Psychiatry Research: Neuroimaging 255 (2016) 43–49

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

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

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ARTICLE INFO

Article history:
Received 13 January 2016
Received in revised form
1 July 2016
Accepted 4 August 2016
Available online 5 August 2016

Keywords:
Non-suicidal self-injury
fMRI
Social exclusion
Cyberball
NSSI diagnosis

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.

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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http://dx.doi.org/10.1016/j.pscychresns.2016.08.001

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					
Postraumatic Stress	N = 0		N = 4					
Disorder	N = 2		N = 3					
Eating Disorder	N = 2		N = 1					
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

(Chi^2=.58, p=.70), with seven participants in the depression group and five participants in the NSSI group showing elevated impulsivity scores. Healthy controls were matched to patient groups with regards to age, gender, and IQ.

The study was approved by the Institutional Review Board of Ulm University, Ulm, Germany. Written informed consent was obtained from legal guardians and participants. All procedures were performed according to the Declaration of Helsinki.

2.2. Psychometric measurements

Diagnoses were assessed using the German version of the clinical interview *Schedule for Affective Disorders and Schizophrenia for School-Age-Children-Present and Lifetime* (K-SADS-PL) for DSM-IV diagnoses (Delmo et al., 2000). Impulsivity was screened for by the item "impulsivity" of the K-SADS-PL. The semi-structured *Self-injurious thoughts and behaviors interview* (SITBI; (Nock et al., 2007)) was used to obtain detailed information about participants' NSSI (present and lifetime). The interview consists of 169 items assessing frequency, functions and other characteristics of several self-injurious thoughts and behaviors (Fischer et al., 2014). In order to assess current depressive symptoms, the *Beck Depression Inventory, second edition* (BDI-II; (Beck et al., 1996)); German version: (Hautzinger et al., 2006) and the semi-structured interview *Children's Depression Rating Scale, Revised* (CDRS-R; (Poznanski and Mokros, 1996); German version: (Keller et al., 2011)) were applied. The IQ of each participant was either taken from clinical files (where applicable) or measured by the *Prüfsystem für Schul- und Bildungsberatung für 6.–13. Klassen* (PSB, (Horn et al., 2003)), a validated and normed German tool to reliably assess the IQ of adolescents. IQs of inpatients from clinical files were either assessed using the *PSB* or the *Wechsler intelligence scale for children* (WISC-IV; Wechsler, (Petermann and Petermann, 2011)).

The Rejection Sensitivity Questionnaire (RSQ); (Downey and Feldman, 1996) was translated from its original English version for adolescents into German. Furthermore, an existing German version for adults (Staebler et al., 2011a) was adapted for adolescents. Items were then matched from both versions and compiled to a questionnaire of 18 items. Total scores were calculated according to Staebler et al. (2011a) by multiplying the scale 'anxiety or concern' with the inverted scores of the scale 'expectancy of acceptance' and dividing the result by the number of items. The 20-item *Need-Threat-Scale* (NTS; (Jamieson et al., 2010)) was translated into German. It is a well-established scale for measuring distress after social exclusion elicited by the task 'Cyberball'. Items are divided into four sub-scales ("Feeling excluded", "Low self-worth", "Meaningless existence", "Control") comprising five items each. Each item was rated on a scale from 1 (not at all) to 5 (very much). Total scores were calculated by dividing the final result by 20. Therefore, reaction to Cyberball can range from 1 (no distress) to 5 (very high distress).

2.3. Experimental task

In order to elicit social rejection, the well-established Cyberball task (Williams et al., 2000) was used. Participants were made to believe that they were playing a virtual ball-tossing game with other adolescents, who were sitting in another room and were connected to the computer in the fMRI-scanner. In reality, the other players did not exist and all actions were pre-programmed. The other players were represented as animated comic-strip characters (for details see (Eisenberger et al., 2003; Williams et al., 2000)). Participants were represented by a hand at the bottom part of the screen. All participants played three rounds of Cyberball, with every round lasting 60 throws (around two minutes). In the first round ("Baseline"), participants were told to only watch all three players tossing the ball to each other, while their character was controlled by the computer. In the second round ("Inclusion"), participants had a random ball possession in one third of tosses. The third round ("Exclusion") started with 10 throws of 30% randomized ball-possession. For the remaining 50 throws, participants were excluded from the game. Before round one and after round three, participants were asked to rate their current emotional state with regards to several feelings (angry, sad, frustrated, helpless, anxious, happy, content). Information about the real nature of the game and an explanation for the necessity of deception in this experiment was given after the experiment in a debriefing session.

