Psychiatria Danubina, 2015; Vol. 27, No. 4, pp 346-354 *Review*

ALTERED PAIN PERCEPTION IN SELF-INJURIOUS BEHAVIOR AND THE ASSOCIATION OF PSYCHOLOGICAL ELEMENTS WITH PAIN PERCEPTION MEASURES: A SYSTEMATIC REVIEW

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received: 10.6.2015; revised: 21.8.2015; accepted: 28.8.2015

SUMMARY

Background: *The pathophysiology of non-suicidal self-injury (NSSI) is controversial. There is growing evidence of altered pain perception in people engaging in NSSI. Some hypotheses have been made on addictive aspects of this behavior. Pain and addictive behavior are modulated by the opioid system, which makes the endogenous opioids one of the candidate neurotransmitters related to NSSI. This article explains the theoretical background on NSSI as an addictive behavior, endogenous opioids involvement and pain perception changes in NSSI and updates the latest findings in this field. The main aim of this paper is a comprehensive review of published studies on pain perception in NSSI and an evaluation of the impact of NSSI functions and other psychological elements on pain perception measures.*

Subjects and methods: *We have reviewed six studies of pain perception in participants with NSSI compared with controls. The participants of these studies were not mentally disabled or autistic and did not have a diagnosed personality disorder.*

Results: *The reviewed studies have demonstrated a higher pain threshold and longer pain tolerance or endurance in five of six studies. Emotional dysregulation was significantly associated with all pain perception variables in one study. Neuroticism, self-criticism and painful and provocative experiences revealed correlated with pain endurance or pain tolerance. No correlation between pain perception measures and dissociation, hopelessness or locus of control was found.*

Conclusions: *Pain perception was altered in participants with NSSI. Pain perception was associated to emotional dysregulation, self-criticism, neuroticism and painful and provocative experiences. Because of the small number of studies reviewed, results should be seen as guidelines for further studies. They should be replicated on a bigger sample of studies. Further research should focus on pain perception measures in participants with NSSI and an excluded personality disorder.*

Key words: *self-injurious behavior - NSSI - deliberate self-harm - pain perception - nociception – receptors - opioid*

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INTRODUCTION

Non-suicidal self–injury (NSSI) is a behavior characterized by causing pain to oneself with a non-lethal method and with no suicidal intent. The methods most commonly used are cutting, banging, scratching, burning and interfering with wound healing. The prevalence is growing and is the highest in adolescence (13.9-21.4%) (Barrocas et al. 2011). NSSI is connected to borderline personality disorder, depression, anxiety, PTSD, substance abuse and eating disorders. Since 2013 it has been included into the Diagnostic and Statistical Manual of Mental Disorders, the 5th edition, as a separate diagnosis with fixed diagnostic criteria, but in the section where further research is needed and desirable. There is a lot of knowledge about the psychological background and mechanisms of this behavior, but the underlying pathophysiology is controversial. Some hypothetical theories predispose an involvement of the serotonin (5-HT) system and others the endogenous opioids (EO) system. First, we will make an update on the knowledge of the psychological functions of NSSI and pathophysiology of NSSI, than we will focus on the EO system and pain perception. The pain response in people with NSSI has been shown to be altered (Nock & Prinsten 2005). We will provide a comprehensive review of the studies on pain threshold (PTh), pain tolerance (PT) or pain endurance (PE) and pain perception in people with NSSI. Next, we will outline the influence of the NSSI psychological functions on pain nociception/perception determinants in the studies reviewed. To our knowledge, this is the first review to show the connection of pain determinants with different psychological elements in studies of self-harming participants in community samples.

The functions of NSSI

The functions of NSSI have been well established by ED Klonsky in a review of 18 empirical studies. He has emphasized the importance of seven NSSI functions (the first three are listed by the strength of evidence and frequency): (a) affect-regulation; (b) self-punishment; (c) anti-dissociation; (d) anti-suicide; (e) interpersonal boundaries; (f) interpersonal-influence; (g) sensation-seeking (Klonsky 2007).

