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Review

The role of endogenous opioids in non-suicidal self-injurious behavior: Methodological challenges

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ABSTRACT

Relief from emotional pain is a frequently cited reason for engaging in non-suicidal self-injury. The exact mechanism by which self-injury brings about this relief is unknown, but the potential role of endogenous opioids in affective regulation has been posited. Few studies have investigated this and there are a number of methodological challenges to measuring endogenous opioid activity in this population. Furthermore as the majority of research to date has focused on inpatients with borderline personality disorder (BPD), it is uncertain if the findings of previous studies would also apply to those who self-injure but who do not have BPD. Whether or not altered endogenous opioid levels are a cause or a consequence of self-injury is unknown and to this end, comparing self-injury ideators with enactors, may offer a window of insight. Another candidate system, the endocannabinoid system, should also be explored in relation to this research question. The current commentary aims to tease apart the methodological issues in this area of research and stimulate further discussion of this topic.

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Bresin and Gordon's (2013) timely and detailed review of the extant literature on the potential role of endogenous opioids in non-suicidal self-injury (NSSI) gives rise to a number of issues. It highlights many important limitations of the current body of evidence; namely the paucity of studies investigating the role of endogenous opioids within self-injury, the lack of studies measuring the effects of experimental manipulation on levels of endogenous opioids and the complete absence of studies that have used non-clinical samples. We were pleased to see this neglected facet of self-injury research receive much needed critical attention and also that their review yields several key hypotheses to guide future studies.

We believe that there are a number of potential methodological challenges to testing these hypotheses, specifically in terms of measuring endogenous opioid activity and also eliciting the release of endogenous opioids within laboratory settings. The primary aim of this commentary is to attempt to tease apart some of these challenges, as well as to stimulate further dialogue on this topic with a view to surmounting some of these obstacles. An additional aim is to expand upon some of the points raised by Bresin and Gordon and to direct attention to other important areas of uncertainty.

1. Measuring endogenous opioid activity

A key problem is that the research community lacks some of the methodological infrastructure required to fully explore the hypotheses identified within Bresin and Gordon's review. The authors highlight the disparity between plasma (peripheral) and

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cerebrospinal fluid (CSF; central) measures of endogenous opioid activity. Indeed there is some evidence to suggest that plasma levels may not be wholly reflective of central circulating levels of opioids (Baker et al., 1997; De Riu et al., 1997), although there appears to be little research on the subject and very few recent studies. De Riu and colleagues' (1997) findings suggest that CSF beta-endorphin levels are not as vulnerable to the effects of stress as plasma levels. In this case, there may be merit in exploring this difference further in order to ascertain whether CSF measures may be more appropriate for natural baseline endogenous opioid levels, whereas those conducting studies requiring more dynamic measures of endogenous opioids following experimental manipulations, may be better using plasma measures.

CSF measures are more invasive and possibly less palatable to potential participants than an intravenous blood draw, which may result in small sample sizes and thus the associated problem of low statistical power; unfortunately this is already a well-known issue within the field of neuroscientific research (Button et al., 2013). Whilst CSF measures of endogenous opioids may always be the gold standard to which we approximate, the relative ease of employing plasma measures in a sufficiently large sample to meet statistical power considerations must also be taken into account when designing studies. Lumbar puncture is more resource intensive than plasma measures and it can also cause more severe side effects, such as post-dural puncture headaches (PDPH). Such reported side effects are a frequent complication of lumbar puncture procedures (Bezov et al., 2010) and in a small number of cases they can result in impaired daily functioning lasting a week or more (Amorim et al., 2012; Tohmo et al., 1998). Evidence would suggest however, that the incidence of PDPH can be greatly reduced by using small gauge or atraumatic needles (e.g. Lavi et al., 2006), although it is uncertain how widely this practice is used (Birnbach et al., 2001; Davis et al., 2014). Small gauge needles should be used as standard practice within CSF research in order to minimize side-effects to participants.

Given that plasma levels of endogenous opioids such as beta-endorphins have been widely employed as outcome measures in numerous studies spanning many different areas of research (e.g. Bruehl et al., 2012; Tordjman et al., 2009) and generally with successful results, we would urge researchers to carefully evaluate the costs and benefits of different methods of endogenous opioid assessment.

The potential for measurement reactivity of CSF sampling may also be a confounding factor when investigating endogenous opioid activity within the context of both pain tolerance and affect regulation. Moreover, work by Gratz et al. (2011) has demonstrated that pain tolerance may vary as a function of distress. Given that altered pain sensitivity has been posited to be the result of differential endogenous opioid activity in those who self-injure, relative to controls, it may be reasonable to anticipate that levels of endogenous opioids may also differ as a function of distress. Investigating such a hypothesis using CSF lumbar puncture may therefore not be a viable option; and plasma measures may be more suitable.