2.4. Functional data acquisition

A 3.0 T MAGNETOM Allegra Scanner (Siemens, Erlangen, Germany) was used to obtain fMRI data. A T2*-sensitive gradient echo sequence was used for functional imaging, with an echo time (TE) of 33 ms, a flip angle of 90°, a field of view (FOV) of 230 mm, and a slice thickness of 2.5 mm with an interslice gap of .5 mm. At a repetition time (TR) of 2000 ms, 35 transversal slices were recorded with an image size of 64×64 pixels during the Cyberball task. Anatomical high resolution T1-weighted images ($1 \times 1 \times 1$ mm voxels) were acquired (band-width (BW)=130 Hz/Pixel, TR=2500 ms, TI=1.1 s, echo time (TE)=4.57 ms, flip angle=12°) for reasons of co-registration and normalization into standardized stereotactic space.

2.5. Data analysis

2.5.1. Behavioral data

Statistical differences were calculated in SPSS (IBM SPSS Statistics, version 21), using ANOVAs and *t*-tests where applicable. Differences in feelings before and after Cyberball were calculated (post-pre) using a Mann-Whitney-Test for testing on specific group differences. Hypothesis-driven post-hoc *t*-tests were conducted to test for differences in feelings between the NSSI group and controls, as differences in emotional reactivity to Cyberball have been found between BPD patients and controls in a previous study (Renneberg et al., 2012).

2.5.2. fMRI-data

The Statistical Parametric Mapping Package 8 (SPM 8, Wellcome Trust Centre for Neuroimaging, London, UK) was used for image data pre-processing and statistical analyses. In order to correct for head movement and slice acquisition delay, realignment and slice timing was performed during pre-processing. Images were normalized to the standard MNI-template (Montreal Neurological Institute). Spatial smoothing was conducted using an 8 mm full width at half maximum (FWHM) Gaussian kernel. Low frequency drifts were removed via high pass filtering, and an AR (1) model was used to account for intrinsic autocorrelations.

For individual first level analyses, a general linear model was used to estimate the variance of voxels for each condition. The Cyberball task was modeled as three separate blocks of condition (baseline, inclusion and exclusion) as has been a common procedure in previous studies (Eisenberger et al., 2009, 2007b). Regressors representing the six motion parameters were integrated into the design matrix.

For second level group analysis, we set up a 3×3 ANOVA model with the two factors 'group' and 'condition' that included first level contrasts for the three ball tossing conditions for each of the three groups. A main effect of 'condition' and an interaction effect of 'group' × 'condition' was entered. A threshold of $p < .001$, uncorrected for multiple comparisons, with a minimum cluster-size of 10 was used for the whole brain analysis, as previously