The pathophysiology of NSSI

Pain perception and endogenous opioid modulation

Overall, the pain-modulating circuit can facilitate or inhibit nociceptive transmission (Fields 1992, Porreca et al. 2002, Urban & Gebhart 1999). Peripheral nocicep-

tion via Aδ-fibers and C-fibers is the first potential opioid modulating point of pain perception. The synaptic transmission to the second order nociceptor neurons in the dorsal horn of the spinal cord is modulated by the substantia gelatinosa (SG), which is rich in opioid receptors (OR) and is the second opioid involvement point. The periaqueductal grey (PAG) is the third. It is a specific region of the midbrain and can inhibit or facilitate the dorsal horn second order neurons information before conducting it to the somatosensory cortex and the cingulate gyrus, which is a part of the limbic system and therefore thought to be responsible for processing emotional states associated with pain. The PAG is also connected to the hypothalamus and the central nucleus of the amygdala (Fields 2004). The μ-opioid receptor agonists can directly inhibit pain transmission in primary and secondary afferent nociceptive neurons (Stein et al. 2003, Grudt & Williams 1994, Glaum et al. 1994). It has been demonstrated that an application of μ-opioid receptor agonist into the posterior hypothalamus or basolateral amygdala causes analgesia which is then reversed by a μ-opioid receptor antagonist microinjected into the PAG (Tershner & Helmstetter 2000). On the other hand, μ-opioid receptor agonist application in the PAG causes analgesia that is opposed by naloxone or a selective μ-opioid receptor antagonist action in the rostral ventral medulla (RVM). (Kiefel et al. 1993, Roychowdhury & Fields, 1996) The affective component of pain perception is demonstrated through the placebo analgesia effect. People receiving placebo (believed to have taken an analgesic) had a diminished pain perception. This has been replicated several times (Fields 2004). It was surprising that the analgesia was terminated with a consumption of naloxone (Levine 1978).

The Ribeiro et al. study demonstrated that women with a sustained pain challenge (having experimentally induced pain in the masseter muscle) and women with a sadness challenge (having induced sadness with a recall of sad memories) had similar effects on EO neurotransmission and μ-receptors in the nucleus accumbens (NAc), ventral pallidum (VP) and in the amygdala on one (pain challenge)/both (sadness challenge) sides of the brain (Ribeiro et al. 2005). The VP and the amygdala are rich in EO receptors. Both experimental challenges were associated with similar increases in negative affect scores (Ribeiro et al. 2005).

There are two distinct pathways of mainly non-opioid pain transmission modulation: a serotonergic and a noradrenergic pathway.

Stress-induced analgesia (SIA) is an inborn mammalian response that occurs during or following a stressful or fearful stimulus (Butler & Finn 2009). Not all aversive stimuli are capable of eliciting analgesia; some can even increase nociception (Butler & Finn 2009). It has been shown in multiple human studies that the induction of anxiety (e. g., anticipation of a noxious stimulus) can increase sensitivity to pain and the induction of fear causes analgesia (Butler & Finn 2009). Vachon-Presseau et al. demonstrated that stronger reactive stress responses measured by cortisol rise are associated with reduced cerebral processing of acute noxious stimuli and result in a diminution of pain unpleasantness (Vachon-Presseau et al. 2013). They showed that reduced pain activation within the anterior mid-cingulate cortex mediated the inverse relation between acute stress and pain (Vachon-Presseau et al. 2013). It was shown in some experiments that people have the ability to learn how to diminish their pain perception and in this case, the PAG became activated in fMRI (Butler & Finn 2009). The amygdala plays a pivotal role in SIA elicited with almost any type of stressor (Butler & Finn 2009). The amygdala receives the nociceptive information from the primary somatosensory cortex and transmits and receives it to/from the PAG (Butler & Finn 2009). It has been demonstrated that the opioid system modulates SIA and that β-endorphin has the prominent role (Butler & Finn 2009). Experiments had shown that the STA analgesic effect is blocked by naloxone.

In the fMRI research of the brain areas involved in NSSI, right midbrain and pons, parahippocampal gyrus, inferior frontal gyrus, amygdala and the orbital frontal cortex showed a greater activation in NSSI participants than in controls in a task of self-administered cold stimuli (a model for NSSI) (Osuch et al. 2014). There was no difference in the externally-administered cold stimulus (Osuch et al. 2014). Surprisingly, no differences in pain perception in between groups were found in either stimuli (Osuch et al. 2014). There are more of the studies indicating an overlap of CNS areas responsible for pain perception and emotion processing (Bresin & Gordon 2013, Eisenberger 2011, Ochsner & Gross 2005, Petovic & Ingvar 2002).