An alternative methodology to both CSF and peripheral measures of endogenous opioids is the use of imaging techniques, such as Positron Emission Tomography (PET). Numerous studies have explored endogenous opioid activity using this method (e.g. Hirvonen et al., 2009; Prossin et al., 2010; Tuominen et al., 2012), employing the radioligand [^{11}C] carfentanil, which selectively binds to μ-opioid receptors; a high-affinity binding site for β-endorphin (McDonald and Lambert, 2005). This technique has yielded promising results when investigating dynamic levels of endogenous opioids in response to peripherally applied noxious stimuli, such as topical capsaicin (Bencherif et al., 2002) and also in response to affective manipulation (Prossin et al., 2010). Imaging techniques allow us a valuable window into central basal and crucially, dynamic endogenous opioid activity; the latter being problematic to assess with CSF and to some extent, also with plasma measures. As with all methodologies, there are caveats: PET imaging often requires arterial blood sampling to be performed, in order to quantitatively assess the metabolic rate and distribution of the radiotracer. This can be an unpleasant experience for participants and the pain and stress that can potentially result from arterial cannulation could also confound results, however there are several non-invasive alternatives that are being explored (see Endres et al., 2003; Hirvonen et al., 2009 for discussion).

Whilst the use of PET gives information about the binding potential (availability) of opioid receptors, the results may not be wholly indicative of whether or not the receptors are in use, but may also denote the number of receptors (Vincent and Tracey, 2010). The interpretation of results from PET as a possible reflection of circulating levels of endogenous opioids, should therefore be made with caution. Furthermore, several studies have highlighted differences in endogenous opioid binding potential as a function of gender (e.g. Smith et al., 2006; Zubieta et al., 1999). Specifically, higher levels of estrogen in women were associated with both increased basal availability of μ-opioid receptors and also increased endogenous opioid activity during application of a painful stimulus (Smith et al., 2006). Irrespective of methodology, this is an important variable to take into consideration when investigating endogenous opioids in relation to non-suicidal self-injury, as women are often overrepresented in this population (Hawton et al., 2010; Nock et al., 2009; O'Connor et al., 2009).

In short, we recommend that further work be conducted to refine the methodological tools that we have at our disposal for investigating the role of endogenous opioids in non-suicidal self-injury, taking account of both static and dynamic levels of endogenous opioids.

2. Experimentally manipulating endogenous opioid levels

Extant research that has explored the role of endogenous opioids in self-injurious behavior has followed two pathways: opioid blockade in the form of the administration of opioid antagonists such as naloxone (Russ et al., 1994) and measurement of resting levels of opioid activity (Stanley et al., 2010). Whilst the use of naloxone and other non-specific opioid antagonists (Herz, 1997) would elicit little information regarding the type of endogenous opioids that were at work, more basic scientific work of this type is needed to demonstrate the role of this system in self-injury more fully. As Bresin and Gordon (2013) highlight, we know little to nothing about dynamic fluctuations in endogenous opioid levels as a function of affect. In addition to the challenges of measuring such activity, being able to reliably elicit the release of endogenous opioids within a laboratory setting is also a topic about which the existing literature is sparse.

3. The role of endogenous opioids in self-injury ideation

Many people contemplate self-harm (ideators) but only a proportion engage in the behavior (enactors). We need to know more about the psychobiological factors that distinguish ideators from enactors and to investigate this by directly comparing these two groups. Whether or not endogenous opioids play a role in self-injury ideation is something that has, to our knowledge, never been investigated and it is perhaps for this reason that no mention of self-harm ideation is made in Bresin and Gordon's (2013) review. The lower resting levels of β-endorphins found in self-injury enactors relative to controls by Stanley et al. (2010) may suggest that low levels of endogenous opioids are a risk factor for developing self-injurious behavior. However, as the individuals in the study had already engaged in self-injury (in addition to having a history of at

least one suicide attempt), it is uncertain whether the low endorphin levels observed were a cause or a consequence of self-injury. Those who ideate about self-injury without engaging in the behavior are sometimes a difficult population to capture (e.g. Hooley et al., 2010). However if we are to gain a greater understanding of the role that endogenous opioids play within self-injury behavior and its genesis, it is crucial to investigate their role within the ideation and intention formation phase of the self-injury process (O'Connor et al., 2012).