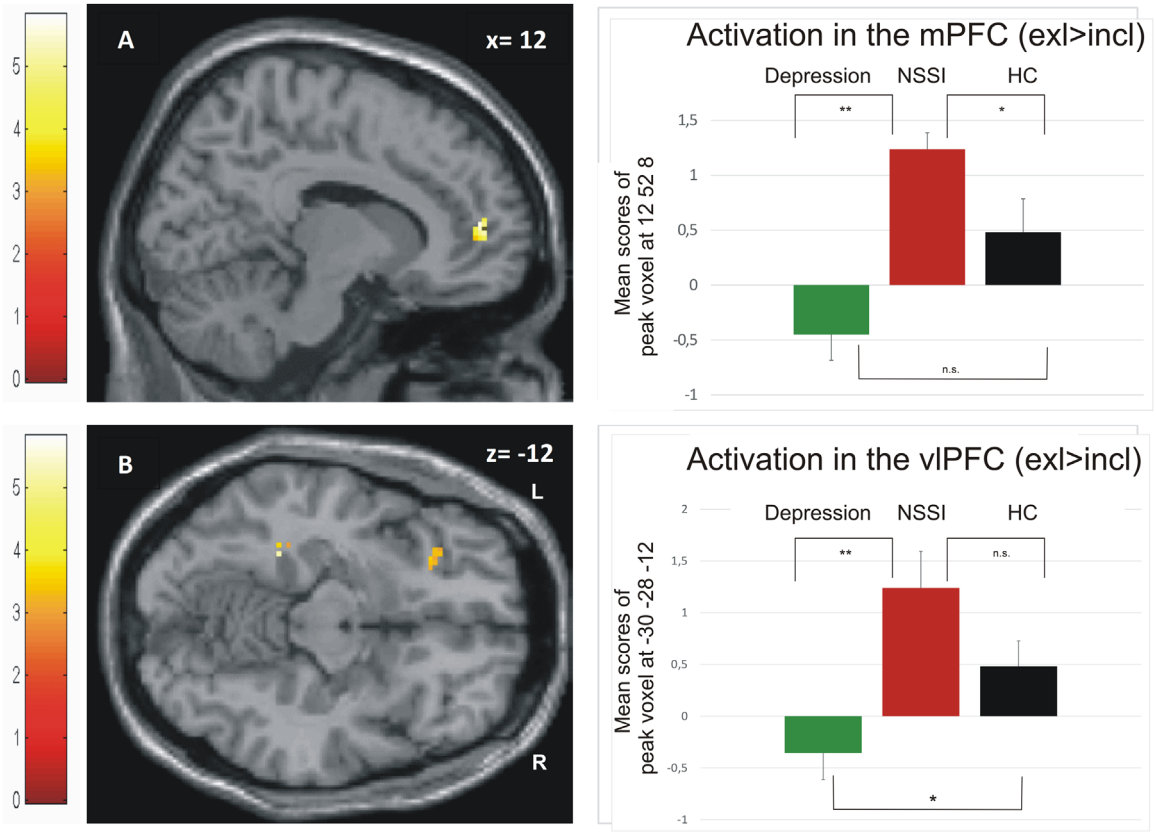

Fig. 1. Activation during social exclusion (Contrast: exclusion > inclusion, NSSI > Depression group) in the right mPFC (A) and the left vlPFC (B). Bar graphs show the mean activation and standard errors of the peak voxels of the contrast in the two patient groups and additionally the activation in the controls in the same voxel. Peak voxel activation during social exclusion was significantly lower in the HCG group in comparison to the NSSI group in the mPFC (T = −2.92, p = .007) and lower by trend (T = −1.75, p = .09) in the vlPFC. On the other hand, activation was significantly higher in the HCG group as compared to the Depression group in the vlPFC (T = 2.32, p = .03) and higher by trend (T = 1.82, p = .08) in the mFPC *Note:***p < .01,*p < .05.

reported by Domsalla et al. (2014) and Eisenberger et al. (2009). For a priori-defined regions of interest (i.e. vlPFC and dACC) whole-brain analyses were repeated at a p < .005 threshold, a method also used by Masten et al. (2010). Post-hoc tests were performed for the contrasts of interest, testing differential effects between groups for 'exclusion > inclusion' at a threshold of p < .001, minimum cluster size 10 voxels. Exclusion > inclusion was chosen as the main contrast of interest concerning ball-tossing conditions according to Eisenberger et al. (2003). Post-hoc tests were restricted to the voxels with an effect in the 3 × 3 ANOVA by using a mask at a threshold of p < .05.

For the two a priori defined regions of interest, i.e. the vlPFC and the mPFC, we extracted beta values of the peak voxels of the whole brain analyses of the post-hoc comparison of NSSI vs. Depression group for demonstration purposes as depicted in Fig. 1. For this peak voxel, we further post hoc compared the activation in each of the patient groups with that in healthy controls using independent *t*-tests.

