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Conceptualizing the neurobiology of non-suicidal self-injury from the perspective of the Research Domain Criteria Project

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Abstract

Non-suicidal self-injury (NSSI) commonly starts in adolescence and is associated with an array of negative outcomes. Neurobiological research investigating NSSI is in its early stages and most studies have examined this behavior within the context of specific diagnoses. However, the Research Domain Criteria (RDoC) initiative encourages researchers to examine brain-behavior relationships across diagnoses. This review on the neurobiology associated with NSSI is organized using the domains proposed by RDoC: Negative Valence, Positive Valence, Cognitive, Social Processes, and Arousal/Regulatory Systems. Evidence of neurobiological anomalies is found in each of these domains. We also propose future research directions, especially in regard to human development. Future NSSI studies should address this behavior independent of diagnosis, examine relevant constructs across multiple units of analysis, and assess how systems change across development and course of illness. These advances will be essential for guiding neurobiologically informed intervention and prevention strategies to target NSSI. In doing so, we may prevent the associated negative outcomes across the lifespan.

Keywords

Non-suicidal self injury; Neurobiology; Neuroimaging; RDoC

1. Introduction

Non-suicidal self-injury is the act of purposely harming one's own body tissue without the intent of suicide (Winchel and Stanley, 1991). NSSI is often repetitive with varying degrees of severity (Tuisku et al., 2009). Although related, non-suicidal and suicidal self-injury are conceptualized as overlapping, but distinct, clinical phenomena (Wichstrøm, 2009). However, NSSI may be a predictor of later suicide attempts (Horwitz et al., 2014; Tang et al., 2011; Victor and Klonsky, 2014). The age of onset for NSSI is typically during adolescence with an average prevalence of approximately 18% within this age group

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(Muehlenkamp et al., 2012). The prevalence of NSSI was increasing around the turn of the century (O'Loughlin and Sherwood, 2005), and have remained stable at this high level (Barrocas et al., 2012; Muehlenkamp et al., 2012).

Because NSSI occurs in patients with a range of disorders, such as major depressive disorder (MDD; Hintikka et al., 2009), borderline personality disorder (BPD; Cerutti et al., 2011), other disorders (Apter et al., 2008; Chartrand et al., 2012; Fliege et al., 2009; MaClean et al., 2010; Serras et al., 2010) and no disorder (Stanford and Jones, 2009), it is important to consider NSSI independent of diagnosis. Indeed, a neuroscience approach to defining psychopathology has increasingly recognized the limitations of traditional categorical approaches for examining mental health. Collective efforts of many top scientists have been organized by the National Institute of Mental Health to yield a preliminary framework for this inquiry, the Research Domain Criteria (RDoC) Project. Specifically, the RDoC has been implemented to promote research examining the dimensions of disordered behavior and the associated mechanisms of psychopathology. The goal of this initiative is to enhance understanding of the etiology of diseases and use this information to develop more effective preventions and interventions by uncoupling research from clinically familiar categories to focus on fundamental mechanisms (Sanislow et al., 2010). This approach involves the use of experimental research criteria with methods that may cut across multiple traditional diagnostic categories.

The current RDoC framework consists of a matrix, or table, which categorizes five higher-level neurobehavioral systems that are called "domains." These domains are represented as rows and are labeled as follows: negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems. For each domain, specific lower-level dimensions of behavior are identified, which are called "constructs." The matrix then has columns, which represent categories of research approach, or "units of analysis". These include the following: genes, molecules, cells, circuits, physiology, behavior, self-reports, and paradigms. These units of analysis are ways in which to study the constructs. Table 1 is a modified representation of this matrix, with the exception of including the units of analysis most relevant to this review, which are physiology and circuits in particular.

The primary goal of this paper is to review the literature relevant to identifying neurobiological factors centrally implicated in NSSI by using the structure of RDoC as an organizational framework. Building on one previous review on this topic that summarized NSSI findings across genetic, physiology, neurotransmitter, lipid, and brain activity modalities (Groschwitz and Plener, 2012), this review provides an in-depth focus on two units of analysis proposed by RDoC: circuits (represented by findings from neuroimaging studies) and physiology (specifically the hypothalamic-pituitary-adrenal [HPA] axis). Our working assumption is that, although NSSI is a heterogeneous behavior, advancing understanding of NSSI is likely to be clarified not by applying psychiatric diagnoses, but by understanding the diverse underlying biological mechanisms that lead to this behavior. Although we aim to provide a working model of existing NSSI research, it is important to highlight that the current rendering of RDoC domains and constructs are a work in progress and subject to change based upon future research. With this in mind, we adopt this

framework for organizing this review where possible and point out areas where this classification is difficult, such as when there is overlap across domains and constructs.

2. Method

This review summarizes published neuroimaging and neuroendocrine studies relevant to NSSI. The electronic databases PubMed and Google Scholar were used to search for peer-reviewed primary research articles published or in press and available online until June 1, 2015. Search terms included combinations of “self-injury,” “non-suicidal self-injury,” “deliberate self-harm,” “non-suicidal self-injurious behavior,” “MRI,” “HPA,” and “cortisol.”

The most relevant studies for this review are those that have examined neurobiology related to NSSI independent of diagnosis; however, since these are relatively few in number, we include those that report NSSI findings in the context of specific diagnoses. Unfortunately, the use of adolescent samples within the NSSI literature is sparse, making it difficult to delineate the course of the development of NSSI. Thus, we provide suggestions as to how these gaps can be addressed. Studies are excluded if they explicitly studied self-injury only in the context of suicide, however there are a few studies that did not specify whether the self-harm behavior in their sample was suicidal or non-suicidal. In these cases, we have included such studies and encourage future research to ensure that a distinction is made between these two behaviors. Emphasis is placed on studies with samples without developmental disorders, as those with developmental disorders often exhibit a very different clinical presentation. However, given the paucity of the literature in non-developmental disorder populations in some areas such as examination of the opiate system, we include some studies of NSSI in developmental disorders to supplement existing literature on NSSI in non-developmental disorder populations and to guide potential future research directions.

