsky (2013) found the overlap of BPD and NSSI disorder comparable to the overlap of BPD and other axis 1 disorders (like anxiety or depression) in a sample of adolescent psychiatric patients. Furthermore, NSSID was significantly associated with higher levels of loneliness and emotion dysregulation, as well as suicidal ideation and

suicide attempts in the past month, independently of BPD. Another distinguishing factor is the fact that participants meeting NSSI disorder criteria and BPD criteria reported higher levels of emotion dysregulation than participants only meeting NSSI disorder criteria (Bracken-Minor & McDevitt-Murphy, 2014). Concerning the functionality of NSSI, Bracken-Minor and McDevitt-Murphy reported NSSI to serve higher functions of self-punishment, anti-suicide, and anti-dissociation in young adults with BPD compared to individuals without BPD. Concerning BPD criteria, Wichstrom (2009) found that an unstable self-construct (an important criterion for BPD) was not associated with NSSI. As NSSI is a symptom of BPD, it is crucial to distinguish NSSI from BPD in order to achieve diagnostic validity. Current studies have shown that NSSI does occur outside of BPD, differs in its functionality and leads to functional impairment above and beyond BPD. However, longitudinal studies showing the association of NSSI in adolescence and BPD in adulthood would be valuable in order to further investigate diagnostic validity for NSSID.

2.3.2 NSSI disorder and suicidal behavior disorder

In contrary to other definitions of self-harming behaviors, such as Deliberate Self-Harm (DSH), which also includes suicidal behaviors (Gratz, 2001), NSSID criterion A specifically excludes behaviors with suicidal intent. In the DSM-5, section III (American Psychiatric Association, 2013), Suicidal Behavior Disorder (SBD) has also been added as independent diagnoses in the condition to further study section. In order to be diagnosed with SBD, an individual has to have attempted suicide at least once within the last 24 months (in early remission), or within the last 12 months (current). Independent of the method used, the individual has to state that the behavior was undertaken in the expectation to end one's life. To the best of my knowledge, there is no study concerning

the distinction of both, NSSID and SBD, as suggested in the DSM-5. However, a growing body of studies has found differences between both behaviors (NSSI and suicidal behaviors). Both behaviors differ with regards to intent, frequency, method, functionality, type of injury, and age of onset (Andover, Morris, Wren, & Bruzzese, 2012; Jacobson & Gould, 2007; Muehlenkamp, et al., 2012a; Nock et al., 2013). Furthermore, an anti-suicidal function of NSSI is reported quite frequently, showing a clearly distinguished intent by affected individuals (Klonsky & Muehlenkamp, 2007). Unique risk factors (i.e. previous NSSI) and protective factors (i.e. satisfaction with social support) for NSSI as compared to suicide attempts were found in a longitudinal study (Wichstrom, 2009). Furthermore, risk and protective factors for suicide attempts, independent of NSSI (i.e. conduct problems), were identified in the same study.

On the other hand, NSSI is a well-established risk factor for suicidal thoughts and behaviors (Klonsky, et al., 2013; Tuisku et al., 2014; Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011), as well as completed suicides (Hawton et al., 2015). In a meta-analysis, Victor & Klonsky (2014) found number of methods, NSSI frequency and hopelessness to be the most significant predictors of suicide attempts. Furthermore, adolescents meeting NSSID criteria reported significantly higher rates of suicidal ideation and suicide attempts (Glenn & Klonsky, 2013). Three major theories link NSSI to suicidal behaviors. The Gateway theory (1), which suggests NSSI and suicidal behaviors to be on a continuum of self-injuring behaviors (Stanley, Winchel, Molcho, Simeon, & Stanley, 1992), the third variable theory (2), which suggests underlying variables to be responsible for the co-occurrence of NSSI and suicidality (Hamza, Stewart, & Willoughby, 2012), and Joiners' interpersonal psychological theory (3) (Joiner, 2005). According to this theory, an acquired capability for suicide, namely a lowered pain threshold and lowered fear of death, along

with feelings of isolation and being a burden to others, are essential for an individual to attempt suicide. As all three theories are supported by empirical data and seem to be valid, but by themselves do not account for all aspects of the co-occurrence of NSSI and suicidality, Hamza et al. (2012) joined those three theories to an integrated model (see figure 2).

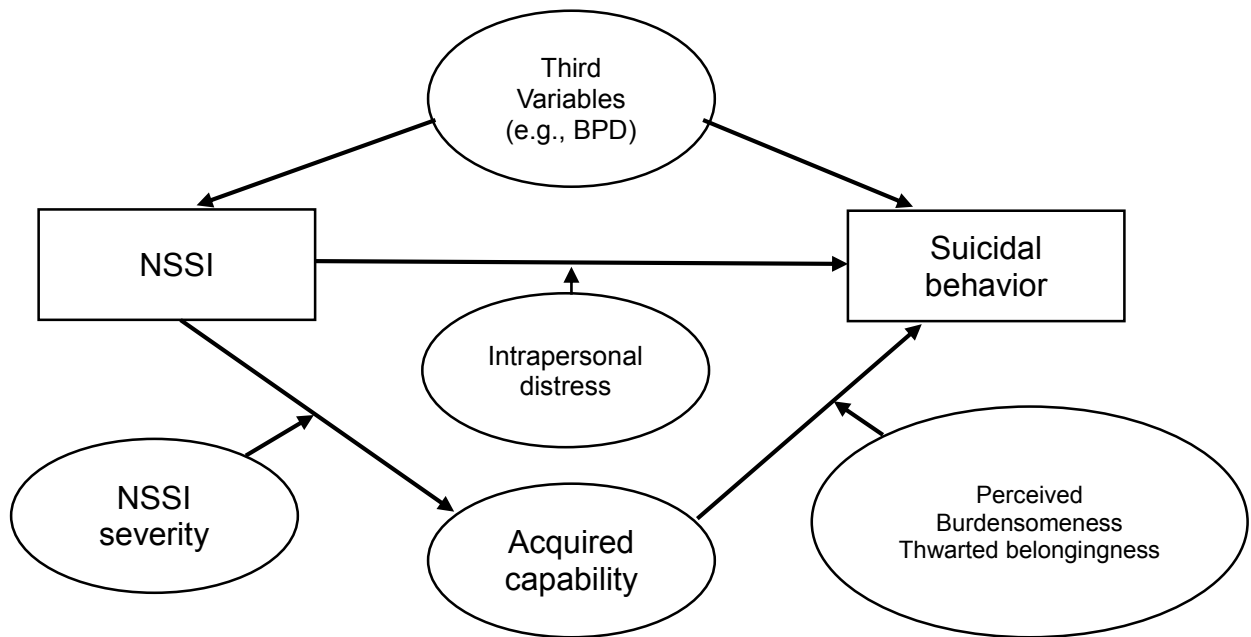


Figure 2: Integrated model of the link between NSSI and suicidal behavior ((Hamza, et al., 2012) p. 492).

It includes the gateway theory, with NSSI as a starting point and directly predicting suicide attempts as a finishing point due to the mutual experiential properties of NSSI and suicidal behavior (Hamza, et al., 2012). The model predicts that this relationship is moderated by intrapersonal distress, due to all studies on this topic finding greater levels of distress in individuals with NSSI and suicidal behaviors, as compared to individuals solely engaging in NSSI. It also implements the third variable theory by taking mutual risk factors into account. For example, three independent genetic studies on twins showed a significant

overlap (47%-76%) of genetic variation between NSSI and suicidal ideation and suicide attempts (Durrett, 2006; Maciejewski et al., 2014; McLaughlin, 2015).

Joiners' (2005) interpersonal psychological theory is included by adding the acquired capability for suicide and feelings of burdensomeness and thwarted belongingness to the model, as an indirect way of NSSI influencing the development of suicidal behavior. The model also predicts NSSI severity to be moderating the effect of NSSI on the development of acquired capability for suicide. The integrated model seems to fit existing empirical data on the link between NSSI and suicide attempts (for an overview see (Hamza, et al., 2012). However, more research is needed in order to test the model in its entirety.

Overall, existing evidence points towards crucial factors discriminating NSSI and suicidal behaviors from each other. However, NSSI and suicidal behaviors seem to share risk-factors (with NSSI being a risk-factor for suicide attempts in itself) and co-occur quite frequently. Therefore, more research is needed in order to establish diagnostic validity for both potential disorders.

2.3.3 NSSI disorder and axis 1 disorders

NSSI often occurs comorbid to a number of axis 1 disorders, including depression (Asarnow et al., 2011; Wilkinson, et al., 2011), (social) anxiety disorders (In-Albon, et al., 2013b), posttraumatic stress disorder (PTSD; (Dyer et al., 2009)), eating disorders (Muehlenkamp, Peat, Claes, & Smits, 2012b; Paul, Schroeter, Dahme, & Nutzinger, 2002), and substance use disorders (Evren, Dalbudak, Evren, Cetin, & Durkaya, 2011; Gratz & Tull, 2010). Two studies showed a prevalence of around 70% of major depressive disorder in adolescents meeting NSSID criteria (Glenn & Klonsky, 2013; In-Albon, et al.,

2013b). In a study by Gratz et al. (2015), participants meeting NSSID criteria showed greater severity of anxiety, depression, as well as higher rates of PTSD, social anxiety disorder, bipolar disorder and alcohol dependence as participants engaging in NSSI, but not fully meeting DSM-5 criteria. Of all participants meeting NSSI disorder criteria, 87.5% had a lifetime diagnosis of a mood disorder (72.5% major depressive disorder), 72.5% had a lifetime diagnosis of an anxiety disorder (including PTSD of 25%) and 65% had a lifetime substance use disorder.

Results from those studies show a high overlap of NSSID with other axis 1 disorders. However, this overlap does not seem to be specific for one particular axis 1 disorder and most studies were conducted in clinical psychiatric populations, in which all participants would naturally be diagnosed with an axis 1 disorder.