3. Results

3.1. Behavioral data

Using a variance analytical approach (1 × 3 ANOVA with factor group), significant differences were found among all three groups concerning trait sensitivity, as measured by the RSQ (F = 9.57, p < .001, df = 2). Post-hoc *t*-tests revealed no significant differences between the two patients' groups with regards to trait sensitivity of social rejection ($T = -1.1$, p = .28; $M_D = 92.3$ (M = mean) ($SD = 40.5$), $M_{NSSI} = 112.9$ ($SD = 50.5$)). However, both, the depression group ($T = 3.467$, $p = .002$) and the NSSI group ($T = 4.351$, $p < .001$) scored significantly higher than the HCG ($M_{HCG} = 49.9$ ($SD = 22.2$)).

Overall, participants reported that they felt excluded and distressed after the 'Exclusion' condition of Cyberball according to the Need-Threat-Scale ($M = 3.7$, $SD = .97$, min = 2.5, max = 4.95; possible maximum = 5). Participants in the NSSI group reported the highest ratings of feeling excluded ($M_{NSSI} = 3.71$ (1.01)), followed by the Depression group ($M_D = 3.62$, (.86)), and the HCG ($M_{HCG} = 3.16$ (.91)). However, there were no significant differences among the three groups (F = 1.34, p = .28, df = 2).

In general, all participants felt significantly more angry ($p = .006$, $Z = 2.74$), more frustrated ($p = .003$, $Z = 2.94$), and less content ($p = .001$, $Z = 3.27$), after Cyberball than before. A multifactorial ANOVA did not show significant differences in feelings among the three groups. Post-hoc tests that were conducted according to the findings of (Renneberg et al., 2012) revealed that the NSSI group reported feeling significantly more helpless after Cyberball than healthy controls ($T = -2.27$, $p = .032$).

3.2. Neuroimaging data

3.2.1. Main effect of condition

A main effect of condition across all three groups was seen in areas previously linked to the Cyberball task, including the anterior Insula, the ACC and the parahippocampus. Additional clusters were found in the pre supplementary motor area (pre SMA) and secondary visual regions. A correlational analysis between behavioral and neuroimaging data revealed no significant results.

Table 2
Interaction effect of group × condition.

	L/R	BA	x/y/z	*k*	Z	p
Medial prefrontal cortex	L	9/10	−8/42/6	26	3.69	<.001
Parahippocampus	L	36	−28/−40/−16	18	3.72	<.001
pre supplementary motor region	R	6	54/4/30	13	3.45	<.001

Whole brain 3 × 3 ANOVA, independent factor: 'group' (NSSI, Depression, Healthy Controls), repeated measure factor: 'condition' (inclusion, exclusion, baseline), significance level at p < .001, uncorrected, min. 10 voxels per cluster.
Note: L and R = left and right hemispheres; BA = Brodmann's Area; x, y, and z = MNI coordinates in the left-right, anterior-posterior, and interior-superior dimensions, respectively; *k* = cluster size; Z and p = Z- and p-score at corresponding coordinates, respectively (local maxima).

3.2.2. *Interaction effect of group and ball tossing condition*

Significant interaction effects of group and condition (p < .001) were found in the parahippocampus (28/−40/−16), the mPFC (−8/42/6), and the pre SMA (54/4/30). These results are presented in Table 2 in more detail. At a significance threshold of p < .005, for a priori defined regions, significant differences in activation in the left vlPFC (−30/26/−14) were additionally found.

3.2.3. *Effect of NSSI on social exclusion in depressed adolescents*

Post-hoc analyses revealed increased brain activation in the NSSI-group compared to the Depression-group in the mPFC (12/52/8), the vlPFC (−30/28/−12) and the parahippocampus (−28/−40/−12) (see Table 3) upon social exclusion minus inclusion. Depressed adolescents without NSSI did not show relatively increased differential activation in any brain region, as compared to the NSSI-group. Post-hoc analysis did not show differences among the NSSI or the Depression and the HCG-group at given thresholds of p < .001 in the whole brain analyses.

3.2.4. *Region of interest analyses*

In a final step, we explored brain activation in the mPFC and vlPFC in more detail to find out how the activation in the patient groups related to the activation in controls. Peak voxel activation in the mPFC and vlPFC, as the two most prominent regions with differences between patient groups, was extracted for both patient groups and also HC. An ANOVA on this peak voxel activation confirmed significant differences among the three groups regarding the mPFC (F = 12.36, p < .001) and the vlPFC (F = 7.35, p = .002). Post-hoc *t*-tests were performed to explore those differences in more detail (see Fig. 1).

