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Neuroethology as a translational neuroscience strategy in the era of the NIMH Research Domain Criteria

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When a dog looks sad and ashamed after being chastised for misbehaving, is it experiencing something related to sadness and shame? Loosely speaking, this is probably the case. This possibility arises because humans are extremely observant of subtle details in behavior that convey information about the behavioral state of others, be they humans or creatures of other species. Also, we have the capacity to manage gaps in the information that we have about others through our capacity to imagine their behavioral state, a capacity known as “theory of mind” (Frith & Frith, 2005). As a result, although fraught with its own challenges, neuroethology (i.e., the study of the neurobiology of behaviors naturally expressed by humans and other species) presents a research platform for learning about aspects of the biology of complex behaviors. In their interesting study of chimpanzees published in this issue, Latzman and his colleagues (2015) make the case that the risk for displaying negative affect is modified by variation in the gene coding for arginine vasopressin receptor 1A (*AVPR1A*) and sex. A novel aspect of their study is the ethological approach employed by the authors, that is, the reliance on scratching as a behavioral signal of a negative affective state.

Scratching as a Displacement Behavior Associated With Negative Emotion

The authors make two important assertions about scratching as a marker of negative affective state, one explicitly and the other implicitly. Most importantly, the authors provide evidence that scratching is expressed across species in the context of negative arousal. There is strong evidence that nonhuman primates are prone to scratch themselves when aroused in an extremely wide range of anxiogenic contexts, including carbon dioxide inhalation (Krystal, Woods, Levesque, Heninger, & Heninger, 1989), drug withdrawal states (Krystal, Walker, & Heninger, 1989), and inflammation (Felger et al., 2007). Thus, increases in scratching could provide a sensitive measure of arousal associated with negative emotion in a wide variety of contexts.

Is scratching an effective ethological measure of negative affective state, one that might also be incorporated in human studies of negative affect? To answer this question, one needs to understand details about the relationship between these two dimensions of behavior. For example, it would be important to understand whether the intensity of scratching tracks in a predictable linear way with the severity of negative affective states. This question is

important because many behaviors exhibit non-linear relationships with arousal, and are therefore useful measures only within a particular range of arousal intensity. This property was illustrated in studies of opiate withdrawal in rodents (Blasig, Herz, Reinhold, & Zieglgansberger, 1973) and fear in rodents and primates (Redmond & Huang, 1979), where the display of certain arousal-related behaviors plateaued at relatively mild levels of arousal, whereas other behaviors only emerged with more intense arousal.

Second, the utility of scratching as a marker of negative affective states may be related to the specificity of the association between scratching and negative emotion; that is, it should not occur with arousal associated with positive affect. Latzman, Young, & Hopkins (2015) note that scratching increases in association with states that evoke negative affect, such as social conflict or the administration of anxiogenic substances, and decreases with social support and the administration of anxiolytic substances. However, it is not yet clear whether reward-related arousal also increases scratching. In humans, scratching can be rewarding in itself even when there is no underlying itch (Papoiu et al., 2013). Thus, it would be helpful to know whether cues associated with reward evoke scratching in a manner similar to stress-related cues.

Third, scratching would be most useful as a biomarker of negative affect if it were free of obvious confounds. In the case of the Latzman et al. (2015) study, for example, it would be important to know whether the propensity for dermatologic irritation alters the relationship between negative emotion and scratching. Arginine vasopressin may have some effects on body temperature, cardiovascular regulation, and perspiration (Doris 1984), factors that may contribute to itch. It would also be important to understand the impact of obvious environmental factors, such as ambient temperature, that might influence the propensity to perspire. Thus, while scratching or other individual behaviors may provide important and useful information about a particular behavioral state, it is important to understand the factors that may complicate the interpretation of the resulting ethological findings.

The authors describe scratching as a displacement behavior, suggesting that they hypothesize that scratching is expressed as a displacement of negative emotion. This assertion is wonderfully Freudian, reflecting an unexpected convergence of neuroethology and neuropsychanalysis. The notion of displacement (*verschiebung*) was described by Sigmund Freud in the 1930s as an unconscious mechanism through which negative emotional states might lead to thoughts or behaviors that are not directly expressions of that negative emotion (Freud, 1932–1936/1964). Around the same time, Nikolaas Tinbergen used the term displacement activity (*übersprungbewegung*) to describe distinctive behaviors that are expressed when strongly emotional behavior, such as aggression or sexual behavior, could not be expressed. He illustrated his point with the example of the tendency of male stickleback fish to exhibit repetitive bottom feeding when they could not directly express other aggressive behaviors toward an intruding male (Tinbergen & van Iersel, 1947). Latzman and colleagues (in press), building on prior conceptual work (Maestripieri, Schino, Aureli, & Troisi, 1992), suggest that chimpanzees scratch themselves instead of actively engaging in social conflict or confronting a frustrating stimulus. By using the term *displacement behavior*, the authors seem to be suggesting that scratching is not a direct consequence of negative affect but is, instead, a behavior emitted from a repertoire of

intrinsically unrelated behaviors that these primates have learned to express in association with negative affective states, perhaps in the service of self-soothing.