Overall, the overlap of NSSID with BPD, suicidality, and a number of axis 1 disorders points towards high impairment of individuals meeting NSSID criteria and calls for more research distinguishing NSSI disorder from other psychiatric impairment.

2.4 Follow-up study (phase 4)

2.4.1 Longitudinal course of NSSI

In a recent systematic review on the longitudinal course of NSSI and deliberate self-harm, Plener et al. (2015) found 22 naturalistic follow-up studies describing the course of NSSI. Across all studies, an increase in the rates of NSSI from early adolescence (around 12 years) to a peak in mid-adolescence (around 16 years) and a decrease in late adolescence and early adulthood was found. However, most studies had quite short follow-up intervals from the first to last observation (around 19 months on average). One large Australian study (1943 participants, aged 16 at T1), followed up participants over

consecutive 14 years in nine waves (Moran et al., 2012). The study found a steep decline of NSSI from around 6% at 16 years of age to around 2% at 18 years, to a further decline at 21 years to less than 1%.

To date, only few studies examining reasons for cessation of NSSI exist. In a prospective 1-year follow-up study, those participants who had discontinued NSSI showed a lower overall lifetime-frequency of NSSI, less serious wounds, higher cognitive reappraisal, and lower emotional suppression than those participants who had continued to self-injure (Andrews, Martin, Hasking, & Page, 2013). On a similar note, individuals with a history of NSSI, but no NSSI within the last year reported higher family support, higher satisfaction with life, and higher self-esteem (Rotolone & Martin, 2012) than individuals with current NSSI. Family support was also found to be the most salient variable in the cessation of NSSI in a longitudinal study (Tatnell, et al., 2014). Taliaferro and Muehlenkamp (2015) found hopelessness, history of verbal or physical abuse, and depressive symptoms to be distinguishing factors between adolescents and adults with current or discontinued NSSI. Most of these results were replicated by Whitlock and colleagues (2015) who found lower lifetime frequency, less NSSI forms and functions, and less current psychological distress to be more prevalent in young adults with ceased NSSI. Interestingly, those participants who still engaged in NSSI, were more likely to identify with the behavior and regard themselves as 'a self-injurer', were less likely to view self-injury to be interfering with their lives, that therapy was helpful, that they perceived social support, having a sense of meaning in life, and to use alternative emotion regulation strategies.

Overall, NSSI seems to be highly prevalent in adolescence, with descending prevalence rates in young adulthood. Cessation of NSSI seems to be moderated by a number of social and psychological factors. However, longitudinal studies are scarce and

methodological differences between studies make comparisons of prevalence rates between studies difficult (Swannell, et al., 2014).

2.4.2 Psychotherapy of NSSI

In recent years, several systematic reviews on psychotherapy of NSSI have been published. However, evidence for the treatment of NSSI, especially in adolescence, is rare. Most studies on the treatment of self-injurious behaviors were conducted in adult BPD populations and did not specify NSSI as outcome measure. Most often, terms like 'deliberate self-harm' or 'parasuicidality', thus not differentiating between suicidal and non-suicidal behaviors, were defined.

2.4.3 Treatment of NSSI in adults

Three recent systematic reviews of the literature (Glenn, Franklin, & Nock, 2015; Groschwitz & Plener, 2013; Ougrin, Tranah, Stahl, & Moran, 2015) identified three major forms of treatments for the treatment of self-harming behaviors: Dialectical Behavioral Therapy (DBT, (Linehan, 1993)), Mentalization Based Treatment (MBT, (Bateman & Fonagy, 1999)), and Cognitive Behavioral Therapy (CBT). DBT was originally developed for the treatment of chronically suicidal or parasuicidal female patients diagnosed with BPD (Linehan, 1993). In DBT, self-injurious thoughts and behaviors are viewed as maladaptive coping strategies. The treatment consists of a multidimensional approach, which involves dialectic strategies (i.e. balance of change and acceptance), CBT strategies and elements of Zen-Buddhism. The treatment is conceptualized as group-treatment, with continuous group sessions. It involves skills training for teaching alternatives to self-injury, emotion regulation strategies, stress tolerance training,

interpersonal skills and acceptance based treatment. DBT has been shown to be effective for the treatment of BPD patients in numerous international studies (Bohus et al., 2004; Stanley, Brodsky, Nelson, & Dulit, 2007).

Mentalization based treatment (MBT) is a psychodynamic therapy, which aims to improve mentalization and impulse control skills. Mentalization is understood as the ability to understand the relationship of one's own and others' internal thoughts and feeling states and the corresponding behaviors. MBT is based on the idea that patients with BPD have difficulties mentalizing, by i.e. interpreting neutral social cues as threatening. In two randomized controlled trials (RCTs), MBT was shown to be more effective in reducing self-harm in BPD patients, as compared to treatment as usual (Bateman & Fonagy, 1999, 2009).

Several cognitive behavioral approaches have been developed for the treatment of BPD. Like in DBT, self-injury is viewed as dysfunctional coping mechanism. Participants learn to understand the relationship of feelings, thoughts and behaviors, to identify stressful situations and triggers, as well as dysfunctional cognitions. Alternative behaviors to self-harm are trained, dysfunctional cognitions are challenged, and participants learn social, as well as problem solving skills. One study has shown enhanced efficacy of CBT as compared to TAU for the reduction of self-harm in adult BPD patients (Slee, Garnefski, van der Leeden, Arensman, & Spinhoven, 2008).

2.4.4 Treatment of NSSI in adolescents

In a systematic review, Glenn, Franklin and Nock (2015) did not find any treatments meeting the highest level of evaluation of the Journal of Clinical Child and Adolescent Psychology (JCCAP), which requires at least two RCTs by two independent research

groups. However, first promising results had been found concerning DBT for adolescents (DBT-A; (Rathus & Miller, 2002)), MBT for adolescents (MBT-A; (Rossouw & Fonagy, 2012)), and CBT (Taylor et al., 2011). In a recent meta-analysis and systematic review, Ougrin et al. (2015) still did not find sufficient evidence in order to recommend any specific treatment for NSSI in adolescence. However, in a meta-analysis of 19 RCTs, they found a significantly greater reduction of self-harm in specific treatments for self-harm as compared to TAU. The number needed to treat in order to prevent one episode of NSSI (for a 10 month period) was 13 for self-harm (including suicide attempts) and 10 for NSSI. Highest effect-sizes were found for MBT-A, DBT-A, and CBT. A treatment combining DBT, CBT, and psychodynamic skills training, called developmental group therapy (Wood, Trainor, Rothwell, Moore, & Harrington, 2001), showed positive (but not significant) effects on the reduction of self-harm in adolescents in one study. However, two subsequent studies (Green et al., 2011; Hazell et al., 2009) did not find a positive effect of developmental group therapy compared to TAU.

As evidence is currently best for MBT-A, DBT-A, and CBT to be of benefit for the reduction of NSSI in adolescents, those treatments will be discussed subsequently.

In order to adjust DBT to the treatment of adolescents, a new module called “walking the middle path” was added to the program. Adolescents and their families participate in so-called ‘multi-family-groups’ where typical adolescent related topics are being discussed (i.e. being too permissive vs. being too restrictive). One RCT by Fleischhaker et al. (Fleischhaker et al., 2011; Fleischhaker, Munz, Böhme, Sixt, & Schulz, 2006) found a significant reduction of NSSI after DBT-A as compared to TAU directly after therapy and in the 1-year follow-up. However, the sample size was quite small (N=23) with a high attrition rate (N=16 finished the training). A more recent study from Norway (Mehlum et

al., 2014) found a significant effect of group and time on self-harm as compared to TAU, which remained significant at 52-week follow-up (Mehlum et al., 2016). However, both treatments in this study were not entirely comparable, as the DBT-A group was strictly controlled for attendance (participants who missed 3 sessions or more were excluded from analyses) and for treatment quality (strict supervision of therapists, only best scoring 8 therapists out of 15 were chosen). Such measures of control of quality were not undertaken in the TAU group. Despite those limitations, DBT-A still showed a significantly higher reduction of self-harm than TAU in those two independent RCTs.

MBT-A has so far been evaluated in one RCT (Rossouw & Fonagy, 2012). The treatment showed to be effective when compared to TAU, after 12 months of treatment. In addition, effects were mediated by improvement of mentalization skills and a reduction of attachment anxiety, which are both major aims of MBT-A.

Taylor et al. (Taylor, et al., 2011) developed a manual for CBT in adolescents with NSSI. The treatment consists of 8-10 sessions and involves motivational interviewing (if necessary), psycho-education on NSSI, emotions, and CBT, cognitive restructuring, problem-solving, alternative skills and relapse prevention. The treatment effectively reduced NSSI at the end of the treatment and in the 3-month follow-up. Currently, a German version of this treatment is evaluated in Heidelberg, Germany in a randomized controlled trial with an active control group (Fischer, Brunner, Parzer, Resch, & Kaess, 2013).

In conclusion, several different treatments have been developed for the treatment of NSSI in adults and adolescents. However, future research is urgently needed, as most studies comprise small sample sizes, do not define NSSI as outcome measure, and encompass other methodological problems. To date, DBT (-A), MBT (-A), and CBT (for adults and

adolescents) seem to be the most promising treatments, but are in need of further evaluation in RCTs (defining NSSID criteria as outcome measure) and concerning long-term effects. Furthermore, it has not yet been evaluated whether all adolescents with NSSI (and in some cases mere NSSI) need a full treatment of DBT-A, or could also benefit appropriately from i.e. skills-training alone. With the establishment of NSSID, such specific treatments might be more easily evaluated and implemented.

2.5 Family study (Phase 5)

To date, very few studies examining the co-existence of NSSI in close family members exist. Aim of phase 5 is to establish diagnostic validity by the co-existence of the same diagnostic entity in close family members independent of its etiology (Robins & Guze, 1970).