Addiction and the endogenous opioid system

The opioid system represents together with the dopamine system a well-known and essential substrate for addictive behavior. All drugs of abuse increase the activity of dopamine in the neuronal pathway from the ventral tegmental area (VTA) to the NAc and medial prefrontal cortex (PFC) by increasing the extracellular concentration of dopamine (DA) (Shippenberg et al. 2008). This is the main reward projection and crucial for eliciting the rewarding effects of drug intake and further drug consumption. The brain areas with high concentrations of OR are the amygdala, NAc, globus pallidus, part of stria terminalis and the VTA (Shippenberg et al. 2008). Some neurons in the striatum and NAc contain enkephalins, others dynorphins (Shippenberg et al., 2008). In immunoreactivity research, β-endorphin activity was found in the amygdala, VTA and the NAc (Khachaturian et al. 1993). MOR opioid binding is especially high in prefrontal and cingulate cortex (Shippenberg et al. 2008). The VTA OR have a critical

role in dopamine release (from the VTA) following administration of MOR agonists, which has been demonstrated in several researches (Shippenberg et al. 2008). On the other hand, the intra-VTA administration of a MOR antagonist produces dopamine release in the NAc (Shippenberg et al. 2008). Repeated drug administration causes neuroadaptation within the reward circuit: limbic cortical-striatopallidal circuit (Shippenberg et al. 2008). The neuroadaptation process is the basis of dependence. Parts of the reward circuit have an important role in mood, incentive motivation and habit learning (Shippenberg et al. 2008). EO acting in the central amygdala may be responsible for stimulus-reward learning (Shippenberg et al. 2008). Conditioned reward is produced by the intraventricular administration of β-endorphin or δ-opioid receptor (DOR) agonists, indicating that either MOR or DOR activation produces rewarding effects (Shippenberg et al. 1998). There is growing evidence, that DOR is modulating the rewarding effects of MOR agonists (Shippenberg et al. 2008). Diverse addictive drugs (ethanol, cocaine…) increase extracellular concentrations of β-endorphin in the NAc (Shippenberg et al. 2008). Chronic morphine administration is responsible for down-regulation of the hypothalamic pro-opiomelanocortin, the precursor of β-endorphin (Garcia de Yebenes & Pelletier 1993).

Endogenous opioids in NSSI

Being connected to addiction and analgesia, the MOR-s are the most important candidate OR-s on the topic of NSSI. Stanley et al. compared the cerebrospinal fluid levels of endogenous opioids, 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) in a sample of patients with NSSI and controls. They found a significant reduction in the mean β-endorphin (patient-91.4 (SD 14.1) ng/ml, controls-105.9 (SD 19.2) ng/ml, $t=2.18$, $p<0.05$) and met-enkephalin (patient-45.7 (SD 8.1) ng/ml, controls-58.4 (SD 12.1) ng/ml, $t=3.11$, $p<0.01$) levels (Stanley et al. 2010). Dynorphin, 5-HIAA and HVA did not differ significantly among the groups (Stanley et al. 2010). This is empirical evidence indicating an EO involvement in the pathophysiology of NSSI. Serotonergic and dopaminergic dysfunction did not appear to be related to NSSI in this study (Stanley et al. 2010). We have to mention that all participants (controls also) had a Cluster B personality disorder (i.e., borderline, antisocial, narcissistic, histrionic) and committed at least one suicide attempt in the past, so the difference in EO levels cannot be attributed to a personality disorder or suicidality proneness. There was no significant difference in the rate of current depression between the groups, but the mean Beck Hopelessness Scale results were higher in the NSSI group ($p<0.05$) (Stanley et al. 2010). According to the review by Bresin and Gordon, low EO can be related to NSSI in two ways (Bresin & Gordon 2013). First, lower levels of β-endorphin (and possibly enkephalin) and relatively normal levels of dynorphins may lead to an imbalance of the opioid system and through that to dissociative feelings (Bresin & Gordon 2013). As proposed by Bresin and Gordon, increasing the level of EO may reduce the need/desire to NSSI (Bresin & Gordon 2013). This has been shown in a small sample of depressive adolescents, treated with acupuncture, which was found to increase β-endorphin and enkephalin levels in previous research (Nixon et al. 2003). Aerobic physical exercise had been shown to stimulate the release of β-endorphin and it significantly lowered the frequency of NSSI and the urge to NSSI in a single case study (Wallenstein & Nock 2007). However, the theories of the EO system role in NSSI are contradictive. Multiple studies have found that dissociation symptoms decrease when treated with opioid antagonists, suggesting that high levels of EO would be responsible for the dissociation (Bresin & Gordon 2013). In this context, there is evidence of positive clinical outcome in mentally disabled or autistic self-harming patients treated with opioid antagonists (e. g. naltrexone, naloxone) (Sandman & Kemp 2011, Ricketts et al. 1993). We did not find a study on the effectiveness of opioid antagonist made on non-disabled patients without pervasive disorder. Second, low levels of some EO lead to increased sensitivity and number of μ- (and possibly δ) OR-s (Bresin & Gordon 2013). Due to that, the effect of EO (e.g., analgesia, euphoria) in such persons might be stronger and the reward value of NSSI greater (Bresin & Gordon 2013). The limitation of this theory is the fact, that no longitudinal study has demonstrated the temporal relationship of low resting EO levels and NSSI so far. The low resting EO levels could have been present before NSSI or they could be a by-product of NSSI (Bresin & Gordon 2013).