Findings from studies that have incorporated either neuroimaging or neuroendocrine measures specifically among those with NSSI and no developmental disorders are organized in Table 1. This table serves to highlight the areas that have received attention thus far in the NSSI literature and provide a visualization of gaps within research that remain to be addressed. Although this table is meant to represent the RDoC matrix, we have limited the scope of this table to neuroimaging and neuroendocrine measures, which fall under the units of analysis physiology and circuits. Thus, the columns for genes or behavior show limited information and the columns for other units of analysis (i.e. cells and molecules) are not included. It is important to note that this table includes only the studies in this review that have used either neuroimaging or neuroendocrine measures to study NSSI in non-developmental disorder populations. We would also like to note that although we only include these particular units of analysis in this review, research incorporating the other units of analysis is highly encouraged.

3. Negative valence systems

Studies examining the function of NSSI have found that in most cases, negative affect precedes self injury, and that NSSI is performed with the purpose of relieving negative affect

(Klonsky, 2007). Indeed, for many, engaging in NSSI serves as a temporary relief from negative affect, although the negative affect persists long-term. The negative valence domain, particularly involving the detection and response to perceived threat, has been well characterized and comprises a complex array of systems throughout the brain and body. In the central nervous system, these processes are mediated by a network of brain regions comprising cortico-limbic neural circuitry (LeDoux, 2000; Phillips et al., 2003). Core components of this network include the amygdala, which underserves the emotional response to negative stimuli such as threat, and the insula, which provides information on the salience of internal and external stimuli, including the perception of pain. The anterior cingulate cortex (ACC) serves to monitor for conflict and regulate limbic emotional reactivity (Allman et al., 2001). Cortical areas such as the prefrontal cortex (PFC) interpret and regulate emotional responses (Ghashghaei and Barbas, 2002). Diverse methodologies have been used to measure threat systems including neuroimaging studies to measure volume and functioning of fronto-limbic regions and neuroendocrine response studies.

The RDoC negative valence domain includes five constructs: (a) acute threat (fear), which involves a threat that is imminent and of high probability; (b) potential harm (anxiety), in which the threat is of lower probability; (c) sustained threat; (d) frustrative non-reward, which involves the inability to experience positive reward despite repeated attempts; (e) and loss, which involves deprivation of social or non-social objects or situations that hold motivational significance. As outlined in Table 1, current research has provided information within the negative valence domain. In particular, this research falls within two of these five constructs: acute threat and sustained threat.

3.1. Acute threat (fear)

The construct of acute threat can be described as the mechanisms involved in activating the body's defensive response to imminent danger, and is typically an adaptive response when successfully utilized to protect oneself. This system can quickly become maladaptive when an individual's threat system frequently responds, even in instances of low likelihood of threat. Research using neuroimaging and/or peripheral physiological measures examined this construct by incorporating paradigms involving the presentation of negative stimuli and measuring the response. In regards to neuroimaging studies, BPD patients with a history of NSSI had greater amygdala activation in response to both negative and neutral pictures compared to controls, and that in the BPD group, amygdala activation was positively correlated with self-reported affective dysregulation (Niedtfeld et al., 2010). Since the amygdala is centrally implicated in threat, the findings of generalized activation to neutral stimuli suggest that these individuals may be predisposed toward interpreting neutral stimuli as threatening.

Further amygdala dysfunction has been found in a pilot study of female adolescents with and without NSSI. Plener et al. (2012) reported that the NSSI group showed a significantly stronger brain response in the amygdala, hippocampus and anterior cingulate cortex when exposed to emotional pictures, and rated pictures with self-injurious reference as significantly more arousing than controls. Amygdala dysfunction has also been found using a paradigm involving physical injury. After a stress-induction task, those with BPD and

NSSI showed a significantly greater decrease in subjective stress and amygdala activity as well as normalized functional connectivity with the superior frontal gyrus after receiving an small incision with a scalpel on the right forearm versus a sham, which involved pressing the handle of the scalpel on the right forearm (Reitz et al., 2015).

Another fairly well studied unit of analysis included in the RDoC matrix for acute threat is the measurement of HPA functioning. Two NSSI studies have documented attenuated HPA responses in response to socially relevant stimuli, or acute threat. In a study of female adolescents with NSSI, Kaess et al. (2012) showed an attenuated cortisol response to a social challenge, despite equal self-reported emotional response in comparison to controls. Similarly, in young adults, Powers and McArdle (2003) found that young women with NSSI exhibited lower cortisol during a conflict discussion task if they typically used emotional support to cope with stress. However, different coping strategies moderated the relationship between self-injury and cortisol for males.

3.2. Sustained threat

Sustained threat involves the exposure of a prolonged situation that elicits a defensive response affecting cognition, affect, physiology, and behavior. Responses to sustained threat can become maladaptive when prolonged activation leads to alterations within neurobiology and/or when these defensive responses persist even after the threat has abated. A study of young adults with BPD and histories of NSSI used structural MRI, and found that the number of self-harm incidents was positively associated with pituitary volume, suggesting hyper-reactivity of the stress response system (Jovev et al., 2008). These findings in conjunction with the HPA findings under the acute threat construct suggest an allostatic shift to accommodate chronic stress, which is a concept described by Juster et al. (2010). The significance of such a shift may result in a blunted HPA response in the presence of stressors, which includes illnesses. Thus, this adaptation may lead to poor physical health outcomes, which may then further increase the burden of stress upon individuals with NSSI. The regulatory processes that have been in place may in turn modulate the degree of emotion reactivity to stressors.