Only one study so far investigated the trans-generational occurrence of NSSI. In this study, paternal histories of NSSI, suicide attempts, and abuse were not predictive of NSSI in 352 children of parents with current mood disorders (n=212), who were followed-up annually for a mean duration of 3.8 years (Cox et al., 2012).

Maciejewski et al. (2014) evaluated genetic and environmental influences on NSSI in a sample of 10,678 adult twins from the Australian Twin registry. The sample consisted of 3,694 monozygotic, 5,128 dizygotic, and 1,856 single twins (58.5% of the whole sample being female). In a bivariate genetic model, 37% of the variance of NSSI in men, and 59% in women were explained by genetic factors. The rest of the variance was explained by non-shared environmental influences and measurement error, rather than by shared (family) environmental influences. Similar results were found in a sample of N=1925 monozygotic and N=1511 dizygotic female twins, who were interviewed at four waves

between the ages of on average 15.5 years (wave 1) and 21.7 years (wave 4) (Durrett, 2006). In this study, genetic factors explained 37% of the variation of self-harm. While non-shared environmental influences significantly added to explanation of the variance, shared environmental influences did not account for any additional explanation.

In order to examine specific genetic risk for NSSI, Hankin et al. (2015) explored the interaction of the Transporter-Linked Polymorphic Region (5-HTTLPR) of the gene SLC6A4 and chronic interpersonal stress regarding the occurrence of NSSI. The 5-HTTLPR was chosen, as it was related to emotion regulation, suicidal behavior, and behavior control problems in previous studies (see (Hankin, et al., 2015)). Two independent samples of high-school-students (N=300 and 271, respectively) were interviewed using the SITBI. Similar results were found for both samples. Results showed a strong interaction of 5-HTTLPR and chronic interpersonal stress for carriers of the short-short (SS) allele (higher interpersonal stress leading to higher engagement in NSSI), medium interaction with the short-long (SL) allele, and no interaction with the long-long (LL) allele. However, as results were cross-sectional, no predictive values of this gene-environment interaction can be made.

Considering trans-generational effects, only one study examined the link between parental NSSI and NSSI in offspring and did not find an association between the two. Furthermore, genetic studies found evidence for genetic components of NSSI, but all studies found environmental factors outside the family to explain more variety than familial environmental factors. However, in order to establish family clusters of NSSI, and further the knowledge about genetic and environmental influences, specific cross-generational studies are needed.

3 Aims of this thesis

NSSI has only been proposed as independent diagnostic entity in the DSM-5 recently. The major aim of this thesis is to elucidate the diagnostic validity of NSSI as independent disorder, following the five phases suggested by Robins and Guze (1970). Their proposed phases of research in order to establish diagnostic (construct) validity are: (1) clinical description, (2) laboratory study, (3) exclusion of other disorders, (4) follow-up study, and (5) family study. The thesis will focus on phases 1-4, including studies on the epidemiology, diagnostic instruments, neural processing, association of NSSI and suicidality, BPD and axis 1 disorders, as well as one naturalistic follow-up study.

4 Results

4.1 Phase 1 – Clinical description including epidemiological features

4.1.1 Study 1: Prevalence of NSSID in the general population of Germany

Paul L. Plener, Marc Allroggen, Nestor D. Kapusta, Elmar Brähler, Jörg M. Fegert, **Rebecca C. Groschwitz** (2016). The prevalence of NSSI in a representative sample of the German population, *BMC Psychiatry*, 16, 353.

This study is the first to investigate the prevalence of NSSI, and specifically NSSID in the general population of Germany. Important research questions in order to further diagnostic validity of NSSID are (1) the prevalence of NSSID in the general population and (2) the comparability of prevalence rates in Germany with those found in other countries.

Introduction: While the prevalence of NSSI is quite well researched in adolescent samples in Germany, to date, no data on the situation in the general adult population

exists. Furthermore, the prevalence of NSSID in an adult sample has so far only been evaluated in one online study from the US, which did not recruit a representative sample.

Methods: A randomly selected, representative sample of the German population (N=2509, mean age=48.8 years, SD=18.1, female 55.4%) was selected. Participants were visited in their homes. In this study, results from the NSSI section of the German version of the Self-Injurious-Thoughts-and-Behaviors-Interview (SITBI-G) are presented. The SITBI-G was administered as a questionnaire in this study, but participants were able to ask questions, if they had trouble understanding an item.

Results: Around 3% of all participants reported a lifetime history of NSSI. Lifetime prevalence rates were lower in older age groups than in younger participants. In total, 0.3% of the sample met NSSID criteria. Participants with NSSI rated automatic negative functions higher than automatic positive or social functions. However, those participants meeting NSSID criteria reported significantly higher levels of automatic positive reinforcement than those participants not meeting NSSID criteria.

Discussion: This is the first study worldwide to assess NSSID criteria in a sample of the general population. Prevalence of NSSID was quite low, with 0.3% meeting NSSID criteria in the overall population. However, prevalence rates were higher in younger age groups than in older age groups. These findings call for the need of longitudinal studies to gather more knowledge about the stability of the disorder. Furthermore, the development of specific treatments for younger age groups seems to be especially valuable.

4.2 Phase 2: Laboratory studies including psychological tests

4.2.1 Study 2: Validation of a structured clinical interview in German language

Gloria Fischer, Nina Ameis, Peter Parzer, Paul L. Plener, **Rebecca C. Groschwitz**, Eva Vonderlin, Michael Kölch, Romuald Brunner, Michael Kaess (2014). The German version of the self-injurious thoughts and behaviors interview (SITBI-G): a tool to assess non-suicidal self-injury and suicidal behavior disorder. *BMC Psychiatry*, 14, 265.

A systematic review of diagnostic instruments assessing NSSI showed a lack of validated structured interviews for the assessment of NSSI in German language (Groschwitz, et al., 2014). The use of structured clinical interviews was strongly recommended by Aboraya et al. (2005) in order to achieve diagnostic validity of a disorder. Therefore, a German version of the Self-injurious Thoughts and Behaviors Interview (SITBI-G; (Nock, et al., 2007)) was validated.

Introduction: Although clinical interviews are considered the gold standard for the assessment of psychiatric disorders, no structured interview for the assessment of NSSI has been validated in German language. Aim of this study was to validate a German version of the Self-Injurious Thoughts and Behaviors Interview (SITBI). The SITBI is validated in English language and is used widely in international research. As an addition to previous validation studies, the reliability and validity of the SITBI in order to assess NSSID and SBD as suggested in the DSM-5, were evaluated.

Methods: A sample of N=111 adolescent psychiatric inpatients were interviewed using the German version of the SITBI (SITBI-G). The sample was recruited from inpatient units of the departments of Child and Adolescent Psychiatry in Berlin, Heidelberg, and Ulm. Participants were 12-19 years old ($M=15.38$, $SD=1.72$) and 73% were female. The Self-Harm-Behavior-Questionnaire (SHBQ) was used to assess construct validity. Re-Test-

Reliability was tested in a sub-sample after 25 days on average. Interrater-reliability was also assessed in a sub-sample.

Results: Moderate to good test-retest-reliability for SBD ($\kappa = .64$), current SBD ($\kappa = .52$), and NSSI disorder ($\kappa = .60$) was found. While test-retest-reliability for the general presence of NSSI ($\kappa = .70$) and suicide attempts ($\kappa = .75$) was good, assessment of the frequencies (past year) showed moderate to good reliability ($\kappa = .50$ - $\kappa = .64$). Interrater reliability was good for NSSI ($\kappa = .77$) and perfect for suicide attempts ($\kappa = 1.00$). Results point towards very good construct validity of the SITBI-G, as there was very good agreement with the SHBQ with regards to NSSI ($\kappa = .89$) and suicide attempts ($\kappa = .86$). DSM-5 criteria for NSSI and SBD can be derived from questions of the SITBI-G, except criterion E for NSSI (clinical impairment).

Discussion: Psychometric properties of the SITBI-G are comparable to the English version. As applicable to all self-report instruments, memory recall biases have to be taken into consideration when interpreting results of this study and may have influenced reliability scores. A valuable addition to the SITBI-G would be questions about clinical impairment caused by NSSI. Furthermore, a more specific definition of NSSI could help to improve interrater-reliability. Overall, the SITBI-G can be considered a reliable and valid instrument in order to assess SBD and NSSI as suggested in the DSM-5.

4.2.2 Study 3: Neural processing of social exclusion in adolescents with NSSI

Rebecca C Groschwitz, Paul L Plener, Georg Groen, Martina Bonenberger, Birgit Abler (2016). Differential neural processing of social exclusion in adolescents with non-suicidal self-injury: An fMRI study. *Psychiatry Research: Neuroimaging*, 255, 43-49.

Social exclusion, or bullying, has been shown to be an important risk-factor for adolescent NSSI and depression (Fisher, et al., 2012; Lereya, et al., 2013). This study aimed to distinguish NSSID from adolescent depression by experimentally investigating the neural processing of social exclusion in adolescents with NSSID and depression, adolescents with mere depression, and healthy controls. Therefore, this study is a combination of phase 2 (laboratory study) and phase 3 (exclusion of other disorders).

Introduction: Social exclusion is an important risk factor for the development of both, NSSI and depression in adolescence. Furthermore, there is a high co-occurrence of NSSI and depression, with around 70% of adolescents with NSSI also meeting criteria for major depression. In order to establish further validity of NSSID, differences in the neural processing of social exclusion in adolescents with NSSI and major depression in adolescents with mere major depression were investigated.