Table 3
Differences in activation between the Depression and NSSI and the Depression without NSSI group during social exclusion.

Contrast Depression and NSSI > Depression without NSSI	**L/R**	**BA**	**x/y/z**	***k***	**T**
Medial prefrontal cortex	R	9/10	12/52/8	22	3.57
Ventrolateral prefrontal cortex	L	11	−30/28/−12	15	3.64
Parahippocampus	L	36	−28/−40/−12	157	4.54

Cyberball: exclusion > inclusion, significance level at p < .001 uncorrected, cluster threshold 10 voxels, masked by results of interaction analysis at a p < .05 threshold.
Note: L and R = left and right hemispheres; BA = Brodmann's Area; x, y, and z = MNI coordinates in the left-right, anterior-posterior, and interior-superior dimensions, respectively; *k* = cluster size; t and p = t- and p-score at corresponding coordinates, respectively (local maxima).

4. Discussion

The present study investigated differences in neural processing of social exclusion in adolescents with major depression with and without NSSI and healthy controls. Although subjective feelings of being excluded were equal in both patients groups, activation in the mPFC and the vlPFC were relatively increased in depressed adolescents with NSSI. Post-hoc comparisons of both clinical groups against a group of healthy controls revealed that activation differed among all three groups. While activation in the mPFC was significantly higher during social inclusion in the NSSI group than the HC group, activation was significantly lower in the Depression group than the HC group in the vlPFC. This finding supports the view that those differences are not merely a result of different samples, but most likely associated with the presence or absence of NSSI in adolescents with depression.

Reported feelings of social exclusion in this study were comparable to, or slightly higher than those reported in other studies using the Cyberball paradigm in healthy (Masten et al., 2009) and depressed (Masten et al., 2011) adolescents before. These results support the validity of the task as used in the current samples. Our results of increased feelings of social exclusion in depressed adolescents irrespectively of ongoing NSSI is in line with several studies that have identified bullying and social rejection as potent risk factors for adolescent depression (Reijntjes et al., 2010; Stapinski et al., 2015; Ttofi et al., 2011). Furthermore, one meta-analysis (Reijntjes et al., 2010) of longitudinal studies found depressive symptoms both, antecedent and as a consequence of bullying. Therefore, increased subjective feelings of being socially excluded might on the one hand relate to generally more frequent experiences of social exclusion in depressed adolescents. On the other hand, currently depressed adolescents might be generally prone to feelings of social exclusion due to a cognitive bias leading to interpreting (and consequently reacting to) mildly negative social experiences in a more intense way than healthy adolescents.

Interestingly, despite similar subjective ratings of feeling excluded and similar sensitivity to social rejection, presence or absence of NSSI in depressed adolescents modulated the neural processing of a task on social exclusion in specific regions. Relatively enhanced activation in the vlPFC has been related to the processing of negative experiences, including the experience of social exclusion, along with reduced activation in pain and affect related areas (DeWall et al., 2011; Eisenberger et al., 2003; Lieberman et al., 2007; Moor et al., 2011). Phelps et al. (2004) suggested regulation of the amygdala by lateral prefrontal regions through their projections to the mPFC, which was underlined by results of a study by Lieberman et al. (2007) concerning the right vlPFC and mPFC. Increased activation in depressed adolescents with NSSI in the vlPFC and mPFC may hereby point towards an increased regulatory effort that, however, may be rather unsuccessful as particularly subjects with NSSI felt more helpless after Cyberball than healthy controls, while there were no significant differences between the depressed adolescents without NSSI and healthy controls. Modulation of the activation in the vlPFC and mPFC might point towards different neural pathways of emotion regulation related to the presence or absence of ongoing NSSI. The interpretation of effortful but ineffective emotion regulation would be in line with results of another fMRI study on emotion regulation in adolescents with NSSI (Plener et al., 2012) that linked increased activation within respective networks to ineffective emotion regulation. Interpreting increased activation in the mPFC in the same vein, results might suggest that adolescents with NSSI think more about why they are rejected and evaluate social exclusion more negatively. Activation in the mPFC has been linked to self-referential processes, evaluation of negative feeling states, and mentalizing (Domsalla et al., 2013; Ochsner et al.,

2004), meaning the ability to read and understand others' mental states (Frith and Frith, 1999; Gallagher and Frith, 2003).