The addictive component of NSSI

There is growing evidence from research and clinical practice that NSSI may exhibit some key features of addictive behavior (in the context of diagnostic criteria valid for substance addiction). 73.8 % of adolescents in the Nixon et al. study stated that the frequency and/or intensity of NSSI increased in order to achieve the same effect (Nixon et al. 2002). This might be a sign of tolerance for NSSI. The mechanism is jet unknown. By extrapolating chronic NSSI to chronic substance use, an unbalance of dopaminergic activity in the reward circuit would seem logical. On the other hand, there could be some undiscovered changes in pain response, which could contribute to a changed pain perception and through that to increased frequency and/or intensity of NSSI. The adolescents in the Nixon et al. study stated even more features consisted with addictive behavior: NSSI continues despite recognizing it as harmful (95.2%), NSSI urges are upsetting but not enough to stop (81.0%), NSSI causes problems socially (73.8%), the behavior is time-consuming (64.3%) (Nixon et al. 2002). Victor et al. constructed a study based on

craving. They found out that in substance use, drugs are craved in many situations (positive or negative feelings can be present in an individual before substance use) (Victor et al. 2012). NSSI appears to be craved almost exclusively in the context of negative emotions (Victor et al. 2012). They also found that craving can be significantly stronger for substance use than for NSSI (Victor et al. 2012).

Pain perception in borderline personality disorder

There is strong evidence of attenuated pain perception during an act of NSSI in borderline personality disorder (Ludäscher et al. 2015, Pavony & Lenzenweger 2014, Magerl et al. 2012, Niedtfeld et al. 2010, Bohus et al. 2000).

Table 1. Characteristics of reviewed studies on pain threshold and pain tolerance or endurance in subjects with NSSI

Source	Inclusion criteria	Participants with NSSI (PWN) (n)	Controls (C) (n)
Hooley et al. 2010	PWN: lifetime history of NSSI (63% reported minimal 1 event of NSSI in the last month), C: a lifetime history of no NSSI	31	29
McCoy et al. 2010	PWN: 1 event of NSSI in lifetime history, C: a lifetime history of no NSSI	11	33
Franklin et al. 2011	PWN: lifetime history of cutting / burning / scraping the skin, C: a lifetime history of no NSSI	16	51
Franklin et al. 2012	PWN: more than six events of NSSI (cutting, burning or scraping the skin) in the last year (the non-suicidal intent was emphasized), C: a lifetime history of no NSSI	25	47
St. Germain & Hooley 2013	PWN: minimal 1 event of NSSI in the last month (the non-suicidal intent was emphasized), C: a lifetime history of no NSSI (also in the indirect group, but 1 event of indirect self-injury in the last month in the indirect self-injury group). For all: no recent analgesic use, only right-handed.	48	63 + 37* * engaging only in indirect self-injury
Glenn et al. 2014	PWN: a history of NSSI (41 reported minimal 1 event of NSSI in the last month, C: a lifetime history of no NSSI)	58	21