Methods: Using fMRI, the processing of social exclusion in n=14 adolescents with NSSI and depression, n=14 adolescents with mere depression, and n=15 healthy controls was investigated. Groups were matched for age, gender, IQ, and both patient groups were matched for severity of depression. Average age was 15.2 years (SD=1.8), and 79% were female. NSSI was assessed using the SITBI-G, depression was assessed using the Children's Depression rating scale (CDRS-R) and the Beck Depression Inventory, 2nd edition (BDI-II). Reaction to social rejection was measured using the Need-Threat-Scale. Social exclusion was evoked using the well-established paradigm 'Cyberball'. Data was

obtained using a 3-Tesla fMRI-Scanner and was analyzed with Statistical Parametric Mapping (SPM-8).

Results: While both patient groups showed enhanced levels of trait sensitivity to social exclusion, none of the groups differed in their reported feelings of social exclusion after the 'Cyberball' task. However, participants with NSSI showed relatively enhanced activation in the ventrolateral prefrontal cortex (vlPFC) and the medial prefrontal cortex (mPFC) as compared to adolescents with mere depression and healthy controls.

Discussion: The mPFC and the vlPFC have been shown to be involved in the processing of social situations repeatedly. Interestingly, adolescents with NSSI and depression and adolescents with mere depression showed divergent activation in both regions. Although social exclusion is a risk factor for both psychiatric disorders, its differential neural processing may strengthen the consideration of NSSI as an independent disorder and may inspire research on treatment approaches specific to NSSI.

4.3 Phase 3: Exclusion of other disorders

4.3.1 Study 4: NSSID and suicidal behavior disorder as described in the DSM-5

Rebecca C. Groschwitz, Michael Kaess, Gloria Fischer, Nina Ameis, Ulrike ME Schulze, Romuald Brunner, Michael Koelch, Paul L. Plener (2015). The association of Non-Suicidal Self-Injury and Suicidal Behavior according to DSM-5 in adolescent psychiatric inpatients. *Psychiatry Research*, 30, 454-61.

Both, NSSI and suicidal behavior have been suggested as separate diagnostic entities in the DSM-5 (American Psychiatric Association, 2013). Therefore, the association and distinguishing factors of both diagnostic entities were investigated in a sample of adolescent psychiatric inpatients.

Introduction: NSSI and suicidal behaviors have been linked by several theoretical approaches and empirical findings. Furthermore, NSSI is a significant risk-factor for suicide attempts. However, the relationship of both new diagnostic entities as proposed in the DSM-5 has not yet been investigated.

Methods: In this study, data of the same psychiatric adolescent sample as described in study 2 (Validation of a structured clinical interview in German language by Fischer et al., 2014) was used to investigate the relationship of NSSID and SBD. It was comprised of N=111 adolescents (mean age=15.38 years, SD=1.72) of which 73% were female. Data was assessed using the Self-Injurious-Thoughts-and-Behaviors-Interview German (SITBI-G).

Results: Overall, a high co-occurrence of NSSI disorder and SBD was found. However, both suggested disorders also occurred independently of each other. NSSI disorder and SBD were differentiated by a number of variables: NSSI occurred significantly earlier in life for the first time than suicide attempts. Furthermore, non-suicidal self-injurious acts occurred significantly more frequently than suicide attempts. Moreover, participants rated positive automatic functions (i.e. “to feel something”) and social functions significantly higher for NSSID than SBD. Nevertheless, NSSID and SBD also shared common risk factors like female gender, or comorbid affective disorders.

Discussion: Although SBD and NSSID both involve self-injurious acts and share common risk factors and functionalities, they can clearly be distinguished by several factors like intent, age of onset and frequency. Furthermore, NSSID and SBD did occur independently of each other in a subsample of this study. Additionally, individuals engaging in both, NSSI and suicidal behaviors, can clearly distinguish between the two. Therefore, this study supports the suggestion of NSSI and suicidal behavior being two

separate diagnostic entities. Due to their high co-morbidity, however, suicidality should always also be evaluated when assessing NSSI.

4.4 Phase 4: Follow-up study including studies on psychotherapy

4.4.1 Study 5: Follow-up study on former adolescents engaging in NSSI as young adults

Rebecca C. Groschwitz, Paul L. Plener, Michael Kaess, Teresa Schumacher, Ramona Stoehr, Isabel Boege (2015). The situation of former adolescent self-injurers as young adults: a follow-up study. *BMC Psychiatry*, 15, 160-168.

The presented study includes both, phase 3 (exclusion of other disorders like BPD and axis 1 disorders) and phase 4 (follow-up study). Former adolescent psychiatric patients were followed up as young adults and their history of NSSI and axis 1 disorders, as well as their current axis 1 and axis 2 disorders were assessed.

Introduction: The longitudinal development of NSSI is still well under researched. Especially the transition from adolescence (where NSSI is highly prevalent) to young adulthood (where prevalence rates of NSSI decline) is of high interest. This period of life is also interesting because personality disorders, like Borderline Personality Disorder (BPD) often manifest during late adolescence or young adulthood. Aims of this study were to investigate the psycho-social development of young adults who had engaged in NSSI in their adolescence.

Methods: A total of N=52 young adults, who had been in treatment at the departments of child and adolescent psychiatry and psychotherapy in Ulm and Ravensburg, and who had engaged in NSSI during their stay at the ward, were recruited for this study. Participants were on average 21.5 years old (SD=2.6) and were predominantly female (94.2%). The

Self-Injurious-Thoughts-and-Behaviors-Interview German (SITBI-G), the Diagnostic Interview for Mental Disorders – Short version (MINI-DIPS), the Structured Clinical Interview for DSM-IV, Axis II, Personality Disorders (SCID-II) were used to assess NSSI and suicidality, as well as current axis 1 and axis 2 disorders. Further psychological examination included questionnaires like the Beck Depression Inventory, 2nd edition (BDI-II) and the Brief Symptom Inventory (BSI).

Results: Although around 50% of all participants had engaged in NSSI within the last year and around 50% met diagnostic criteria for BPD, both diagnostic entities occurred rather independently of each other. However, those participants who had started engaging in NSSI earlier in life or had engaged in NSSI for a longer time period in their adolescence, were significantly more likely to have developed BPD. Participants who still engaged in NSSI, were more likely to be diagnosed with a current axis 1 disorder, reported more suicide attempts in their lifetime and had engaged in NSSI more often than those who had ceased NSSI.

Discussion: Even in this sample of former highly impaired adolescents, NSSI had declined significantly in young adulthood. Interestingly, NSSI in adolescence, as well as prevailing NSSI in young adulthood did not seem to be highly predictive of the development of BPD. However, earlier onset of NSSI seemed to be a significant risk-factor for BPD. Nevertheless, this study showed NSSI to be rather independent of other axis 1 or axis 2 disorders over time and results of this study are therefore supportive of NSSI as independent diagnostic entity.

5 General discussion

Non-suicidal self-injury (NSSI) has been suggested as independent diagnostic entity in the DSM-5, section 3, condition to further study (American Psychiatric Association, 2013). Several recent reviews of the literature (In-Albon, 2015; Selby, et al., 2015; Zetterqvist, 2015) have pointed out the need for more research in order to achieve diagnostic validity for NSSI disorder (NSSID). Aim of this thesis was to strengthen and investigate diagnostic validity of NSSI as independent disorder, by adding relevant studies to the existing literature. As a framework, Robins and Guze's (1970) five phases to achieve diagnostic validity were applied. The first phase in Robins and Guze's model is the clinical description of a disorder, including studies on epidemiology. When using NSSID criteria, prevalence rates of 1.5%-6.7% in child and adolescent community samples and rates around 35-50% in adolescent psychiatric samples have been found (Zetterqvist, 2015). Studies in adult populations using NSSID criteria are rare. One online study (Andover, 2014) found prevalence rates of 3% of NSSID in an adult population. Two studies presented in this thesis investigated the prevalence of NSSI. Both studies used the German version of the structured self-injurious thoughts and behaviors interview (SITBI-G). The first study (Plener et al., in press) added on to the literature by investigating prevalence rates in the general adult population of Germany. A prevalence of around 3% for lifetime NSSI and 0.3% for current NSSID were found. These rates are rather low when compared to results of the online survey conducted by Andover (2014), who found a lifetime prevalence of 23% of NSSI and 3% of participants met NSSID criteria. However, this study may have been biased by self-selection of participants, as it was an online study on NSSI. In contrast, participants in our study were chosen randomly. In another study of the US general population (n=439, Mage=55.5, SD=16.6), using random digit dialing, Klonsky

(2011) found very similar rates to the rates in Germany with a lifetime prevalence of NSSI of 5.9% and a 12 month prevalence of 0.9%. Furthermore, NSSID criteria were not assessed specifically in this study, which would have most likely diminished the 12-month prevalence rate even further (i.e. only including participants with at least 5 episodes of NSSI within the last year). A similar comparability of prevalence rates between the US and Germany were shown in two matched adolescent samples of 665 adolescents, which did not show significant differences between both samples (Plener, Libal, Keller, Fegert, & Muehlenkamp, 2009). Furthermore, two systematic reviews did not find significant differences between rates of NSSI worldwide (Muehlenkamp, et al., 2012a; Swannell, et al., 2014). Overall, these results strengthen the validity of NSSID as (1) NSSID seems to be a significant concern in the general population and (2) prevalence rates seem to be rather comparable internationally. The second study presented in this thesis found a prevalence of NSSID of 36.9% in a sample of adolescent psychiatric inpatients (Fischer et al., 2014). This study was included in the review by Zetterqvist (2015) and accounts for the lowest prevalence rate found in studies on psychiatric adolescent inpatients, which range from 36.9-50%. Reasons for this relatively low rate are speculative. On the one hand, it could be due to the use of a clinical interview, which has been shown to produce lower prevalence rates than more anonymous self-report questionnaires (Swannell, et al., 2014). Furthermore, except for criterion E (NSSI causing clinically significant distress, which can be assumed in an inpatient sample), all criteria of NSSI disorder were carefully evaluated. This is different from the study by Glenn and Klonsky (2013), who found a prevalence rate of around 50% in their adolescent inpatient sample. In their study, participants were rated to meet NSSID criteria, if they had self-injured at least once within the last year (but more than 5 times within their lifetime). Furthermore, most other criteria

were administered more indirectly, as data was assessed using the Inventory of Statements about Self-Injury (ISAS), which was not specifically designed to assess NSSID criteria (Glenn & Klonsky, 2013). Another study reporting a higher prevalence rate was the one by In-Albon, Ruf, and Schmid (2013b), showing a prevalence rate of 56.2% by using a clinical interview to assess NSSID criteria in an adolescent inpatient sample. However, results may have been biased, as it was a purely female sample, whereas in our sample 73% were females. Overall, results from clinical samples point towards a much higher prevalence of NSSID in adolescents with axis 1 or axis 2 disorders, as compared to adolescents of the general population. Due to this apparent high comorbidity, it is crucial to distinguish NSSID from other disorders, in order to warrant its consideration as an independent diagnostic entity.