3.3. Negative valence domain: gaps and directions for future research

This review of the research to date examining negative valence constructs in patients with NSSI highlights several gaps in knowledge and points the way to future directions in research. First, negative valence abnormalities (in particular, the acute and sustained threat constructs) reflect both under- and over-responding patterns, depending on whether it is a response to potential or chronic threat. As described by the RDoC negative valence work group, these system's operations are dynamic, such that the body's responses to perceived threat encompasses three phases: reaction, regulation, and recovery (NIMH, 2011). Next steps in NSSI research should examine threat constructs across these phases using both neuroendocrine and neuroimaging methods, which may help to disentangle the conflicting results to date.

Second, there is a paucity of research in the understanding of how the other three negative valence constructs (potential harm, frustrative non-reward, and loss) may be represented in

the context of NSSI. There are many possibilities for using neuroimaging and neuroendocrine research to investigate these constructs. In particular, sample characteristics, such as abuse history and levels of anxiety, can be used as potential moderators or mediators in statistical models.

Third, the studies that have examined negative valence domain constructs have employed methods and reported findings that overlap with other domains within the RDoC, particularly social systems. Such research exemplifies the high complexity of systems related to these constructs, and the need to consider their functioning in the context of interpersonal relationships. Finally, the above studies have focused primarily on females with NSSI. This is understandable as there are significantly more females than males who engage in NSSI (Andrews et al., 2014; Zetterqvist et al., 2013). However, future research would benefit from examining whether the neurobiological mechanisms associated with NSSI are similar for both sexes given documented sex differences in the development of both neurocircuitry (Giedd et al., 1999) and neuroendocrinology (Kaess et al., 2013).

Across all of these different potential research directions, longitudinal studies are highly important to track the development of both the HPA axis as well as the structure and functioning of brain regions associated with threat response. Developmental research is a necessary and valuable step in the progression of RDoC, as it provides information about the developmental trajectory, sensitive periods within development, and dynamic interaction of the systems within RDoC (Casey et al., 2014). Longitudinal research is particularly promising for the negative valence system domain as the way an individual responds to all types of threat is likely to be highly influenced by experiences in early development and interact highly with other RDoC domains (i.e. cognitive systems and social processes).

4. Positive valence systems

The positive valence systems domain encompasses reward and habit formation, which can be broken down into phases of reward seeking, attainment, fulfillment, and maintenance. The neural circuitry of reward has been extensively studied in animals and humans, and involves key areas such the ventral tegmental area, nucleus accumbens, dorsal striatum, and related connections to the ventral prefrontal cortex (Kalivas and Nakamura, 1999). RDoC has proposed several constructs within this domain: approach motivation, initial and sustained responsiveness to reward attainment, reward learning, and habit. The extant literature directly relevant to NSSI primarily addresses reward learning, which is reviewed here and briefly outlined in Table 1.

4.1. Reward learning

Reward learning involves the process of acquiring information about thoughts, behavior, etc. that are reinforced with desirable outcomes. The neurobiological processes involved with reward learning are relevant to the establishment and maintenance of NSSI. Reward-based motivation to engage NSSI could potentially be viewed under two mechanisms: (a) primary gain in that individuals experience the injury as rewarding (Chapman et al., 2009), and (b) secondary gain in that receiving attention from others may be a rewarding factor that contributes to the maintenance of NSSI (Scoliers et al., 2009).

Osuch and colleagues illustrate a good example of how individuals may experience injury as rewarding. They found that while youth aged 16–24 with NSSI and control participants reported equivalent levels of pain in response to cold stimuli, the NSSI group reported greater relief following the painful stimuli. Within the NSSI group, relief after self-afflicted cold stimuli was positively related to blood oxygen level dependent (BOLD) signal within the dorsal striatum, which is part of reward circuitry, as well as the thalamus and precuneus, regions involved in self-referential processing and conscious awareness (Osuch et al., 2014).

4.2. Positive valence systems: current gaps and directions for future research

Despite some positive strides in understanding the positive valence system in NSSI, there are clear gaps in the literature, especially regarding the constructs of approach motivation, initial responsiveness to reward attainment, sustained responsiveness to reward attainment, and habit. Future research is needed to examine these constructs, potentially using paradigms such as Monetary Incentive Delay, gambling tasks, and delay discounting in the context of neuroimaging and/or neuroendocrine measures. This information will help in understanding which steps in the reward process are implicated in NSSI. Further, longitudinal studies examining the development of these systems in populations at high risk for NSSI may provide fruitful information about how these systems may go awry over time. Such information will be beneficial for future research on NSSI intervention strategies.

The habit construct is particularly well-primed for further NSSI research as some have viewed NSSI as an addictive behavior (Faye, 1995). For example, among hospitalized adolescents with NSSI, most had urges to self-injure more than once a week and also endorsed three or more addictive symptoms, which included increased frequency or severity of NSSI and continuation of NSSI despite harm (Nixon et al., 2002). In the case of NSSI, whether the reinforcing factor is relief of negative affect or attention from others, the behavior can become highly routinized response to obtain the desired outcome. Habit involves the initiation and completion of an action without full conscious awareness. Delegating routine behaviors to subcortical structures in this way can be beneficial in that it can free up cognitive resources for more demanding tasks. Thus, research examining the interplay between the development of NSSI and subcortical structures may highlight the associated neurobiology involved in the formation of NSSI as a habit.

