# Depression and the Brain's Input: Intrinsic Brain Activity and Difference-based Coding

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In their impressive target paper, Douglas Watt and Jaak Panksepp aim to consider the "psychological properties of the brain and its adaptive mandates" in the pathophysiology of depression. They argue that depression is "fundamentally connected to social attachment," the neurobiology of which they consider to be related to the separation-distress mechanism. In this commentary I do not want to go into the neurochemical and neuroanatomical details of their impressive hypothesis but will briefly focus on one particular aspect of the brain's input. I want to raise the question for the kind of coding mechanisms that must be presupposed by the brain in order to link its intrinsic activity and the brain's input to the stimulus-induced activity. In doing so, I will briefly indicate how an abnormally altered brain's input may yield the kind of changes observed in depression.

How is it possible that the brain's internal separation-distress mechanisms can impact stimulus-induced activity? This occurs only if the neurobiological underpinnings of the brain's internal separation-distress mechanisms modulate and impact stimulus-induced activity in an abnormal way. In these circumstances, withdrawal from the social environment, together with the consecutive increased self-focus that is one of the hallmarks of depression, are generated. Hence, we must presuppose that the pathologically altered separation-distress system apparently decreases stimulus-induced neural-activity changes from the environment. The question I want to raise here concerns the kind of neural coding that must be presupposed in order for the brain (and its input) to have such disastrous effects on stimulus-induced activity. How must the brain code its neural-activity changes in order, first, to link its own input to the intrinsic activity and, second, to link the stimulus-induced activity to the environment?

Watt & Panksepp seem to remain unclear about the exact mechanisms of the interaction between the organism's separation-distress disposition and the external stimulus's salience attribution. How the organism's internal separation-distress disposition and the external factors interact, and are linked together, remains unclear. There must be some kind of common currency, or coding, since otherwise interaction and linkage remain impossible. What, then, is the common currency between intrinsic separation-distress disposition and the degree of salience of external stimulus? Is there a special instance for coordinating and translating intrinsic separation-distress disposition and the salience of the external stimulus? Or are both coded in a common currency that makes the assumption of some kind of additional coordination and translation superfluous?

It is at this point that the concept of relational coding as difference-based can be introduced. As in the case of mental and social-context stimuli (described above), the external stimulus is coded in relation to the organism's *intrinsic* stimuli—that is, the activity and stimuli reflecting the organism's separation-distress disposition. What the brain's intrinsic activity (and hence its separation-distress disposition) provides is the neuronal "context" for how the brain can encounter (i.e., get excited by, engage in, and approach) external stimuli—that is, potentially rewarding stimuli, and their triggering of possible neuronal activity changes. How can the brain's intrinsic activity and the neural-activity changes related to the stimulus be linked and coordinated with each other? Rather than assuming some additional coordination or translation, I claim that such linkage is made possible by coding the *difference* between both: the gap between the level of the brain's intrinsic seeking disposition, and the potential neuronal activity changes related to the degree of salience of the stimulus. Hence, it is the difference between the brain's intrinsic resting-state activity level and the stimulus-induced activity changes that is coded in the brain's actual activity level. Thus, the degree of possible neuronal activity changes that the stimulus can induce is set from the very beginning in relation to the brain's actual intrinsic activity level—the latter serves as reference, standard, or measure for the former.

Such inclusion of the brain's intrinsic level of activity, as a neuronal context in difference-based coding, makes the question for possible coordination and integration superfluous. The question need not even be

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raised, because there is coordination and integration from the very beginning of the process. Thus, by virtue of difference-based coding, brain and stimulus no longer need to be coordinated and linked, because the neural-activity changes themselves mirror the relation between the brain's intrinsic activity level and possible stimulus-induced neuronal activity changes.

If we wish to understand the pathophysiological mechanisms of depression, we must reveal the kind of neural coding that links the brain's intrinsic activity to the stimulus-induced activity. My hypothesis is that the intrinsic brain activity is abnormally high, which in turn may make it impossible for the external stimulus to induce any change in the brain's intrinsic activity level. Accordingly, the difference between the brain's intrinsic activity and the potential stimulus-induced activity is shifted to one extreme—resulting in an imbalance—with the predominant impact being the former (intrinsic activity) at the expense of the latter (events in the external world).

If this holds true, one would expect that external stimuli can no longer induce changes in neural activity in those regions that show high resting-state activity, such as the cortical midline structures that are also involved in constituting self-relatedness. This is at least indirectly supported empirically by imaging studies from others (Grecius, Krasnow, Reiss, & Menon, 2003; Grimm et el., 2003, 2009, in press; Mayberg, 2003; Mayberg et al., 1999.) and from our group, showing (1) an abnormally high resting-state activity in subcortical and cortical midline structures in depression and (2) that this variable no longer parametrically modulates stimulus-induced activity from either external emotions or self-relatedness in any fine-grained way. Watt & Panksepp's proposal may well be a testable hypothesis that can be investigated both in animals and in humans with depression. This may help to explain why, metaphorically speaking, relational coding seems to mute into self-referential coding in depression, with circulating and ruminating affects and cognitions that refer almost exclusively to the self rather than to the environment, resulting in what can be described as increased self-focus.

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