Phase two of Robins and Guze's model concerns laboratory studies, including psychological tests. Furthermore, Aboyara et al. (2005) strongly recommend the use of structured clinical interviews to help establishing diagnostic validity. The Self-Injurious-Thoughts-and-Behaviors-Interview (SITBI, (Nock, et al., 2007)) is a validated interview in English language and has been used in several international studies. Information about age of onset/cessation, frequency, precipitating factors, functionalities, methods, etc. is gathered for each of the self-injurious thoughts and behaviors. The second study presented in this thesis (Fischer et al., 2014) investigated the diagnostic validity and reliability of the German version of the SITBI (SITBI-G), in order to assess NSSID and SBD. Mainly comparable reliability and validity scores to the English version were found. They included moderate to good test-retest reliability, very good interrater-reliability, and good construct validity (compared to the SHBQ, (Gutierrez, Osman, Barrios, & Kopper, 2001)). However, test-retest reliability concerning lifetime prevalence of NSSI was much

weaker in our study than in the study by Nock and colleagues ($\kappa=.70$ compared to $\kappa=1.0$). In our study, lifetime-prevalence of NSSI was higher at T2 than at T1. Considering the age of participants (around 15 years, where prevalence rates of NSSI tend to incline (Plener, et al., 2015)) and the fact that they were psychiatric inpatients, it is very likely that some participants started engaging in NSSI between T1 and T2. Results were not controlled for this possibility. In the study by Nock et al. (2007), results were controlled for newly occurring NSSI within the follow-up period. This could explain the differences in test-retest-reliability and is one weakness of our study. In total, test-retest-reliability only showed moderate to good values. As data was assessed very carefully, using a clinical interview conducted by trained clinicians, those low values might be explained by memory bias. Due to the high frequency of NSSI in some patients (i.e. daily or several times a week) numbers on the frequency of NSSI within the last year or month were only estimations. Therefore, results from studies using retrospective data, especially on the frequency of NSSI, should be interpreted with care. Another weakness of the SITBI-G is the lack of a question concerning criterion E (NSSI causing clinically significant distress or interference in interpersonal, academic, or other important areas of functioning) of NSSID. However, criterion E has been shown to reach the lowest agreement in several studies using self-report instruments (Gratz, et al., 2015; In-Albon, et al., 2013b). One reason might be that affected adolescents consider NSSI to be a beneficial behavior, which facilitates interpersonal connections and helps to reduce aversive emotions (Klonsky, 2007; Whitlock, Eckenrode, & Silverman, 2006). Therefore, the validity of assessing criterion E in self-report is very questionable. It should be taken into consideration to evaluate criterion E by objective measures (i.e. performance at school, participation in activities) and taking self-, as well external report (i.e. parents, teachers),

into account. Besides those limitations, the SITBI-G can be considered a valid and reliable instrument in order to assess NSSI in adolescents. As the interview is quite extensive, the validation of a revised short version should be considered for future research.

The third study presented in this thesis (Groschwitz, Plener, Groen, Bonenberger, & Abler, 2016), adds on to phase 2, laboratory studies. The need for research defining specific features of NSSI, which can distinguish NSSI from frequently co-occurring mental illnesses (like depression or anxiety disorders), has been demanded repeatedly. One well-known factor in the etiology of NSSI is being bullied or perceiving little social support (Fisher, et al., 2012; Lereya, et al., 2013). However, bullying and social rejection have also been described as a significant risk-factor for adolescent depression (Stapinski, 2015; Ttofi, Farrington, Lösel, & Loeber, 2011a; Ttofi, Özdemir, & Stattin, 2011b). One study, however, showed enhanced feelings of loneliness in adolescents with NSSI, even when controlled for depressive symptoms (Glenn & Klonsky, 2013). Our study was therefore designed to examine differences in neural processing of social rejection in depressed adolescents with and without NSSI. The experimental design included a ball-tossing game called Cyberball, where participants were first included in the game and then excluded (no longer receiving the ball) for two minutes. They were told they were playing with two other adolescents via the internet. Several feelings were evaluated before and after playing Cyberball (i.e. anxiety, helplessness, anger, joy) and participants completed the Need-Threat-Scale (Jamieson, Harkins, & Williams, 2010). All participants (NSSI, Depression, and Healthy Control group) reported feelings of social exclusion which were comparable to, or slightly higher than feelings reported in other studies using Cyberball in depressed (Masten et al., 2011) and healthy (Masten et al., 2009) adolescents.

Adolescents with NSSI reported a stronger increase of feelings of helplessness after Cyberball than before, compared to depressed adolescents without NSSI and healthy controls. This might be one distinguishing factor of social exclusion in depressed adolescents with or without NSSI. Increased feelings of helplessness might lead to adolescents engaging in NSSI as a coping mechanism to reduce negative emotions. In turn, NSSI might increase feelings of self-efficacy by reducing negative emotions through self-administered actions.

Results from fMRI-analyses showed that social rejection led to enhanced activation in the ACC and the anterior insula in all three groups. These results strengthen the validity of the task, since those brain areas have been shown to be involved with the processing of social exclusion repeatedly (Bolling et al., 2011; Eisenberger, Lieberman, & Williams, 2003). Besides those similarities, adolescents with NSSI showed relatively enhanced activation in the vIPFC and the mPFC as compared to depressed adolescents without NSSI and healthy controls. Especially activation in the mPFC has been linked to the evaluation of negative feelings, self-referential processes and mentalizing (Domsalla, et al., 2014; Ochsner et al., 2004) which means the ability to understand others' and one's own mental states (Frith & Frith, 1999; Gallagher & Frith, 2003). Enhanced activation in the vIPFC has been related to the processing of negative emotions and social rejection in several studies (DeWall et al., 2011; Eisenberger, et al., 2003; Moor et al., 2012). Interestingly, Phelps and colleagues (2004) suggested prefrontal regions (i.e. the vIPFC, (Lieberman et al., 2007)) to regulate activity of the amygdala through projections to the mPFC. Therefore, enhanced activation in those regions in adolescents with NSSI might point towards an increased, but unsuccessful regulative effort, as they still reported similar feelings of social exclusion and higher feelings of helplessness as the other participants.

On a similar note, Plener et al. (2012) linked increased activation in the anterior cingulate cortex with simultaneously increased activation in the amygdala (bilaterally) to an insufficient regulatory effort in adolescents with NSSI.

Although there seemed to be similar reactions to social exclusion in both patient groups on a behavioral level, some differences in neural activity were found. This strengthens the validity of NSSID, since NSSID can be differentiated from depression in an experimental setting on a neurobiological basis. However, longitudinal studies are needed to confirm whether those changes facilitate the development of NSSI, or result from engaging in NSSI.

The fourth study presented in this thesis added on to phase 3. While suicidal thoughts and behaviors are symptoms of major depression, SBD has been added in the DSM-5, section 3 (American Psychiatric Association, 2013). Both, NSSI and suicidal behaviors represent self-injurious acts and are mainly distinguished by the intention to die, but also with regards to other factors like frequency, method, and age of onset (Andover, et al., 2012; Jacobson & Gould, 2007; Nock, et al., 2013). Our study (Groschwitz et al., 2015a) added on to the literature, by being the first study to compare both proposed diagnostic entities, as described in the DSM-5. Like in studies comparing NSSI and suicidal behaviors, adolescents with NSSID and SBD had engaged in NSSI significantly more frequently than having attempted suicide and differed in their use of methods (mostly cutting for NSSI vs. overdose for suicide attempts). Interestingly, NSSID and SBD significantly differed with regard to their functionality. While both behaviors mainly served automatic negative reinforcement (i.e. getting rid of bad feelings), automatic positive reinforcement (i.e. feeling something) and social positive reinforcement (i.e. getting attention) were rated

significantly higher regarding NSSID than SBD. Both behaviors serving mainly automatic negative functions is in line with previous research (Klonsky, 2007; Nock, et al., 2007). These results are not surprising, as NSSI mainly serves emotion regulative functions and suicide could be regarded as an ultimate way of ending negative feelings or thoughts. Higher automatic positive reinforcement for NSSI can be interpreted as NSSI being viewed as a coping mechanism, with emotion regulation leading to a more positive state of mind (Klonsky, 2007). Although social positive reinforcement was rated significantly higher for NSSID than for SBD, it was still rated quite low when compared to the other functions. This effect has also been shown in previous studies (for review see (Bentley, 2014)) and might be due to effects of social desirability, as adolescents with NSSI might not want to be considered 'attention seekers' (Fortune, Sinclair, & Hawton, 2008). Overall, there seemed to be a clear differentiation in functionalities, with SBD mainly serving automatic negative functions, and NSSID additionally serving positive automatic and social functions. Despite those clearly differentiating factors, there was a high co-occurrence of NSSID and SBD in our study (51.2% of adolescents with NSSID also met SBD criteria, and 65.6% of adolescents with SBD also met NSSID criteria). This comorbidity is slightly lower than the 70% reported in previous studies (In-Albon, et al., 2013b; Nock, et al., 2013). However, those studies assessed the co-occurrence of NSSI and suicide-attempts and not SBD, which may have led to slightly different results in our study. This high comorbidity is probably due to NSSI being a significant risk-factor for suicidal behaviors (Hawton, et al., 2015; Klonsky, et al., 2013; Tuisku, et al., 2014; Wilkinson, et al., 2011). Results of our study support this notion, when regarding the age of onset of those behaviors in adolescents who met criteria for both, NSSID and SBD. While NSSI started at around the same time as suicidal ideation and suicide plans in most

adolescents, first suicides were mostly attempted at around 2 years after having started to engage in NSSI. Results of our study support Hamza's (2012) integrated model linking NSSI to suicidal behaviors. We found mutual risk-factors, or underlying third variables, like affective disorders and female gender. Furthermore, NSSI started significantly earlier in life, which would support the notion of NSSI and suicide attempts lying on one continuum of self-injurious behaviors. Interestingly, 70% of all suicide attempts were undertaken in individuals who also reported a combination of frequent NSSI, suicidal ideation and suicide plans. Furthermore, NSSI frequency was significantly higher in individuals with SBD, even when controlled for suicidal ideation. This is in line with the notion of frequent NSSI leading to an acquired capability for suicide (Joiner, 2005). In future research, it would be interesting to explore Hamza's model further, by taking perceived burdensomeness, thwarted belongingness, and interpersonal distress into account.