Further treatment research may be a successful way to serve as a probe to better understand the heterogeneity of NSSI. The opiate system may be a mechanism involved in the reinforcement of NSSI, and has been fairly well studied in particular in people with developmental disorders and NSSI (Sher and Stanley, 2008). Specifically, NSSI may lead to the release of endogenous opioids (endorphins) that may otherwise be abnormally low in individuals with NSSI. In adults with cluster B personality disorders, which includes antisocial, borderline, narcissistic, and histrionic personality disorders, those with NSSI had lower levels of beta-endorphin and met-enkephalin (Stanley et al., 2010). Additionally, beta-endorphin levels among adults with developmental disorders were found to be higher after an episode of NSSI in comparison to morning levels (Sandman et al., 1997).

The utility of using a treatment approach to understand heterogeneity is highlighted by research investigating opiate antagonists, such as naltrexone and naloxone. These work to

inhibit the pleasurable effects of habitual behaviors (Modesto-Lowe and Van Kirk, 2002), and have been used in the treatment of NSSI. A review found that naloxone improved NSSI in 80% of participants with intellectual disabilities (Symons et al., 2004) and naltrexone has also been found to be helpful in studies of patients with BPD (Sonne et al., 1996), MDD (Agarwal et al., 2011), and obsessive-compulsive disorder (Godart et al., 2000). Conversely, not all patients show improvement with opiate antagonists (Sandman et al., 2000). Elevated levels of beta-endorphins within the blood at baseline have been shown to predict treatment response to naltrexone among developmentally disabled individuals with NSSI (Sandman et al., 1997). This highlights the heterogeneity of mechanisms at play across individuals with NSSI as well as the importance of identifying predictors for treatment response.

In addition to using treatment as a probe to understand the heterogeneity of NSSI, treatment research can also help in understanding brain regions that may play a key role in NSSI. As an example, deep brain stimulation of the globus pallidus internus, a basal ganglia region involved in movement, learning, and habit development, in an adult patient with Lesch-Nyhan disease (a disorder associated with severe NSSI), was found to eliminate NSSI (Piedimonte et al., 2015). An additional case study of deep brain stimulation of the globus pallidus in a 15-year-old with Lesch-Nyhan disease also found a dramatic reduction in NSSI following treatment (Abel et al., 2014). Further research would benefit from investigating whether there is disruption of the globus pallidus or other areas of the basal ganglia in individuals with NSSI and no developmental disorders and whether less invasive options such as transcranial magnetic stimulation may be a successful treatment option.

5. Cognitive systems

Of the RDoC domains, the cognitive systems domain likely overlaps with the others to the greatest degree and has received considerable attention in NSSI research, which can be seen in Table 1. This domain encompasses the basic processes that underlie thought and experience. Proposed constructs include: (a) attention, which involves awareness and includes the concepts of divided and selected attention; (b) perception, which involves how one experiences the external environment and includes all sensory modalities; (c) declarative memory, which involves the storage and retrieval of facts and events; (d) language, described as symbolic representations that allow for communication and labeling of abstract concepts; and (e) cognitive control, which involves goal-directed behavior, response selection, inhibition, and impulsivity. The construct of perception has relevance given that individuals with NSSI may have altered pain perception, which we review first. Then we review the construct of cognitive control, which has received the most attention from NSSI researchers.

5.1. Perception

Perception involves the collection of sensory data to construct a representation of the external environment, which then aids in making predictions and guiding actions. Research on perception in NSSI is limited to that of pain. Individuals with NSSI may experience pain differently than those without NSSI. Instead of the typical negative feedback that nociception provides to discourage future behaviors that place the individual at risk for injuries, individuals with NSSI appear to demonstrate a feed-forward system where painful

stimuli serve to encourage these behaviors. Indeed, a study of the pain offset model by Franklin et al. (2013) found that those with NSSI had reduced startle and greater positive affect (measured by post auricular reactivity) after shock. This study provides an example of how the desire for pain may reinforce NSSI and is thus, well-suited for discussion within the reward learning construct; however, it also suggests that NSSI may also involve abnormalities in lower-order pain perception (the experience and processing of pain). Studies of neural networks have investigated the pain system in NSSI.

In an fMRI study of adults with BPD and NSSI, both externally-generated and self-generated painful stimuli resulted in insula and secondary somatosensory cortex activity, but when the stimuli were self-generated, activation in the primary somatosensory activity was attenuated (Helmchen et al., 2006). A series of studies by Schmahl and colleagues have investigated how pain networks interact with emotion systems in patients with BPD and NSSI. In one study, patients exhibited greater activation to pain stimuli in the dorsolateral PFC but less activation in the posterior parietal cortex than healthy controls (Schmahl et al., 2006). Interestingly, this study also found that in patients, pain produced neural deactivation in the perigenual ACC and amygdala, which suggests that NSSI may serve as a way to normalize what is otherwise exaggerated activity in these areas. Altogether, Schmahl et al. (2006) suggest that these findings provide neurobiological evidence for antinociception, or reduced pain sensitivity among those with BPD and NSSI. A later paper reported that BPD patients with NSSI had different activation patterns in response to pain stimuli than controls (greater in cingulate, superior temporal and insular cortices; less in occipital and middle frontal areas) (Niedtfeld et al., 2010). Insula activation has also been found to be related to the catechol-O-methyl transferase (COMT) polymorphism, which has been implicated in emotion processing (Schmahl et al., 2012). Niedtfeld et al. (2012) later examined functional connectivity and found that within emotion networks, pain enhanced negative coupling between left amygdala and frontal lobe when negative picture stimuli were combined with pain stimuli among patients but not controls. Examination of the default mode network (which includes regions of the posterior cingulate, cuneus, temporal lobes, and PFC) revealed that while experiencing painful stimuli, the NSSI group had lower connectivity between posterior cingulate cortex and the left dorsolateral PFC, which was felt to reflect altered appraisal of pain as less self-relevant (Kluetsch et al., 2012). Together, these findings demonstrate the importance of including multiple units of analysis in research examining the neurobiology of NSSI.