Source	Age (years)	Male (n)	Pain perception measurement method	Psycho-metric tests
Hooley et al. 2010	Mean: 22.4 (SD=5.2)	11	Pressure algometer (PTh, PE)	NEO-FFI, BHS, LCB, DES, SRS
McCoy et al. 2010	18-37	8	Pressure algometer (PTh, PT), VAS	DSHI, DES, BDI-II, BHS, ASI
Franklin et al. 2011	18-29	20	Cold pressor task (PTh, PT), VAS (ITh, IT)	PPE scale, ACS questionnaire, FASM
Franklin et al. 2012	18-29	20	Cold pressor task with pre-task induction of acute stress provided by a speech task (PTh, PT), VAS (ITh, IT)	Screening questionnaire (NSSI measure, affect dysregulation levels), DERS, FASM, Subjective units of distress scale
St. Germain & Hooley 2013	Mean: 25,4 (SD=9.1)	42	Pressure algometer (PTh, PE)	Interview with a similar content as the SITBI, SCID, MAST, DAST, EDEQ, SHI, SNAP: SUICIP, SNAP: LSE
Glenn et al. 2014	12-19	16	Pressure algometer (Pth, PE)	SITBI, A-DES, SRS

LEGEND: *Indirect self-injury: clinically significant substance abuse, eating disorder (e.g. binge-eating), continuous involvement in abusive relationships, risky/reckless behavior.

Pain threshold (PTh): is the time interval people need from the beginning of the task util they first experience pain. It is usually presented in seconds. Pain tolerance (PT): is the time needed to reach the unbearable pain. In most of research settings, an upper limit for pain tolerance is set ahead of testing. Pain endurance (PE): is calculated as pain tolerance subtracted by pain threshold. It is therefore the actual time a person can withstand pain. Visual analogue scale (VAS): a subjective estimation of pain intensity at a line from "no pain" to "maximum pain". Intensity at threshold (ITh): is the pain intensity at threshold estimated with VAS. Intensity at tolerance (IT): is the pain intensity at tolerance estimated with VAS.

Other abbreviations: NEO Five Factor Inventory (NEO-FFI), Beck Hopelessness Scale (BHS), Locus of control and efficacy (LCB), Dissociative Experiences Scale (DES), The Self-Rating Scale (SRS), Deliberate Self-Harm Inventory (DSHI), Beck Depression Inventory-2ed. (BDI-II), Anxiety Sensitivity Inventory (ASI), Painful and Provocative Experiences Scale (PPE), Acquired Capability for Suicide Scale (ACS questionnaire), Functional Assessment of Self-Mutilation (FASM), Difficulties in Emotion Regulation Scale (DERS), Self-Injurious Thoughts and Behaviors Interview (SITBI), Structured Clinical Interview for DSM (SCID), Michigan Alcoholism Screening Test (MAST), Drug Abuse Screen Test (DAST), Eating Disorder Examination Questionnaire (EDEQ), Self-Harm Inventory (SHI), Schedule for Non-adaptive and Adaptive personality (SNAP), SNAP Self-Harm Subscale: Suicide Proneness (SNAP: SUICIP), SNAP Self-Harm Subscale: Low Self Esteem (SNAP: LSE), Adolescent Dissociative Experiences Scale-II (A-DES)

Pain perception in non-borderline samples of people with NSSI

As listed above, changes in pain perception in non-borderline samples are the main topic of this review. Nock and Prinsten found subjective pain analgesia and hypoalgesia in a sample of 89 inpatient adolescents (Nock & Prinstein 2005). They were using a semi-structured clinical interview revealing a number of 42 participants with "no pain" during an episode of NSSI, 29 with "little pain", 11 with "moderate pain" and 7 with "severe pain" (Nock & Prinstein 2005). In the next few chapters of this article, we are going to review the research made on this topic.

SUBJECTS AND METHODS

We have searched the Pubmed and the ScienceDirect electronic databases for the following keywords: non suicidal self injury, non-suicidal self-injury, non-suicidal self injury, non suicidal self-injury, nonsuicidal self-injury, nonsuicidal self injury and NSSI. We have excluded the studies that were made on mentally disabled population, on patients with any of autism spectrum disorders and war veterans. There was no limitation according to time of publishing. Next, we searched for studies that investigated pain perception in people with NSSI in comparison with controls without NSSI. Afterwards, we excluded studies in which borderline personality disorder could play a crucial role in the difference of pain perception (see 1.4. Pain perception in borderline personality disorder for detail). We have found six studies that completely matched our review criteria. All of the studies were published in English and were laboratory-based pain studies on community samples. The characteristics of reviewed studies are listed in table 1.

RESULTS

Pain threshold measurements in participants with NSSI and controls without NSSI in the six reviewed studies are demonstrated in table 2.

