



# Differential neural processing of social exclusion in adolescents with non-suicidal self-injury: An fMRI study



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## ABSTRACT

Non-suicidal self-injury (NSSI) is highly prevalent in adolescence and has been suggested as an autonomous diagnosis in the Diagnostic and Statistical Manual (DSM-5). Social rejection is as potential risk-factor for NSSI and depression in adolescence. Objectives of this study were to identify differences in neural processing of social rejection in depressed adolescents with and without co-morbid NSSI and healthy controls. Participants were 28 depressed adolescents (14 with co-morbid NSSI, 79% females) and 15 healthy controls, with an average age of 15.2 years ( $SD=1.8$ ). Social exclusion was implemented using the Cyberball paradigm 'Cyberball' during functional magnetic resonance imaging (fMRI). All participants reported feelings of social exclusion after fMRI scanning. Investigating the effects of NSSI, we found that depressed adolescents with NSSI showed relatively enhanced activation of the medial prefrontal cortex (mPFC) and the ventrolateral prefrontal cortex (vlPFC) compared to depressed adolescents without NSSI and also compared to healthy controls. Results point towards divergent processing of social exclusion in depressed adolescents with NSSI as compared to adolescents with mere depression in brain regions previously related to the processing of social exclusion. This finding of distinct neurophysiological responses may stimulate further research on individual treatment approaches.

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## 1. Introduction

Non-suicidal self-injury (NSSI) is a common phenomenon in adolescence. Lifetime prevalence rates of about 18% were found in international samples (Muehlenkamp et al., 2012), and 12-month prevalence rates for repetitive NSSI range between 4% and 6.7% (Plener et al., 2014; Zetterqvist et al., 2013). Hereby, NSSI in adolescence, other than in adulthood seems to occur rather independently of Borderline Personality Disorder (BPD) (Kaess et al., 2014; Nock et al., 2006). In clinical samples, around 70–80% of adolescents engaging in NSSI are also diagnosed with major depression (Glenn and Klonsky, 2013; Groschwitz et al., 2015a; In-Albon et al., 2013), but the phenomenon also occurs without any further psychopathology (Stanford and Jones, 2009). Independent of a comorbid psychopathology, however, NSSI is often associated with emotional and social functional impairment (Turner et al., 2012) and NSSI has been proposed as a separate diagnosis in DSM-5, Section 3 (APA, 2013).

First evidence regarding a distinct neurobiology of NSSI was

demonstrated in one study, showing altered activation of amygdala, anterior cingulate cortex (ACC) and hippocampus in a pilot functional magnetic resonance imaging (fMRI) study in adolescents with NSSI compared to healthy controls while viewing emotional pictures (Plener et al., 2012). In young adults, a history of NSSI modulated the reactivity of the insula to physical pain (Bonenberger et al., 2015).

The expectation to regulate emotions through NSSI seems to occur particularly in the context of interpersonal problems. In several longitudinal studies, being bullied by peers (Fisher et al., 2012; Lereya et al., 2013) and siblings (Bowes et al., 2014) has been shown as a risk factor for NSSI in adolescence and young adulthood (for review: Plener et al. (2015)), while social support has been identified as a significant protective factor (Tatnell et al., 2014). In a large European sample (SEYLE-study; Brunner et al. (2014)), self-injurious behaviors were strongly linked to peer-related rejection and peer-victimization. Furthermore, adolescents with NSSI reported greater levels of loneliness compared to a clinical control-group (Glenn and Klonsky, 2013). In a real-time ecological assessment study of adolescents and young adults, feelings of rejection were associated with increased risk of engaging in NSSI (Nock et al., 2009). Besides being a risk-factor for NSSI, social exclusion has also been shown to increase the risk of

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adolescent depression (Stapinski et al., 2015; Ttofi et al., 2011).

To further elucidate the neurobiological underpinnings of the link between social rejection and NSSI in adolescents, we used the ‘Cyberball’ paradigm (Eisenberger et al., 2003; Williams et al., 2000), as a well-established experimental tool to elicit feelings of social exclusion under laboratory settings. Participants play a virtual ball-tossing game, during which they are made to believe that they play against two other real players, while in fact the other players are operated by a computer. Usually, an ‘Inclusion’ condition where participants receive one third of all tosses, and an ‘Exclusion’ condition where participants do no longer receive the ball are conducted. Cyberball has been successfully applied in several fMRI studies with healthy adolescents. Like in healthy adult samples, enhanced activation in the anterior insula, the ventral lateral prefrontal cortex (vlPFC), and the mPFC when contrasting the exclusion condition against the inclusion condition were described (Bolling et al., 2011; Masten et al., 2009, 2010). The suitability of the task for investigating clinical samples has been shown with adult BPD patients that clearly felt more rejected than healthy controls during the Cyberball task. Interestingly, this was true for the ‘Inclusion’ condition as well as the ‘Exclusion’ condition (Staebler et al., 2011b). In a study using fMRI, Domsalla et al. (2013) replicated these findings and found enhanced activation in the dorsal anterior cingulate cortex (dACC), and the medial prefrontal cortex (mPFC) across all conditions (inclusion and exclusion) in BPD patients. Ruocco et al. (2010) reported enhanced activation in the dlPFC in BPD-patients during social exclusion in a functional near-infrared spectroscopy study (fNIRS).