5.2. Cognitive (effortful) control

Cognitive control involves several sub-constructs involved in modulating cognitive and emotional systems. Cognitive control is of particular interest in NSSI as individuals with NSSI often describe “urges” to engage in NSSI that can be difficult to restrain. As discussed in Section 3, the act of self-injury itself is often seen as a maladaptive response to various negative stimuli and, as discussed in Section 4, those with NSSI may have difficulty abstaining from self-injury when events exceed their capacity to regulate themselves adaptively. These examples are highly related to deficits within the Cognitive Control sub-constructs of Response Selection, Inhibition, and Suppression.

Impulsivity, a behavioral dimension related to cognitive control sub-constructs response selection, inhibition and suppression, has been associated with both clinical and nonclinical populations who engage in NSSI (Stanford and Jones, 2009) and with suicidal behaviors among hospitalized adolescents (Horesh et al., 2003). However, findings have been mixed in the association between NSSI and impulsivity. For example, those with NSSI self-report higher levels of impulsivity, but do not differ from controls in performance-based measures of impulsivity (Janis and Nock, 2009). Glenn and Klonsky (2010) did find NSSI-related abnormalities when they deconstructed impulsivity into several sub-factors: negative urgency (or the likelihood of making rash decisions when faced with negative emotions), perseverance (lack of), premeditation (lack of), and sensation seeking. They found that those with NSSI reported a higher rate of negative urgency and lower levels of premeditation and sensation-seeking compared to controls (Glenn and Klonsky, 2010). Glenn and Klonsky also found that lack of perseverance predicted more frequent and more recent NSSI behaviors. These finding suggest that while the broadly-defined construct of “impulsivity” may not explain NSSI behavior, application of narrower sub-constructs within this umbrella are useful in illustrating the underlying abnormalities of NSSI.

Further studies have suggested that after NSSI has been established as a routine behavior and upon experiencing a trigger, individuals are faced with controlling the impulse to self-injure (Fikke et al., 2011), which requires the ability to successfully employ cognitive control. Neuroimaging research on individuals with NSSI has implicated frontal brain regions, which are known to be responsible for controlling impulses. Kraus et al. (2010) reported that compared to controls, patients with BPD and NSSI showed lower activation of the orbitofrontal cortex (OFC) and mid-cingulate cortex, but greater activation of the dorsolateral PFC while listening to a description of an act of NSSI. Another study found compromised white matter microstructure within the frontal lobe in adult females with BPD with NSSI compared to healthy controls, potentially suggesting a neural substrate for impaired frontal control of emotional impulses (Grant et al., 2007).

5.3. Cognitive systems: current gaps and directions for future research

Much remains to be learned from the cognitive systems domain. Although some research has been conducted on pain perception in individuals with NSSI, these studies have largely been conducted in patients with BPD or developmental disorders. Future research should extend this work across NSSI populations. Disruptions in sensory processing have been shown to be the most important risk factor for NSSI in children and adolescents with autism spectrum disorders (Duerden et al., 2012). For instance, a model has been proposed in which the mechanisms regulating peripheral and central transmission of painful stimuli are related to and regulate self-injury in this population (Symons, 2011). In this nociceptive model, which involves pain sensitivity, the self-inflicted injury incites a cascade of peripheral sensory and neurochemical events. For example, adults with developmental disorders and NSSI show abnormal morphology of epidermal nerve fibers and increased density of Substance P fiber density compared to controls (Symons et al., 2008), which suggests altered pain perception. However, it is unclear whether increased Substance P fiber density indicates increased or decreased sensitivity to pain.

Conversely, in adults with developmental disorders, Symons et al. (2009) found higher signs of pain (e.g. vocalizations, mood or behavior, or facial signs) in those with NSSI, and that levels of overall pain signs correlated with NSSI severity. This may suggest a feed-forward pattern in some patients in which pain perpetuates rather than discourages self-injurious behavior. Research is necessary to elaborate on the mechanisms relevant to pain and to better understand these conflicting findings. Furthermore, the vast majority of existing research has investigated this nociceptive model with individuals with developmental disorders and NSSI. It is of high importance to examine this model among samples of individuals with NSSI and no developmental disorders, as the mechanisms associated with NSSI may be different between these groups.

Future research should incorporate longitudinal designs to examine the time course of events in the pathophysiology involving the perception of pain as well as the other constructs within this domain, particularly declarative memory, attention, and cognitive control. In regards to pain perception, it is imperative to link self-reported pain with neurobiological indices. According to Joiner's interpersonal theory of suicide, NSSI may lead to future suicidality by gradually habituating the individual to pain, thus altering its perception and increasing the individual's capability for suicide (Joiner, 2007). This theory has been supported by studies showing that those with NSSI demonstrate both greater pain tolerance and endurance compared to healthy controls (Franklin et al., 2012; Hooley et al., 2010; St Germain and Hooley, 2013). However, further study investigating the neurobiological correlates using neuroimaging and/or neuroendocrine measures is needed.

Chronicity of NSSI is likely to be a critically important factor, as evidenced by research showing that individuals with longer-standing NSSI experience more intense psychic pain prior to NSSI episodes and are more soothed by NSSI than those with fewer past episodes (Gordon et al., 2010). Research investigating the relationship of declarative memory on NSSI may yield interesting findings, as it is possible that memories for events may be recollected with a negative bias among NSSI populations. Research on attention would also be of interest as NSSI patients may be biased toward attending to negative stimuli or features, which may increase the likelihood of engaging in NSSI. Such biases may be an important target in NSSI intervention.