In comparison with the controls (without NSSI) pain threshold revealed significantly higher in participants with NSSI in five of six studies. It also was insignificantly higher in the sixth- the McCoy et al. study. In the St. Germain and Hooley study the indirect self-injury group had the highest pain threshold values, but the Games-Howell post-hoc follow-up tests indicated that there were no significant differences between the NSSI and the indirect self-injury group (p=0.73) (St. Germain & Hooley 2013).

Pain tolerance or endurance measurements in participants with NSSI and controls without NSSI in the six reviewed studies are demonstrated in table 3.

Pain tolerance/endurance was significantly longer in the NSSI group in five of six studies. In contrast to pain threshold, pain endurance showed no meaningful difference between the indirect self-injury group and the NSSI group at all. Three studies demonstrate the data of timed-out participants, e. g. participants, who did not terminate the trial in pre-set maximum time, and had to be asked to stop. In the St. Germain and Hooley study 20.8% of the NSSI group, 10.8% of the indirect self-injury group timed-out and 3.2% of controls (p=0.003) (St. Germain & Hooley 2013). 13 participants with NSSI and zero controls timed-out in the Glenn et al. study (p=0.01) and 46.6% (p=0.002) NSSI participants timed-out in the Hooley et al. study (Glenn et al. 2014, Hooley et al. 2010).

Table 2. Pain threshold in participants with NSSI vs. controls

Study	Mean pain threshold, mean (SD), (seconds) Participants with NSSI	Participants without NSSI	F	d^2	d	t-value	partial η^2
Hooley et al. 2010	60.90 (65.50)	38.02 (28.05)	/	/	/	1.75 (p=0.044)	/
McCoy et al. 2010	41.30 (87.95)	13.99 (19.41)	2.89 (not significant)	0.06	/	/	/
Franklin et al. 2011	12.07 (7.01)	8.91 (4.78)	/	/	/	2.00 (p<0.05)	/
Franklin et al. 2012	15.64 (12.89)	8.59 (4.51)	11.39 (p<0.001)	0.81	/	/	/
St. Germain & Hooley 2013	55.2 (58.4)	33.3 (46.2) *engaging only in indirect self-injury: 66.3 (72.0)	4.1 (p=0.02)	/	/	/	0.07
Glenn et al. 2014	59.6 (39.5)	30.8 (22.7)	/	/	0.89	4.02 (p<0.001)	/

LEGEND: *Indirect self-injury: clinically significant substance abuse, eating disorder (e.g. binge-eating), continuous involvement in abusive relationships, risky/reckless behavior.
Pain threshold (PTh): is the time interval people need from the beginning of the task until they first experience pain. It is usually presented in seconds.

Table 3. Pain tolerance / endurance in participants with NSSI vs. controls

Study	Mean pain tolerance (PT)/ endurance (PE), mean (SD), (seconds) Participants with NSSI	Participants without NSSI	F	d^2	d	t-value	partial η^2
Hooley et al. 2010	(PE) 197.91 (154.00)	(PE) 81.98 (107.1)	/	/	/	3.34 (p=0.001)	/
McCoy et al. 2010	(PT) 109.18 (127.02)	(PT) 44.75 (63.83)	4.93 (p<0.05)	0.11	/	/	/
Franklin et al. 2011	(PT) 50.28 (32.05)	(PT) 37.69 (26.81)	/	/	/	1.56 (p<0.10)	/
Franklin et al. 2012	(PT) 54.13 (35.45)	(PT) 34.94 (22.26)	7.81 (p<0.01)	0.67	/	/	/
St. Germain & Hooley 2013	(PE) 138.6 (147.9)	(PE) 66.3 (87.4) *engaging only in indirect self-injury: 122.8 (140.5)	5.78 (p=0.005)	/	/	/	0.07
Glenn et al. 2014	(PE) 104.1 (118.6)	(PE) 36.9 (33.1)	/	/	0.77	3.83 (p<0.001)	/

LEGEND: *Indirect self-injury: clinically significant substance abuse, eating disorder (e.g. binge-eating), continuous involvement in abusive relationships, risky/reckless behavior.
Pain tolerance (PT): is the time needed to reach the unbearable pain. In most of research settings, an upper limit for pain tolerance is set ahead of testing. Pain endurance (PE): is calculated as pain tolerance subtracted by pain threshold. It is therefore the actual time a person can withstand pain.