Since NSSI is a symptom of BPD, it is crucial to distinguish NSSI from BPD in order to strengthen diagnostic validity. Studies on NSSID have found NSSID to occur rather independently of BPD, with around 20% of participants with NSSID also being diagnosed with BPD (In-Albon, et al., 2013b; Odelius & Ramklint, 2014). In our study on young adults, who had engaged in NSSI as adolescents (Groschwitz et al., 2015b), 50% also met BPD criteria. This is comparable to a study of adolescent inpatients with NSSI, of which 51.7% showed BPD (Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006). The reasons of why the percentage of participants with BPD was significantly higher in our study than in the other two studies mentioned above, can only be speculated upon. One reason might be that our sample consisted of young adults who had engaged in NSSI since their adolescence and had been highly psychologically impaired, while Odelius and Ramklint

had recruited outpatients. The sample studied by In-Albon, Ruf, and Schmid consisted of adolescent patients, where BPD traits may not yet have been as fully developed as in our study on young adults.

Despite an overlap of 50% of prevailing NSSI and diagnosis of BPD, 50% of those participants who had ceased from NSSI were also diagnosed with BPD. However, although there was no significant association between current NSSI and BPD, earlier age of onset and longer duration of NSSI were significantly correlated with the development of BPD. This result fits in with the Biosocial Development Model of BPD, which considers trait impulsivity and emotion dysregulation leading to the development of BPD and NSSI, with NSSI developing earlier on in life than a personality disorder (Crowell, Beauchaine, & Linehan, 2009). This might point towards early onset of, and prevailing difficulties in emotion regulation implemented in the personality of patients with BPD, whereas these difficulties might be rather temporary in patients with NSSI who do not develop BPD. Therefore, NSSI might be considered an early indicator for BPD (especially if it starts early on in life), although it has to be kept in mind that only a certain percentage of adolescents with NSSI develop BPD later on in life.

Results from this study are also interesting in the light of phase 4, follow-up study. The majority of participants (70%) still met criteria for an axis 1 disorder. This is in line with findings from other studies, showing ongoing psychological, medical and interpersonal consequences in adolescents, whose NSSI had remitted (Asarnow, et al., 2011; Mars et al., 2014; Nakar et al., 2016). In addition, opposite to results from longitudinal studies, NSSI seemed to be rather consistent over time, as 50% of participants still engaged in NSSI. However, this might be due to (1) the specific group of former highly impaired

adolescents and (2) a self-selection bias of participants to be interested in a study on self-injury.

Regarding the longitudinal course of NSSI, the average age of onset was at around 13 years and the average age of cessation (of those who had discontinued NSSI at least one year ago) was at around 17 years. This is in line with a systematic review by Plener et al. (2015) of longitudinal studies, who found a peak of NSSI at around 16 years. There was no significant difference in the current age of those who had discontinued NSSI and those who still engaged in NSSI. In line with findings of three other studies (Rotolone & Martin, 2012; Taliaferro & Muehlenkamp, 2015; Whitlock, et al., 2015), those participants who had discontinued NSSI within the last year, reported less psychiatric impairment, and met less diagnostic criteria for axis 1 disorders. However, results differed from those by Andrews et al. (2013) and Whitlock, Prussien and Pietrusza (2015), who found a lower frequency of NSSI to be predictive of the discontinuation of NSSI in prospective studies. In our study, frequency of NSSI was not related to the cessation of NSSI. However, while Andrews et al., investigated the time-frame of one year, the time frame in our study was significantly longer and may have been biased by the retrospective nature of the data.

Robins and Guze (1970) suggest longitudinal stability to be a major concern for a psychiatric disorder. Long-term stability in the prevalence of NSSI over time was shown by Muehlenkamp et al. (2009), who did not find changes in prevalence rates in high-school students across a time-span of five years. Furthermore, differences in prevalence rates of NSSI as found by Swannell et al. (2014) were all mainly methodological and conceptual issues, whereas publication date of a study did not play a significant role in the fluctuation of prevalence rates. On the other hand, major research on the epidemiology of NSSI only started in the early 2000s and no valid estimates upon the prevalence of NSSI before that

time can be made. Interestingly, lifetime prevalence rates were much higher in adolescents and young adults up to 30 years (around 6%) than in older adults (41-65 years around 2%) in the first study of the general population presented in this thesis. One explanation might be a recall-bias, as described above (Coughlin, 1990), which is also known from studies on suicide attempts Nock et al. (2008). The other explanation could be that the prevalence of NSSI increased steeply in the late 1990s and has been rather stable since then, meaning that adults over the age of 40 would have 'survived' this trend, but young adults aged around 30 would have been at the same risk in their early adolescence as adolescents nowadays. Nevertheless, prevalence rates of NSSI have been stable over the past 15 years, which would warrant for a stability of the diagnosis on a population level.

However, most of the few existing longitudinal studies, and studies including participants of various phases of life, have found a steep decline in prevalence rates from adolescence to adulthood (Plener, et al., 2015). This might suggest that NSSI is a behavior which occurs in adolescence, but is of no further relevance for the general population and should therefore not be considered an independent diagnosis. On the other hand, other psychiatric disorders, which are included in the DSM-5, also show a steep decline in prevalence from childhood to adolescence and adulthood (i.e. attention deficit hyperactive disorder (ADHD) (Dopfner, Hautmann, Gortz-Dorten, Klasen, & Ravens-Sieberger, 2015)). Therefore, longitudinal stability across the lifespan might not be an essential feature of a psychiatric disorder, as some disorders are influenced by developmental processes. In the case of NSSID, neural development might play a major role. For instance, Casey, Jones and Hare (Casey, Jones, & Hare, 2008) see one reason for elevated impulsivity and emotional reactivity in adolescents in the fact that brain areas that are responsible for

top-down processing (i.e. prefrontal regions) develop later in life than brain areas that are associated with bottom-up processing of emotional content (i.e. amygdala). In emotional situations, adolescent behavior might consequently be controlled rather by emotional than top-down regulated processes. This might be a reason why risk-taking behaviors, and NSSI, are much more common in adolescence than in adulthood. Therefore, it would be very interesting to conduct a longitudinal study on adolescents with NSSI to see whether changes in the prevalence or frequency of NSSI are correspondent to changes in neurological emotional control. Although NSSI seems to cease in young adulthood in most case, studies have shown that NSSI in adolescence is associated with higher overall psychological impairment later in life, even when NSSI has ceased (Asarnow, et al., 2011). This was also found in our follow-up study, which found very high rates (70%) of current psychiatric disorders and lower levels of education than the general population in our follow-up study. Another study also showed an increased level of maladaptive coping behavior like drug and alcohol abuse in young adults who had ceased from NSSI (Nakar, et al., 2016) Depending on the frequency and severity of injuries, individuals who have engaged in NSSI in their adolescence might have to deal with scars for the rest of their lives. Therefore, even though NSSI might be decreasing from adolescence to adulthood, being considered a distinct disorder might help to develop appropriate treatment in order to minimize long-term effects of NSSID.

5.1 Limitations

Several limitations apply to the studies presented in this thesis. Three major limitations applying to most of the studies presented in this thesis are the use of retrospective data, rather low participation rates and predominately-female samples. Those three limitations

are discussed below, while minor limitations applying to the individual studies are discussed in the respective manuscripts.

One limitation applying to all samples is the use of retrospective data collected by questionnaires or interviews. Therefore, all data might be influenced by memory bias. This applies predominately to studies 1 and 5, as the investigated period consisted of several years to decades of one's life. However, this is a problem applying to most psychological research which does not use experimental designs or real-time ecological assessment.

Studies 2 and 4 used the same study sample. The participation rate of 54% was relatively low. However, since no incentive was given, it is higher compared to other studies on NSSI at 38% in studies without incentive and comparable to 55% in studies where an incentive was offered (Swannell, et al., 2014). Nevertheless, it has to be kept in mind that prevalence rates reported from this sample might be biased due to natural selection effects. This holds true even more for study 5, where the participation rate was at around 10% and rates of NSSI in this study cannot be generalized. Results might still have been biased by natural selection effects of i.e. participants with ongoing NSSI being more likely to contribute to the study than those who did no longer engage in NSSI.