Whether this change in network activation as a neurobiological trait, facilitates the occurrence of NSSI or is a consequence, remains a matter of debate. As several studies point towards increased feelings of loneliness in adolescents with NSSI, even when controlled for depression (Glenn and Klonsky, 2013), the ability to take advantage of peer support may be a potential moderator. Wichstrom (2009) showed satisfaction with social support to be a potential protective factor for NSSI. This is in line with findings by Eisenberger et al. (2007a), who found that supportive social interaction is related to reduced neural responses to social exclusion. Whether diminished perception of support in the depression and NSSI group influenced the effects of neural processing of social exclusion in comparison to depressed adolescents without NSSI remains unclear as we did not find correlations of behavioral data and brain activation. Following that line of thought, however, a recent study of 90 adolescents described deficits in emotional face recognition for child fearful and adult sad face recognitions in adolescents with NSSI, but not in adolescents with a history of suicide attempts (Seymour et al., 2015). In line with the findings from our study, this may point to a possible deficit in recognizing and neural processing of social situations that seems to be specific to NSSI. This finding could stimulate further research regarding our clinical understanding of NSSI and its treatment in a way that adolescents with NSSI may be particularly in need of help how to navigate social situations.

Results of this study should be interpreted with care, due to the limited statistical power in our sample of 43 adolescents. In adult populations, NSSI is highly related to Borderline Personality disorder. Although only one participant was diagnosed with BPD, and it has been demonstrated that in adolescence, NSSI and borderline traits or the future development of BPD are not closely related (Glenn and Klonsky, 2013; Groschwitz et al., 2015b; Kaess et al., 2014; Nock et al., 2006; Odelius and Ramklint, 2014), a more detailed assessment of BPD traits beyond impulsivity scores could facilitate interpretations of our results. In order not to interfere with participants' current psychiatric treatment, participants were allowed to continue taking psychotropic medication. Although medication was held stable for at least 2 weeks prior to the scan, medication may have biased the results. Furthermore, there were no significant correlations between behavioral data and imaging results. Therefore, further studies are needed to replicate and strengthen the results from this current study. Results may have also been biased by an order of conditions effect, as 'inclusion' was always presented before 'exclusion'. However, this is a common practice in studies using Cyberball and in fact inherent to the original form of the task (i.e. Eisenberger et al., 2003; Masten et al., 2010). A major strength of this study is the comparison of two adolescent groups of psychiatric patients. This allowed controlling for the effect of depression, which is commonly comorbid to adolescent NSSI. In future studies, a replication of those findings in a larger sample comprising a sub-group of adolescents with NSSI, but without depression and a correspondent control group would be of interest.

Presence or absence of NSSI seems to significantly modulate the neural processing of social exclusion in depressed adolescents even with both groups feeling subjectively equally excluded. These specific alterations regarding processing of unpleasant social situations add on to findings by Osuch et al. (2014), who found differential processing of physical pain offset in youth with NSSI, as compared to psychiatric controls. This finding of distinct neurophysiological responses may stimulate further research on individual treatment approaches such as the inclusion of social skills training into treatment programs for adolescent NSSI, as is done in treatment programs like i.e. the developmental group therapy (Wood et al., 2001) and the dialectic behavioral therapy for adolescents (DBT-A; Miller et al., 1997).

Conflict of interest

Rebecca Groschwitz, Georg Groen, Martina Bonenberger, and Birgit Abler report no competing interests.

Paul Plener reports no direct competing interests. He received research grants from the BMBF (German Ministries for Research and Education), the BfArM (German Federal Institute for Drugs and Medical devices), the Baden Wuerttemberg foundation and the foundation for outpatient child and adolescent psychiatry. He was a PI in a study for Lundbeck. He is not stockholder or share-holder in the pharmaceutical industry.

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