Table 4. Correlation between dissociation and pain threshold / endurance

Study	PTh		PE	
	r	p	r	p
Hooley et al. 2010	-0.07	0.65	0.13	0.31
Glenn et al. 2014	0.13	not significant	0.20	not significant

LEGEND: Pain threshold (PTh): is the time interval people need from the beginning of the task until they first experience pain. It is usually presented in seconds. Pain endurance (PE): is calculated as pain tolerance (the time needed to reach the unbearable pain) subtracted by pain threshold. It is therefore the actual time a person can withstand pain.

In three of the studies, the intensity of pain was measured by VAS. McCoy et al. found a significant difference in subjective pain perception during the pressure task. The mean maximum VAS (0-no pain, 100-maximum pain) score of the NSSI group was 46.51 (SD 21.45) and 60.84 (SD 19.56) for the control group ($F=4.22$, $p<0.05$, $d^2=0.09$) (McCoy et al. 2010). The intensity of the pain at threshold was not significantly different between groups with and without NSSI in both of Franklin's et al. studies (Franklin et al. 2011, Franklin et al. 2012). But the intensity at tolerance (VAS: 1-no pain, 10-maximum pain) differed much. Participants with NSSI had the VAS of 7.13 (SD 1.71) or 7.04 (1.81), controls without NSSI behavior 8.20 (1.59) and 8.32 (1.37) ($p<0.05$ and $p<0.001$) (Franklin et al. 2011, Franklin et al. 2012).

As there was a significant association with one or more of the indicators of pain analgesia / hypoalgesia in all of the reviewed studies, we searched for other properties of the samples used, that would differ among the investigated groups and could have an impact on the modulation of pain perception. Hooley et al. reported that participants, who had longer histories of NSSI, took longer to report the onset of pain (Hooley et al. 2010). Frequency of NSSI was positively correlated with pain endurance for the NSSI group ($r=0.28$, $p=0.05$) in the St. Germain and Hooley study (St. Germain & Hooley 2013). In the same study, frequency of NSSI and years of engagement in NSSI were not related to PTh, nor were the years of engagement related to PE (St. Germain & Hooley 2013). Glenn et al. could not replicate this results-in their study, neither frequency nor years of engaging in NSSI had an impact on PTh or PE (Glenn et al. 2014). Results regarding dissociation were inconsistent: the NSSI group scored significantly higher on the DES in the Hooley et al. study, but has shown no significant difference in the McCoy et al. study (Hooley et al. 2010, McCoy et al. 2010). Correlations between DES or A-DES score and PTh/PE were sought in two studies, but were insignificant (Table 4) (Hooley et al. 2010, Glenn et al. 2014).

The NSSI group and the control group differed in the hopelessness scale in the McCoy et al. ($p<0.01$) and Hooley et al. ($p=0.030$) study, NSSI participants being significantly more hopeless than controls (McCoy et al. 2010, Hooley et al. 2010). Hopelessness did not correlate with PTh or PE. NSSI was significantly connected to neuroticism and extraversion (Hooley et al.

2010). Neuroticism revealed positively correlated with PE (p=0.037) (Hooley et al. 2010). Participants with NSSI displayed a relatively greater external locus of control (p=0.019), but no correlation with pain perception parameters was found (Hooley et al. 2010). NSSI correlated strongly with negative, self-critical beliefs and there was a high positive correlation with PE (r=0.35, p=0.006) (Hooley et al. 2010). In the Glenn et al. study, self-criticism (on SRS) was in significant correlation with PE (r=0.37, p<0.01), but not with PTh (Glenn et al. 2014). In the McCoy et al. study the NSSI group and the control group differed in depression, but had no significant difference in anxiety measure (McCoy et al. 2010). The results on the BDI-II were as follows: NSSI group-19.18 (SD 13) points, controls-9.03 (SD 8.32) points (F=9.15, p<0.01, d^2=0.18) (McCoy et al. 2010). After they corrected the PTh, PT and VAS scores for depression, the average pain tolerance was still significantly different between the groups, but the pain rating (VAS) became insignificant (McCoy et al. 2010). The mean pain threshold stayed non-significant (McCoy et al. 2010). The correction for hopelessness in both groups resulted in a significant difference in average PT and pain rating between the groups, the mean PTh stayed non-significantly different (McCoy et al. 2010).