Another limitation applying to studies 2 to 5 are the predominately female samples. This is probably due to the studies being announced as studies on self-injury. As girls are more likely to engage in NSSI (Bresin & Schoenleber, 2015), they may have been more interested in participating. Furthermore, in study 5, participants were contacted if NSSI had been stated in their clinical files. Most often, NSSI is coded as 'X78' of the ICD-10, which only includes damage to body tissue with a sharp object. As this method is most often endorsed in by female adolescents and gender differences are larger in clinical samples than in the general population (Bresin & Schoenleber, 2015), a mainly female

sample was identified from clinical files. Therefore, our study comprised a rather representative sample of the clinical population of individuals with NSSI with regards to gender differences.

6 Conclusions and perspectives

This thesis aimed to further the validity of NSSID. Results from all five studies presented in this thesis add to the literature concerning four of the five stages of diagnostic validity as suggested by Robins and Guze (1970).

The first study by (Plener, et al., in press) is the first study to evaluate prevalence rates of NSSID in the general population of Germany. Prevalence rates found in this study are in line with studies from the US and confirm NSSID to be a concern in the general population, more so in adolescents and young adults than in older adults. Considering NSSI as distinct diagnosis might therefore help to improve general knowledge of and consideration of NSSI as ‘disorder’ rather than ‘attention seeking behavior’ or ‘Borderline-Personality disorder’ in the general population. However, future research still needs to be conducted on the prevalence of co-morbid diagnoses of individuals meeting NSSID criteria, since prevalence rates are considerably higher in psychiatric samples than in the general population. Furthermore, the frequency threshold of NSSI still warrants further examination (Selby, et al., 2015) and was not addressed in the present study.

In the second study (Fischer, et al., 2014), the German version of the Self-Injurious-Thoughts-and-Behaviors-Interview (SITBI-G) was validated. Clinical interviews are considered the gold standard for the assessment of psychiatric disorders, and the validation of clinical interviews is considered an important step towards diagnostic validity (Aboraya, et al., 2005). As the SITBI-G proved to be a valid instrument for the assessment

of NSSID, it can be considered a valuable instrument, should NSSI be included as psychiatric disorder in the next DSM. Specifically, it addresses a problem mentioned by Selby (Selby, et al., 2015), who requested specific methods of NSSI to be included in NSSID criteria. However, criterion E (evaluation of distress caused by NSSI) would have to be added to the SITBI-G, in order for it to fully assess NSSID-criteria. As an alternative, the questionnaire and semi-structured interview CANDI (Gratz, et al., 2015), which was validated successfully to assess all NSSID criteria, could be translated and validated in German language.

The second phase of diagnostic validity involves laboratory studies, while the third phase considers the exclusion of other disorders. This thesis contributes to both phases by an fMRI-study on the processing of social exclusion in youth with NSSID and depression, youth with mere depression, and healthy controls (Groschwitz, et al., 2016). As social exclusion (i.e. bullying) plays an important role in the development and maintenance of both NSSI and depression in adolescence (Lereya, et al., 2013; Ttofi, et al., 2011b), it is interesting that its neural processing differs significantly between youth with NSSID and depression. This study therefore helps to differentiate NSSID from depression in adolescence on a neurobiological level. For future studies, a number of designs could be interesting in order to validate findings of this study. For example, a sub-group of participants with NSSID, but without depression could be compared to the existing groups in order to rule out the effect of depression. Another interesting study would be the comparison of youth with mere NSSID as compared to youth with Borderline Personality Disorder, as social exclusion also plays an important role in BPD. Furthermore, longitudinal studies in adolescents with NSSID and their reactions to social exclusion in light of the development of BPD, or remission of NSSID with no further psychopathology

could add on to the diagnostic validity of NSSID. Overall, to date, very little is known about the neurobiology of NSSID. Besides social exclusion; neural processing of physical pain, emotional stimuli, stressful events (i.e. error processing or negative social feedback), or the direct effect of self-injury would be interesting subjects for future (longitudinal) fMRI studies on adolescents with NSSID.

In the fourth study of this thesis (Groschwitz, et al., 2015a) , phase 3, the exclusion of other disorders, was addressed. The study aimed to distinguish NSSID from SBD. Although the study showed a large overlap between NSSID and SBD, with greater frequency of NSSI serving as risk factor for SBD; distinguishing factors of both suggested disorders could be found. The most significant divider between NSSID and SBD was the difference in positive functions of NSSID. Participants rated achieving a positive feeling state and positive social reinforcement significantly higher for the act of NSSI than for a suicide attempt. A higher rating of positive effects of NSSI can be considered additional validation of criteria B and C of NSSID. Furthermore, in the first study of this thesis, individuals who met NSSID criteria reported higher automatic positive functions of NSSI than individuals with NSSI, but not meeting NSSID criteria. A constructive idea by Selby (Selby, et al., 2015) might help to strengthen diagnostic validity of those criteria further, by changing ‘to induce a positive feeling state’ to ‘to induce a desired emotional or physical state’. This would include the induction of pain or ‘feeling something when feeling numb’, which is not generally positive, but desired at that moment.

The final study of this thesis (Groschwitz, et al., 2015b) adds on to phase 3 (distinction from other disorders) and phase 4 (follow-up studies). It shows how NSSI in adolescence is not significantly related to BPD in young adulthood. Furthermore, it also shows the consistency of NSSI from adolescence to adulthood (despite treatment), with 50% of all

participants still engaging in NSSI. It has to be considered, though, that participants of this study were formerly highly impaired adolescents, which may have biased results regarding the consistency of NSSI. Although this study strengthens diagnostic validity of NSSID by distinguishing it from BPD and showing longitudinal consistency, it also raises the concern of a lack of validated treatment approaches for NSSI. However, as NSSI had not been recognized as distinguished syndrome for decades, but had rather been considered a symptom of BPD, or mixed with suicidal behaviors by the term 'parasuicidality', treatments focusing on NSSI in adolescence are still scarce. Few treatments show first positive outcomes (i.e. DBT, MBT or CBT). In future research large, randomized controlled trials, in which the major outcome is the reduction of NSSID-symptoms are needed in order to provide appropriate treatment to adolescents with NSSI. This thesis does not add on to the last phase of diagnostic validity, family studies. However, it would be of major interest to conduct cross-generational studies, involving genetic and environmental factors, as to date very little is known about the trans-generational existence and effect of NSSID.

Overall, this thesis furthers the knowledge on diagnostic validity of NSSID by (1) showing a prevalence of 0,3% in the general population in Germany (2) by validating a clinical interview in German language, which can be reliably used to assess NSSID (except for criterion E); (3) by finding distinguishing neurobiological factors between NSSID and depression in adolescents; (4) by clearly distinguishing the act of NSSI from suicidal behaviors (although NSSID was still found a risk factor for SBD), and by (5) by distinguishing adolescent NSSI from adult BPD in a follow-up study.

Future research is still needed to determine a definite frequency threshold of NSSI. This might even involve a dimensional approach to NSSID, by i.e. dividing it into 'mild',

'moderate', or 'severe' NSSI. Another point of interest for further study is the validity of criterion E (clinically significant distress or impairment). Several studies have found instability of the prevalence of NSSI in and beyond adolescence, which would still have to be investigated in more detail in larger longitudinal studies. This would also involve trans-generational family studies. One other major concern is the evaluation of specific treatments for NSSID, as it would be clinically difficult to be able to diagnose a disorder, but not being able to treat it.

Although a significant amount of research is still needed in order to validate NSSID, and changes to the criteria may have to be made, results of this thesis support the consideration of NSSID, by suggesting it to be a clinically significant, prevalent, and independent psychiatric phenomenon.

7 References

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Teile meiner Dissertation wurden bereits in folgenden Fachartikeln veröffentlicht:

Fischer, G., Ameis, N., Parzer, P., Plener, P. L., Groschwitz, R., Vonderlin, E., Koelch, M., Brunner, R. Kaess, M. (2014). The German version of the self-injurious thoughts and behaviors interview (SITBI-G): a tool to assess non-suicidal self-injury and suicidal behavior disorder. *BMC Psychiatry*, 14, 265. DOI: 10.1186/s12888-014-0265-0.

Groschwitz, R. C., Kaess, M., Fischer, G., Ameis, N., Schulze, U. M., Brunner, R., Koelch, M., Plener, P. L. (2015a). The association of non-suicidal self-injury and suicidal behavior according to DSM-5 in adolescent psychiatric inpatients. *Psychiatry Res*, 228, 454-61. DOI: 10.1016/j.psychres.2015.06.019.

Groschwitz, R. C., Plener, P. L., Groen, G., Bonenberger, M., & Abler, B. (2016). Differential neural processing of social exclusion in adolescents with non-suicidal self-injury: An fMRI study. *Psychiatry Research Neuroimaging*, 255, 43-49. DOI: 10.1016/j.pscychresns.2016.08.001.

Groschwitz, R. C., Plener, P. L., Schumacher, T., Stoehr, R., Boege, I., & Kaess, M. (2015b). The situation of former adolescent self-injurers as young adults: A follow-up study. *BMC Psychiatry*, 15, 160-168. DOI: 10.1186/s12888-015-0555-1.

Plener, P., Allroggen, M., Kapusta, N. D., Brähler, E., Fegert, J. M., & Groschwitz, R. C. (2016). The prevalence of NSSI in a representative sample of the German population. *BMC Psychiatry*, 16, 353. DOI: 10.1186/s12888-016-1060-x.