To deeply understand the utility of scratching as a biomarker of negative affective states, it might be helpful to understand relationships between the neural mechanisms that generate negative emotion and those that generate scratching. These links might help explain why, from among all possible behaviors, scratching emerges in the context of negative emotion. Imaging studies suggest that itch perception (Desbordes et al., 2015) and scratching activity (Papoiu et al., 2013) involve many brain regions involved in stress, interoception, and emotion including the insula, cingulate cortex, ventral striatum, ventral tegmental area, and periaqueductal gray matter. The possibility that the circuitry of negative emotion overlaps extensively with the circuitry underlying scratching may indicate that scratching in the context of negative emotion is not expressed as a displacement of the emotional response, but rather as a component of the overall organismal response to negative affect. The selection of scratching from among the repertoire of stress-related behaviors also may be influenced by peripheral consequences of autonomic arousal, such as sweating (Ogawa & Sugeno, 1993), that may in turn increase the experience of itch via triggering cholinergic urticaria (hives; Bito, Sawada, & Tokura, 2012), among other mechanisms. Thus, one might hypothesize that increased activation of brain regions like the insula, which might serve to focus attention on itch (van Laarhoven, Kraaijmaat, Wilder-Smith, & Evers, 2010), combined with sympathetic arousal, which may operate to intensify the experience of itch, could increase the expression of scratching in the context of negative emotion.

Scratching the RDoC Itch

Insights from a Neurogenomics Approach to the Research Domain Criteria Negative Valence Systems Domain

The Research Domain Criteria (RDoC) framework was introduced by Thomas Insel and colleagues at the National Institute of Mental Health (NIMH) as a dimensional approach to characterizing patients with psychiatric disorders (Insel et al., 2010). The RDoC framework draws on knowledge emerging from studies suggesting that there are common transdiagnostic neurobiological and behavioral features among patients who would be characterized by criteria of the *Diagnostic and Statistical Manual of Mental Disorders*—5th edition (DSM-5; American Psychiatric Association [APA], 2013) into distinct diagnostic categories (Insel & Cuthbert, 2015). As described by Kozak and Cuthbert (2015), it specifies an array of biobehavioral constructs, organized into broader “systems” domains, to be investigated at multiple levels of analysis. For example, constructs within the RDoC negative valence systems (NVS) domain include acute threat (“fear”), potential threat (“anxiety”), sustained threat, loss, and frustrative nonreward, which can be studied at levels of genetics, brain circuitry, physiological, and observable behavior. As RDoC emphasizes the quantitative evaluation of specific behaviors, it is more explicitly ethological than the third (APA, 1980), fourth (APA, 1994), and fifth editions of the DSM that, in turn, were more ethological than the first two editions (APA, 1952, 1968).

How has the RDoC perspective informed the study reported by Latzman et al. (2015)? First and foremost, the authors did not attempt to model an anxiety disorder, such as panic

disorder or social anxiety disorder. Instead, they focused on a behavioral dimension of fear within the framework of the NVS domain. This focus supported their effort to explore genetic, sex-specific, and neuroimaging moderators or correlates of scratching in chimpanzees. The authors note that some writers have suggested that studying chimpanzees presents advantages over research with humans because it removes the complex effects of human culture upon behavior. However, one could also assert that chimpanzee troops are highly complex microcultures where neighboring troops exhibit distinctive cultural properties (Luncz & Boesch, 2015). Thus, studying chimpanzees may not remove the impact of culture. Further, humans generally understand a great deal about the culture in which they operate, whereas the cultural features of the chimpanzees studied are not reported. Instead, the chimpanzees in Latzman et al.'s study seem to add value principally by serving as a population isolate with an informative gene variant, the complete deletion of the DupB region of *AVPR1A* that rarely occurs in humans. The prevalence of this gene variant in chimpanzees made it feasible to study the relationship between this alteration in *AVPR1A*, brain structure, and fear-related behaviors in chimpanzees, whereas this study would have been much more difficult to study in humans.

Second, the RDoC perspective places great emphasis on the distinct neural circuits underlying the separate RDoC domains. In this case, reduced functionality of *AVPR1a* was associated with reduced gray matter volume in brain regions involved in the generation of fear behaviors and scratching, such as the insula and cingulate cortices, as well as the executive control of fear and scratching, such as the dorsolateral prefrontal cortex.

Third, it has been hoped that an evidence-based, dimensional, and circuit-based approach, such as RDoC, would also point to novel treatments that might be delivered in a personalized manner. In this regard, this study points to an important interaction between the DupB deletion in *AVPR1A* and sex. In males, the deletion increased the display of scratching, suggesting that enhancing vasopressin V1a receptor signaling might be therapeutic. However, in females, the DupB deletion reduced scratching, raising the possibility that drugs that block V1a receptors might reduce anxiety in females. If so, then enhancing V1a function in unselected populations might give rise to conflicting subgroup responses that might cancel out any overall group benefit.

Conclusions

There is a widespread belief that advancing our understanding of the relationships among genes, brain circuits, and behavior will help guide us toward a deeper understanding of psychiatric conditions. The NIMH RDoC initiative has emerged as a powerful impetus to advance this agenda, one that is highly consistent with the aims of neuroethology. The study by Latzman et al. (2015) in chimpanzees highlights the power of translational neuroscience, in this case framed within the RDoC NVS domain, to advance this agenda.

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