There was a correlation between emotional dysregulation (measured with DERS) and all pain perception variables in the Franklin et al. study (Franklin et al. 2012). It was evident in all participants (with and without the history of NSSI) (Franklin et al. 2012). PT and emotional dysregulation were particularly strongly correlated; the connection in between pain intensity ratings at threshold and emotional dysregulation was the weakest (Franklin et al. 2012). The NSSI group displayed significantly higher emotional dysregulation than the controls (DERS total score: NSSI group-90.54 (SD 20.88), controls-72.73 (SD 17.68) (F=14.24, p<0.001, d^2=0.91) (Franklin et al. 2012). Another etiologically important result from the studies is the correlation of painful and provocative experiences with pain tolerance (β=1.30 (SE 0.62), t-value=2.11, p<0.05) (Franklin et al. 2011). It was apparent in results with covariance of NSSI and without (Franklin et al. 2011). There was no significant difference in the PPE scores between the NSSI and non-NSSI groups (Franklin et al. 2011).

DISCUSSION

In all of the studies reviewed, participants with NSSI had a higher pain threshold or longer tolerance/ endurance of pain or both. Moreover, in three of the six studies, patients with NSSI timed out in great percent. Therefore, the review is supportive of the hypothesis that there is altered pain perception in adolescents and young adults with NSSI and no known diagnosis of personality disorder. To fully confirm this hypothesis, similar pain perception studies would have to be made on NSSI population with an excluded personality disorder. Another important general limitation of this review is the small number of studies included. Consequently, the results might serve as a guideline for further research and not as a basis for clinical practice. Beside the changes in objective pain perception measures, we found lower subjective VAS scores in the NSSI groups of three studies. In one of these studies, the correction for depression resulted in unchanged objective measures, but revealed an impact on subjective pain perception. In the context of a high coincidence of depression and chronic pain syndromes, this might not seem surprising. As the years of engagement in NSSI were not connected to changes of PTh or PE, the frequency of NSSI showed a correlation to PE in only one study and PTh was not correlated to frequency at all, the review did not provide support for the learned diminished pain perception theory. But as said before, the review is too small to make such scientific exclusions. On the other hand, this could mean that the changes in pain perception have no larger impact on the ascending frequency of NSSI through the years. Further prospective research would be necessary to confirm this statement. But for now, it could be enough to leave some room to the addictive theory of NSSI and its eventual role in ascending frequency of NSSI. Although dissociation has been connected to NSSI in past research and showed significantly higher in NSSI participants in one of the reviewed studies, it was not significantly correlated to either PTh nor PE. As mentioned before, ED Klonsky emphasized the role of anti-dissociation as one of the main functions of NSSI. In his theory, NSSI has the intent to end the experience of depersonalization or derealization, which is consistent with the findings regarding dissociation in this article-higher PTh or longer PE. It would seem logical, that the feeling of pain is necessary to change the psychological state of dissociation, but this has to be investigated further. If dissociation in NSSI is not connected to altered pain perception, it might be more likely, that it is connected to NSSI through the changes in the EO system (see Endogenous opioids in NSSI). In our opinion, higher scores on the Beck Hopelessness Scale in NSSI participants are expected, as hopelessness triggers a strong, negative feeling and such usually protrude NSSI. A hopeless person might also have a diminished capacity or motivation to choose a more effective coping mechanism. The positive correlation of painful and provocative experiences (contact sports, witnessing abuse, getting a tattoo…) (PPE) with pain tolerance provides further support for the interpersonal-psychological theory of suicide (Franklin et al. 2011). In the context of the article, it proposes the hypothesis that NSSI, being a PPE itself (Franklin et al. 2011), could alter PT by engaging in it often. But as explained before, in our review the frequency of NSSI and the years of engaging in NSSI had no major effect on pain perception. As we emphasized in the review, the higher

the self-criticism, the more likely people engage in NSSI and the longer was their pain endurance. Self-punishment, the second most common function of NSSI (Klonsky 2007), is conditioned by high self-criticism. The results of the review are coherent with the psychological findings. A strong connection of emotional dysregulation and all pain perception indexes was found in the review, indicating a logical paradigm. People with high emotional dysregulation might have altered pain perception and might have used NSSI for affect-regulation. Further research of this paradigm is needed.

CONCLUSIONS

The review of six studies on self-harming participants with no diagnosed personality disorder demonstrates a change in pain perception. Emotional dysregulation was significantly associated with all pain perception variables in one study. Neuroticism, self-criticism and painful and provocative experiences revealed correlated with pain endurance or pain tolerance. No correlation between pain perception measures and dissociation, hopelessness or locus of control was found. The results might outline some interesting data on pain perception in NSSI, but further research in this field is needed.

Acknowledgements: None.

Conflict of interest: None to declare.

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