6. Systems for social processes

As listed in Table 1, the RDoC constructs falling under the social processes domain include: (a) affiliation and attachment, which involves the development of positive relationships and social interactions; (b) social communication, which includes the reception and production of facial and non-facial communication and has a highly transactional relationship with the environment; (c) perception and understanding of self, which includes the perception of agency and self-knowledge; and (d) perception and understanding of others, which includes animacy, action perception and understanding of mental states.

Social processes overlap with the other domains and its relevance to all the other domains is recognized by the RDoC work group: "The group agreed that the topic of self-regulation is extremely important and only minimally addressed in the cognitive systems and negative

valence systems workshops. As such, the group felt that it is critical to encourage research that examines the interactions among these systems, both at the behavioral and neural levels. Particular emphasis was placed on processes related to emotion/affect regulation, willpower and self-control" (NIMH, 2011).

Within the social processes domain, the constructs of social communication and perception and understanding of self and other are the most studied in NSSI. Research on perception and understanding of self and other aids in our understanding of how interactions and self-reflection are often experienced negatively among those with NSSI. Because research on NSSI relevant to the RDoC constructs of social communication and perception and understanding of others overlaps greatly, we review these to constructs together and then discuss existing research on the construct of perception and understanding of self. These studies are also outlined in Table 1.

6.1. Social communication and perception and understanding of others

Social communication involves both the reception and production of socially relevant information. Perception and understanding of others is defined as using traits, abilities, and cognitive and emotional states to make judgments and reason about other entities. A neural network implicated in both of these constructs comprises the "social brain" network (medial PFC, ACC, temporal-parietal junction, superior temporal sulcus [STS], and, temporal pole), which is thought to mediate interpretation of others' thoughts and feelings (Blakemore, 2008). Unfortunately, no neuroimaging research to date has investigated the relationship between the social brain network, NSSI, and these constructs.

Neuroendocrine research can be relevant to the constructs of social communication and perception and understanding of others when the research involves a paradigm investigating the stress response in an interpersonal context. Two such studies have identified NSSI-related biological abnormalities in the context of interpersonal stress. As reviewed previously under the acute stress construct, those with NSSI show a blunted cortisol response in the context of a psychosocial stress task (Kaess et al., 2012) compared to controls. Additionally, females with NSSI who rely on emotional support as a means of coping show attenuated cortisol response during an interpersonal conflict paradigm (Powers and McArdle, 2003). Taken together, these studies highlight the impact of interpersonal relationships in NSSI as expressed by abnormal HPA stress responses.

6.2. Perception and understanding of the self

The construct of perception and understanding of the self includes agency, or the ability to recognize that one has control over his/her thoughts and actions, and self-knowledge, which involves interpreting ones own internal states, abilities, etc. As shown in Table 1, there has been little research conducted examining this construct in NSSI. As suggested in the RDOC workshop, one neural network that is likely to be highly relevant to this construct is the default mode network (NIMH, 2011). The default mode network is thought to mediate self-referential processes (Gusnard et al., 2001). As noted in the perception construct, one study has found abnormalities within the default mode network in adults with BPD and NSSI during a task that involved viewing negative pictures and pain stimulation (Kluetsch et al.,

2012). Research on self-referential processes may provide insight into why NSSI patterns, once established, are challenging to alter. The default mode network has been implicated in rumination in various psychiatric conditions (Whitfield-Gabrieli and Ford, 2012), and is likely of relevance to investigate in NSSI across diagnoses. No neuroendocrine studies have been published to date that have directly examined this construct in patients with NSSI.

6.3. Social systems: current gaps and directions for future research

Preliminary evidence suggests that neurobiological systems relevant to interpersonal relationships are implicated in NSSI; however, much remains to be learned. Studies under the affiliation and attachment construct, which involves the development of a social bond, may lend insight into how relationships influence the development and maintenance of NSSI. Lack of a secure attachment can lead to negative outcomes, including NSSI. One of the core interpersonal factors that increases desire for suicide, a thwarted sense of belonging, may be relevant to NSSI (Joiner et al., 2005). This concept has relevance both to perception of self and to perception of others. Youth who engage in NSSI commonly suffer from relationship difficulties (Laukkanen et al., 2009) and problems with self-esteem (Claes et al., 2010). In some cases these problems are characterized by attachment disturbance including family problems such as high family expressed emotion (Santos et al., 2009) and poor family connectedness (Kaminski et al., 2010). Additionally, NSSI has been associated with a history of being bullied (McMahon et al., 2010). As adolescents expand their social networks, these foundational experiences and attachment styles may influence establishment and maintenance of coping strategies as well as set the tone for subsequent relationships. These experiences likely impact the neurobiological systems underlying social processes, which are undergoing developmental changes during these years. However, neuroimaging and neuroendocrine studies have yet to explore these constructs in the context of NSSI.

Self-esteem and social rejection are highly relevant to NSSI, and are also related to attachment. Neural networks implicated in self-esteem and social rejection involve areas such as the ACC, insula, PFC and STS (Eisenberger et al., 2011). Future research examining these networks in relation to self esteem and social rejection in patients with NSSI would be likely to be fruitful. Neuroendocrine research may also be useful for shedding light on these constructs in NSSI. Specifically neuroendocrine research suggests that individuals with low self-esteem show greater cortisol elevations in response to signs of interpersonal rejection than those with high self-esteem (Pruessner et al., 1999). This study of those at elevated risk of NSSI demonstrates physiological over-responding to stressors and may be worthy of replication among those with NSSI.