Among those who ideate about and enact self-injurious behavior, there appear to be distinct subgroups, with some spending more time contemplating self-injury before they engage in the behavior and others spending little to no time thinking about it (Hawton et al., 2010; O'Connor et al., 2009). More than 40% of the adolescents who had engaged in self-injury in a recent study (O'Connor et al., 2014) said that they had thought about it for less than an hour beforehand (41%), whereas the remainder had thought about it for several hours (9%), more than a day but less than a week (12%) or in some cases, for more than a week (38%). The amount of time spent ideating about self-injury prior to enactment may also differ depending on the method used; more of those who had engaged in self-injury within an hour of thinking about it, reported self-cutting as opposed to overdose (Hawton et al., 2010). Prospective work should also be conducted to explore how levels of endogenous opioids may fluctuate as a function of longer-term psychological distress and self-injurious thoughts/behaviors.

4. Specificity of endogenous opioid dysfunction to self-injury in borderline personality disorder

Bresin and Gordon (2013) draw attention to the almost exclusive focus of previous research upon psychiatric inpatients and more specifically, individuals with borderline personality disorder (BPD), although this is a pervasive problem within self-injury research in general (Andover and Gibb, 2010; Hawton et al., 2010). Indeed, all participants in the study by Stanley et al. (2010), even those in the non-NSSI control group, had a current diagnosis of BPD and additionally all were psychiatric inpatients. As there have been only a handful of studies directly investigating endogenous opioids in self-injurious behavior; most of which were conducted on patients with BPD (e.g. Coid et al., 1983; Stanley et al., 2010), it is therefore uncertain whether these lower resting levels of beta-endorphins would also be present in those who self-injure but do not have BPD. Future studies should attempt to investigate the involvement of the endogenous opioid system within affect regulation and pain sensitivity in non-clinical samples.

5. Other potential mechanisms of affect regulation and altered pain tolerance

Similar to how endogenous opioids are naturally produced opiate-like substances within the body (Holden et al., 2005), endocannabinoids are naturally occurring cannabinoid-like neurotransmitters (Mechoulam and Parker, 2013). These are thought to act pre-synaptically, relaying signals toward the cell body from the nerve endings as fast retrograde synaptic messengers (Howlett et al., 2002). To our knowledge, no studies have explored the potential role of endocannabinoids in affect regulation or altered pain sensitivity in self-injury. There have been a small number of studies examining their role in depression, however. For example, Hill et al. (2008) found lower levels of the endocannabinoid 2-AG in those with major depression and also that length of depressive episode was significantly negatively correlated with 2-AG level. Endocannabinoids could provide another fertile area for research in terms of affect regulation and self-injury and a recent study by Benedetti et al. (2013) found that framing a painful tourniquet task as positive led, not only to increased pain tolerance, but it appeared to activate the endogenous opioid and endocannabinoid systems. Furthermore, the results suggested that there was differential activation of the two systems across participants, with increased pain tolerance in some participants being associated with endogenous opioids and in others, with endocannabinoids. The anticipation that self-injury would bring relief from a terrible state of mind could mean that the associated pain is viewed positively, leading to increased pain tolerance and activation of the endogenous opioid and endocannabinoid systems. Recently, imaging methods similar to those used to investigate *in vivo* endogenous opioid activity, have also been employed in the investigation of endocannabinoid activity. Hirvonen et al. (2012) used the radioligand [^{18}F]FMPEP-d_2 in a prospective PET study of CB_1 receptor binding potential in patients with alcohol dependence, during early and later-stage abstinence, compared to non-alcohol dependent healthy controls. fMRI has also been used to explore endocannabinoids and a large-scale multi-study investigation into the neurophysiology of the endocannabinoid system is currently underway: the pharmacological imaging of the cannabinoid system (PhICS) study (van Hell et al., 2011). Both techniques suffer similar limitations in their application here as they do in endogenous opioid research: use of arterial cannulation in PET and potential interaction of hormonal cycle with endocannabinoid activity in both PET and fMRI.

Exploring the neurobiological bases of self-injurious thoughts and behaviors is a key area for future research, particularly relating to the role of endogenous opioids, where so many questions remain yet to be defined, as well as to be answered. Investigating the relationship between pain and self-injury is an important gateway that could potentially facilitate the exploration of the affect regulating properties of endogenous opioids within the context of self-injury and should not be overlooked. Methodological advances must be made in terms of measuring endogenous opioid activity if the hypotheses put forward in Bresin and Gordon's (2013) review are to be truly testable. Perhaps the use of more peripheral measures of endogenous opioid activity could be thought of, not as a fatally flawed substitute, but instead as a complementary foundation upon which more refined measures of central opioid activity can be built through the increased research activity that Bresin and Gordon's (2013) hypotheses have the potential to generate. Furthermore as we are still in the early stages of this new and exciting avenue of research, the benefits of forging forward with a perhaps imperfect proxy for central endogenous opioid levels should not be obfuscated by the existence of more direct, but potentially more problematic methodologies.

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