As social exclusion represents a significant risk factor for both, the development of NSSI and depression in adolescents, the aim of the present study was to investigate whether the behavior and neural processing of social exclusion would differ in depressed adolescents with or without NSSI and also from healthy controls. We hypothesized that if NSSI adds variance to the neurophysiological responding in depressed adolescents, significant between-group differences would emerge most likely in brain regions previously linked to the processing of social exclusion.

## 2. Methods

### 2.1. Participants

Participants of this study were 28 adolescents with a diagnosis of Major Depression (see Table 1). Of those depressed adolescents, 14 had a history of NSSI, repeatedly (five times or more) within the last year (“NSSI group”), and met all criteria for NSSI disorder as proposed in Section 3 of DSM-5 (APA, 2013). The other 14 participants met criteria for Major Depression at the time of the study, but had not engaged in NSSI within the last year (“Depression group”). Five participants of the Depression group reported minor lifetime NSSI (two participants once, one participant four times and two participants seven times). One participant of the NSSI group was diagnosed with BPD, while there were no participants with this diagnosis in the Depression group. Participants were recruited from in-patient and outpatient units of the University Hospital for Child and Adolescent Psychiatry and Psychotherapy Ulm, Germany and from a private medical practice for child and adolescent psychiatry in Ulm, Germany. Fifteen healthy controls, who had never been diagnosed with any psychiatric disorder in their lifetime (healthy control group, “HCG”) were recruited as a control group (see Table 1). Of all 43 participants, three were left handed, two reported to smoke cigarettes regularly (smoking was prohibited at least 2 h before fMRI), and none of the participants reported excessive use of alcohol, as assessed by the according section of the K-SADS-PL (description see below). Other substance use disorders were excluded as well as any current medical illnesses. All participants had reached puberty and all female participants were scanned between day one and ten of their menstrual cycle or after at least 14 days of continuous intake of oral contraception. Participants with a history of epilepsy were excluded.

Depressed adolescents with and without NSSI were matched for age, gender, IQ, and depression-scores (see Table 1). In order not to interfere with patients’ medical treatment, participants were not asked to interrupt psychopharmacological treatment. Instead, medication was held stable for at least two weeks before fMRI to ascertain steady state conditions. Regarding impulsivity (see below), both patient groups did not differ significantly

**Table 1**  
Socio-demographic data of participants.

|                               | NSSI group     |       | Depression group |      | HC group       |      | F     | p      |
|-------------------------------|----------------|-------|------------------|------|----------------|------|-------|--------|
| N                             | 14             |       | 14               |      | 15             |      |       |        |
| Gender                        | 11female/3male |       | 11female/3male   |      | 12female/3male |      |       |        |
|                               | M              | SD    | M                | SD   | M              | SD   |       |        |
| Age                           | 15.4           | 1.9   | 15.9             | 1.6  | 14.5           | 1.7  | 2.05  | .142   |
| IQ                            | 101.3          | 13.2  | 101.3            | 11.4 | 110.0          | 10.4 | 2.85  | .07    |
| CDRS-R-Score                  | 51.4           | 13.6  | 55.4             | 8.0  | 21.4           | 2.5  | 23.40 | < .001 |
| BDI-II-Score                  | 21.7           | 12.2  | 25.8             | 11.3 | 2.7            | 3.5  | 58.4  | < .001 |
| Number of NSSI last year      | 90.6           | 226.1 | 0                | –    | 0              | –    | –     | –      |
| Medication                    |                |       |                  |      | –              |      | –     | –      |
| Antidepressants               | n=2            |       | n=7              |      |                |      |       |        |
| Psychostimulants              | n=1            |       |                  |      |                |      |       |        |
| Clinical diagnoses            |                |       |                  |      | –              |      | –     | –      |
| Major Depression              | N=14           |       | N=14             |      |                |      |       |        |
| Anxiety Disorder              | N=1            |       | N=2              |      |                |      |       |        |
| Posttraumatic Stress Disorder | N=0            |       | N=4              |      |                |      |       |        |
| Eating Disorder               | N=2            |       | N=3              |      |                |      |       |        |
| ADHD                          | N=3            |       | N=1              |      |                |      |       |        |
| Conduct Disorder              |                |       |                  |      |                |      |       |        |
| Smoking cigarettes            | –              |       | N=1              |      | N=1            |      |       |        |

Note: M=mean, SD=standard deviation, NSSI=non-suicidal self-injury, HC=Healthy Control, IQ=intelligence quotient, CDRS-R=Children's Depression Rating Scale – Revised, BDI-II: Beck's Depression Inventory 2nd edition

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