Curriculum Vitae

Rebecca Corinna Groschwitz

Work experience

October 2011 – today
University Hospital of Ulm
Department of Child and Adolescent
Psychiatry and Psychotherapy

Research assistant

April 2015- December 2015
University Hospital of Ulm
Department of Child and Adolescent
Psychiatry and Psychotherapy

CBT therapist

Education

October 2011 – April 2015
Centre for Training in Child and
Adolescent Behavior Therapy
Ulm, Germany

Training in Child and Adolescent CBT

October 2009 – April 2011
University of Technology
Braunschweig, Germany

Psychology/Master of Science

March 2008-October 2008
Auckland University of Technology
Auckland, New Zealand

Study Abroad (Psychology)

October 2006 – June 2009
University of Technology
Braunschweig, Germany

Psychology/Bachelor of Science

Editorial Experience

July 2016 – today
Child and Adolescent Psychiatry
and Mental Health (CAPMH)

Associate Editor

January 2016 – July 2016
Child and Adolescent Psychiatry
and Mental Health (CAPMH)

Managing Editor

Scholarships

2015: DAAD (Deutscher Akademischer Austauschdienst) - travel grant

2012-2014: 'Baden-Württemberg-Scholarship' for PHD-students

2012: DAAD (Deutscher Akademischer Austauschdienst) - travel grant

2009: Scholarship of the University of Technology, Braunschweig, Germany

Awards

2016: International Society for the Study of Self-Injury - 2016 Student Presentation Award

Stand: 30.10.2016

Publications

Peer reviewed:

- 2016: Plener PL, Brunner R, Fegert JM, **Groschwitz RC**, In-Albon T, Kaess M, Kapusta ND, Resch F, Becker K (2016). Treating Nonsuicidal Self-Injury (NSSI) in adolescents: Consensus based German guidelines. *Child and Adolescent Psychiatry and Mental Health*, 10, 46.
- Groschwitz RC**, Plener PL, Groen G, Bonenberger M, Abler B (2016). Differential neural processing of social exclusion in adolescents with non-suicidal self-injury: An fMRI study. *Psychiatry Research: Neuroimaging*, 255, 43-49.
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- Plener PL, Fegert JM, Kaess M, Kapusta ND, Brunner R, **Groschwitz RC**, In-Albon T, Resch F, Becker K (2016). Nicht-suizidales selbstverletzendes Verhalten (NSSV) im Jugendalter: Klinische Leitlinie zur Diagnostik und Therapie. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 44, 1-10.
- 2015: Bonenberger M, Plener PL, **Groschwitz RC**, Groen G, Abler B (2015). Differential neural processing of unpleasant haptic sensations in somatic and affective partitions of the insula in non-suicidal self-injury. *Psychiatry Research: Neuroimaging*, 234, 298-304.
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Plener PL, **Groschwitz RC**, Franke C, Fegert JM, Freyberger HJ (2015). Psychiatric in-patient care for adolescents in Germany. *Zeitschrift für Psychiatrie, Psychologie und Psychotherapie*, 63, 181-186.

2014: Fischer G, Ameis N, Parzer P, Plener PL, **Groschwitz RC**, Vonderlin E, Kölch M, Brunner R, Kaess M (2014). The German version of the self-injurious thoughts and behaviors interview (SITBI-G): a tool to assess non-suicidal self-injury and suicidal behavior disorder. *BMC Psychiatry*, 14, 265.

Young R, Sproeber N, **Groschwitz RC**, Preiss M, Plener PL (2014). Why alternative teenagers self-harm: Exploring the link between non-suicidal self-injury, attempted suicide and adolescent identity. *BMC Psychiatry*, 14, 137.

2013: **Groschwitz RC***, Bonenberger M*, Plener PL, Böge I, Petermann F (2013). Instrumente zur standardisierten Diagnostik von nicht-suizidalen selbstverletzendem Verhalten (NSSV) im deutschen Sprachraum. *Zeitschrift für Psychiatrie, Psychologie und Psychotherapie*, 62, 65-71.

*shared first authorship

Bonenberger M*, **Groschwitz RC***, Kumpfmüller D, Groen G, Plener PL, Abler B (2013). It's all about money: oral contraception alters neural reward processing. *NeuroReport*, 24, 951-955.

*shared first authorship

Groschwitz RC, Plener PL (2013). Psychotherapie von nicht suizidalem selbstverletzendem Verhalten. *Nervenheilkunde*, 32, 30-37.

Groschwitz RC, Plener PL (2013). Zusammenhang von nicht-suizidalem selbstverletzendem Verhalten (NSSV) und Suizidalität bei Jugendlichen. *Suizidprophylaxe*, 152, 5-13.

Plener PL, Fischer CJ, In-Albon T, Rollet B, Nixon MK, **Groschwitz RC**, Schmid M (2013). Adolescent Non-Suicidal Self-Injury (NSSI) in German speaking countries: Comparing prevalence rates from three community samples. *Soc Psychiatry Psychiatr Epidemiol*, 48, 1439-45.

2012: **Groschwitz RC**, Plener PL (2012). The neurobiology of non-suicidal self-injury (NSSI): A review. *Suicidology Online*, 3, 24-32.

Not peer reviewed:

- 2013: Plener PL, **Groschwitz RC**, Bonenberger M, Fegert JM (2013). Traumatische Lebenserfahrungen bei Jugendlichen mit nicht-suizidalem selbstverletzendem Verhalten (NSSV). *Kinder- und Jugendschutz in Wissenschaft und Praxis (KJug)*, 58, 81-85.

Presentations

- 2016: **Groschwitz RC**, Plener P, Groen G, Neff D, Bonenberger M, Abler B (2016). Processing of social situations in adolescents with self-injury and adults with borderline personality disorder. Presentation at the 11th Annual Meeting of the International Society for the Study of Self-Injury in EauClaire, USA.
- Groschwitz RC**, Plener P, Groen G, Neff D, Bonenberger M, Abler B (2016). Neuronale Verarbeitung von sozialen Situationen bei Jugendlichen mit selbstverletzendem Verhalten und Erwachsenen mit Borderline-Persönlichkeitsstörung. Presentation at the Forschungstagung der Deutschen Gesellschaft für Kinder- und Jugendpsychiatrie (DGKJP) in Frankfurt, Germany.
- 2015: **Groschwitz RC** (2015). Psychotherapeutic treatment of non-suicidal self-injury in adolescence. Presentation at the 5th Young Psychiatrists Network Meeting in Porto Heli, Greece.
- Groschwitz RC**, Abler B, Groen G, Bonenberger M, Plener P (2015). Neural processing of social rejection and physical pain in adolescents with non-suicidal self-injury – an fMRI-study. Presentation at the 10th Annual Meeting of the International Society for the Study of Self-Injury in Heidelberg, Germany.
- Groschwitz RC**, Abler B, Groen G, Bonenberger M, Plener P (2015). Neuronale Verarbeitung sozialer Ausgrenzung bei Jugendlichen mit nicht-suizidalem selbstverletzenden Verhalten. Presentation at the XXXIV. Congress of the Deutschen Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie (DGKJPP) in Munich, Germany
- Groschwitz RC**, Plener PL (2015). Jugendliche mit nicht-suizidaler Selbstverletzung als junge Erwachsene – eine katamnestische Studie. Presentation at the XXXIV. Congress of the Deutschen Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie (DGKJPP) in Munich, Germany.
- 2014: **Groschwitz RC**, Abler B, Groen G, Bonenberger M, Plener P (2014). Neural correlates of social rejection in adolescents with non-suicidal self-injury – preliminary results. Presentation at the Third International Congress on Borderline Personality Disorder and Allied Disorders in Rome, Italy.

Groschwitz RC, Plener PL (2014): Characteristics of Non-Suicidal Self-Injury (NSSI) in a Community and a Clinical Adolescent Sample. Presentation at the 21st world Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP) in Durban, South Africa.

Groschwitz RC, Plener PL (2014): Addictive characteristics of NSSI. Presentation at the 9th Annual Meeting of the International Society for the Study of Self-Injury in Chicago, USA.

Groschwitz RC, Plener PL (2014): Macht Selbstverletzung süchtig? Vergleich einer klinischen und einer schulischen Stichprobe. Presentation at the 32. Symposium der Fachgruppe für Klinische Psychologie und Psychotherapie der DGPs in Braunschweig, Germany.

2013: **Groschwitz RC, Kaess M, Fischer G, Parzer P, Ulrich N, Koelch M, Plener PL (2013).** Self-Injurious Thoughts and Behaviours in Adolescent Psychiatric Patients. Presentation at the 15. International Congress of the European Society for Child and Adolescent Psychiatry (ESCAP).

Groschwitz, RC (2013). Diagnostik von Selbstverletzendem Verhalten. Presentation at the XXXIII. Congress of the Deutschen Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie (DGKJPP) in Rostock, Germany.

Posters:

2016: **Groschwitz RC, Plener P, Groen G, Neff D, Bonenberger M, Abler B (2016).** Neural processing of social rejection in adolescents with NSSI and adults with BPD. Poster presented at the Annual Conference of the Organization for Human Brain Mapping (OHBM), Geneva, Switzerland.

2015: **Groschwitz RC, Schumacher T, Munz L, Plener PL (2015).** The Course and Predictors of Non-Suicidal Self-Injury and Deliberate Self-Harm: A Systematic Review of Longitudinal Studies. Poster presented at the International Association for Suicide Research (IASR) in New York, USA.

Groschwitz RC, Abler B, Groen G, Bonenberger M, Plener P (2015). Neural correlates of social rejection in adolescents with non-suicidal self-injury – an fMRI-study. Poster presented at the Annual Conference of the Organization for Human Brain Mapping (OHBM), Honolulu, USA.

Groschwitz RC, Plener PL (2015). Immigration as risk factor for suicide attempts in adolescence. Poster presented at the 1st Roman Forum on Suicide in Rome, Italy.

2013: **Groschwitz RC, Kaess M, Fischer G, Parzer P, Ulrich N, Koelch M, Plener PL (2013).** Associations of NSSI and Suicidal Thoughts and Behaviours in Adolescent Psychiatric Patients. Poster presented at the 8th Annual Meeting of the International Society for the Study of Self-Injury, Vancouver, Canada.

2012: **Groschwitz RC**, Du M, Bonenberger MA, Plener PL (2012). Preliminary Results of an Ongoing Catamnestic Study of Adolescent Self-Injurers. Poster presented at the 7th Annual Meeting of the International Society for the Study of Self-Injury, Chapel Hill, North Carolina, USA.