Another construct relevant to self and other processing is the observation that some adolescents are excessively swayed by peer influences and experience difficulty in establishing appropriate boundaries. Specifically, NSSI may be “contagious,” spreading through vulnerable peer groups (Taiminen et al., 1998). The contagion hypothesis has been supported by the demonstration that NSSI among peers (O’Connor et al., 2009) and peer “connectedness” can be risk factors for NSSI (Kaminski et al., 2010). However, in a study examining peer-group identification and NSSI, although those who identified as “alternative” (i.e. “punk” or “goth”) versus non-alternative had significantly greater rates of

NSSI, only a minority claimed to engage in NSSI in order to belong to the group (Young et al., 2014). Indeed, the authors suggest that identifying one's self into a peer group with high rates of NSSI is more likely due to the mechanism of assortive relations, in which those who are already at risk for NSSI seek out others who are similar to them. Nonetheless, the potential impairment of self/other conceptualizations likely serves to enhance stress and both vulnerability to and maintenance of NSSI. In regards to both peer relationship difficulties and the "contagion" hypothesis, NSSI in both of these situations may be driven by rejection sensitivity. Specifically, those with relationship difficulties may be more likely to engage in NSSI in response to rejection while those who are in a peer group that engages in NSSI may do so to avoid rejection. Neurobiological research may aid in determining whether these two different scenarios are represented similarly or differently in the brain and body.

NSSI-relevant research has shown that youth with borderline traits such as NSSI "hypermentalize", or excessively and inaccurately attribute thoughts and feelings to others (Sharp et al., 2011). Individuals with NSSI may have difficulty understanding the verbal and non-verbal signals of others because they are prone to interpreting these signs negatively. Thus, these individuals may be more reactive and engage in NSSI as a way to cope with the distress resulting from social interactions that are perceived as unpleasant. Research has begun to suggest possible neural mechanisms for the propensity to perceive others' mental states as negative. For example, a study of healthy adults in committed relationships showed that when viewing a partner's facial expressions, low neural activity in the ventrolateral PFC was associated with persistently higher levels of negative mood and rumination after interpersonal conflict (Hooker et al., 2010). Because those with NSSI report significantly greater stress during an interpersonal conflict compared to healthy controls and individuals with suicide attempts (Kim et al., 2015), future research may benefit from exploring whether anomalous ventrolateral PFC functioning is related to NSSI.

The above findings provide preliminary evidence that negative interpersonal experiences and conflict may interact with aspects of brain functioning related to NSSI, and we have highlighted areas where there are major gaps in the literature with respect to the RDoC constructs and units of analysis. Additionally, longitudinal research is needed to determine whether abnormalities within these constructs might predict the emergence and/or course of NSSI. For instance, a longitudinal study found that self-esteem, self-efficacy, and attachment anxiety predicted NSSI onset in adolescents (Tatnell et al., 2014). This area of study will provide key information regarding how development of these systems may go awry in at-risk populations and provide beginning steps for interventions promoting healthy development of the systems for social processes.

7. Arousal and regulatory systems

The arousal and regulatory systems domain is composed of three constructs: (a) arousal, (described below); (b) circadian rhythms (related to the body's ability to regulate and time biological systems); and (c) sleep and wakefulness. Although circadian rhythms and sleep and wakefulness have been implicated in disorders related to NSSI, such as depression, research has only addressed the construct of arousal within this domain, which can be seen briefly in Table 1.

7.1. Arousal

Arousal reflects an organism's sensitivity to external and internal stimuli. NSSI research has begun to investigate several physiological systems that are implicated in reactivity and regulation related to emotional stimuli. Because of this, studies here often simultaneously address both arousal and threat systems. Therefore, the research that would support this domain in NSSI has been reviewed above in other sections. As previously highlighted under the acute threat construct, the study by Plener et al. (2012) found stronger brain response in the amygdala, hippocampus and anterior cingulate cortex when exposed to emotional pictures, and rated pictures with self-injurious reference as significantly more arousing than controls. The application of this study to the constructs of both arousal and acute threat provides an illustration of how the proposed RDoC domains do not exist within a vacuum, but are often highly integrated with one another.

7.2. Arousal and regulatory systems: current gaps and directions for future research

Very little information is currently available on how basic arousal systems may be altered in persons with NSSI. Future research should work to examine any potential disturbances within the constructs of circadian rhythms and sleep and wakefulness as sleep-related difficulties within NSSI may be present and impair daily functioning due to the inability to fully benefit from its restorative nature. Disturbances in arousal may impact the ability to react appropriately to external challenges and may be associated anomalous functioning within the brain and/or HPA axis. Sleep abnormalities remains a completely unstudied area in NSSI research. Research within this domain is especially important as difficulties within the arousal and regulatory system may lead to impairment in other domains, such as cognitive systems.

8. Conclusion

Here we have reviewed the existing literature on the neurobiology of NSSI using the domains proposed by RDoC as a framework to guide our organization. Recent evidence has provided initial support that atypical functioning is evident across many of these domains and constructs in NSSI. In this review, we have found that the most well studied constructs in the neurobiology of NSSI include acute and sustained threat, reward learning, and cognitive control. Furthermore, this review has highlighted several areas of research within different constructs that are likely avenues of fruitful inquiry.

A challenge to this organizational approach is that these systems interface with each other substantially. It is likely that several constructs within the RDoC domains are highly interdependent with one another when it comes to the development and/or maintenance of behavior, including NSSI. Future research would benefit from not only examining the association between these constructs and NSSI, but also from exploring how multiple constructs within different domains interact with one another in relation to this behavior. For example, the constructs of sustained threat and perception of self may interact with each other in a way that may explain NSSI severity. Similarly, although the present review focuses exclusively on physiology and circuits, incorporation of the remaining units of analysis is warranted. It is possible that different units of analysis may interact with one

another to help create a neurobiological profile relevant to NSSI. Since the field is still in an early stage of maturity, there are gaps where evidence is not available for all units of analysis. Nevertheless, the goal of the present review is to provide a working model of the existing NSSI research that will be expanded and refined as the field advances.

In regards to gaps in NSSI literature, two main themes emerge. First, few of the studies in this review had examined NSSI independent of psychiatric diagnoses, which limits their application to understanding the behavior in other settings. Now, as the field has begun to consider NSSI as an independent phenomenon (Selby et al., 2012), future neurobiological research would benefit from examination of NSSI independent of diagnosis. Second, additional research is needed to take a developmental perspective on NSSI to determine when and how these systems go awry so that we may identify a critical period that corresponds to the development of this behavior.

Since many of the studies reviewed here have been cross sectional, with subjects that already have established patterns of NSSI, we still lack knowledge about which factors may be predisposing, precipitating, and maintaining NSSI. Where possible, future research should also address how neurobiological abnormalities fit within more proximal temporal frameworks. A recent study used ecological momentary assessment among participants with binging and purging behavior and NSSI and found that thoughts about these behaviors often co-occurred (Shingleton et al., 2013). Such an approach may be particularly useful in relation to the Habit construct. Furthermore, longitudinal designs over the course of adolescence will be ideal for examining how changes evolve before and after onset of NSSI, identifying predictors of treatment response, and elucidating the impact of treatment on aberrant systems in adolescents with NSSI. These advances will be critical for the rapid translation to developing enhanced tools for interventions. Focusing research on adolescence is critical because early intervention during this time of increased neuroplasticity could more successfully avert aberrant processes and promote healthy neurodevelopment. The tentative framework here could serve to guide continued work to pursue the role of constructs within the domains across multiple units of analysis and across developmental stages.

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Table 1

Studies listed here specifically investigated NSSI using either neuroimaging or neuroendocrine methods in non-developmental disorder samples. The gray shaded areas indicate units of analysis beyond the scope of the review (i.e. genes, behavior) that did not also incorporate neuroimaging/neuroendocrine measures in studying the relationship between NSSI and a specific domain and its associated constructs.

	Genes	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems • Acute Threat • *Potential Harm** • *Sustained Threat Frustrative Non-Reward** • *Loss**		Amygdala (Reitz et al., 2015; Plener et al., 2012); Pituitary (Jovev et al., 2008); Hippocampus; Anterior Cingulate Cortex (Plener et al., 2012)	Cortisol (Powers & McArdle, 2003; Kaess et al ., 2012)	Coping strategies (Powers & McArdle, 2003)	Affective dysregulation (Nietdtfeld et al., 2010); Stress response (Reitz et al., 2015); Emotional response (Kaess et al., 2012); Levels of arousal (Plener et al., 2012)	Negative and neutral pictures (Nietdtfeld et al., 2010); Stress induction task (Reitz et al., 2015); Social challenge (Kaess et al., 2012); Conflict discussion (Powers & McArdle, 2003); Pictures with NSSI reference (Plener et al., 2012)
Positive Valence Systems • *Approach Motivation** • Initial Responsiveness to • *Reward Attainment** • *Sustained Responsiveness to Reward Attainment** • Reward Learning • *Habit Formation**		Thalamus; Precuneus; Dorsal striatum (Osuch et al., 2014)	**		Pain perception and relief (Osuch et al., 2014)	Cold stimuli (Osuch et al., 2014)
Cognitive Systems • *Attention** • Perception • *Declarative Memory** • *Language** • Cognitive Control • *Working Memory**	Catechol-O-methyl transferase (Schmahl et al., 2012)	Insula (Helmchen et al., 2006; Schmahl et al., 2006) ; Primary and secondary somatosensory cortices (Helmchen et al., 2006); Dorsolateral prefrontal cortex (Kluetsch et al., 2012; Kraus et al., 2010; Schmahl et al., 2006); Posterior parietal cortex; Perigenual anterior cingulate cortex (Schmahl et al., 2006); Amygdala (Niedtfeld et al., 2012; Schmahl et al., 2006); Cingulate; Superior temporal cortex; Occipital (Niedtfeld et al., 2010); Middle frontal (Grant et al., 2007 ; Niedtfeld et al., 2010); Posterior cingulate cortex; Orbitofrontal cortex; Mid-cingulate cortex (Kraus et al., 2010)	**		**	Externally and self-generated pain stimuli (Helmchen et al., 2006); Pain stimuli (Schmahl et al., 2006; Niedtfeld et al., 2012; Kluetsch et al., 2012); Negative pic tures (Niedtfeld et al., 2012); Auditory descriptions of NSSI (Kraus et al., 2010)

	Genes	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Systems for Social Processes • Affiliation and Attachment • Social Communication • Perception and Understanding of Self • Perception and Understanding of Others		Default mode network (Kluetsch et al., 2012)	Cortisol (Kaess et al., 2012; Powers & McArdle, 2003)		Coping strategies (Powers & McArdle, 2003)	Interpersonal conflict (Powers & McArdle, 2003); Social challenge (Kaess et al., 2012); Negative pictures and pain stimuli (Kluetsch et al., 2012)
Arousal and Regulatory Systems • Arousal • *Circadian Rhythms*[*] • *Sleep and Wakefulness*[*]		Amygdala; Hippocampus; Anterior Cingula te Cortex (Plener et al., 2012)	**		Levels of arousal (Plener et al., 2012)	Pictures with NSSI reference (Plener et al., 2012)

[*] Construct with lacking NSSI research using neuroimaging and/or HPA axis functioning.

[**] Unit of analysis within the scope of this review (i.e. circuits, physiology) that is lacking NSSI research for a specific domain and its associated constructs.