Psychopathology and Pathophysiology of Depression

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Is depression a systemic disorder of oneself and the brain’s intrinsic activity?

What is depression? When talking about depression in this article, I refer to the kind of depression that is part of the major depressive disorders. Let us look at a Case Vignette as the guide to explain what depression is, what it is not, and how it may be treated in the future.

CASE VIGNETTE
Mrs J has been working as an executive assistant for the CEO (Mr X) of a major corporation for 13 years. Mrs J and Mr X have developed a good working relationship—he is generally very nice but is known for this temper. As is often the case in such long-term working relationships, they have developed certain rituals over time. One of those rituals is the Monday morning coffee that she prepares for him, to his taste. This Monday morning, she prepares the coffee in the usual way: nothing out of the ordinary there. However, his reaction is extraordinary. He begins to shout that the coffee tastes bad and that she cannot make a decent cup of coffee. She is surprised and puzzled, although she knows that Mr X has recently been having both private and professional trouble. Three days later, she is hospitalized for the third time with a severe episode of depression.

What does this Case Vignette tell us? First, it tells us that depression is closely related to life events. However, we need to be more specific. It is not the life event itself that is important but rather how the respective person perceives certain events. Although Mrs J knows that Mr X has been under a lot of stress lately and that he occasionally loses his temper, which may explain his rude behavior, she is unable to put things into perspective, just as she had been incapable of doing in the past. Mrs J perceives everyday events subjectively, and if these events are negative, they often trigger a depressive episode. How is this possible? Recent research shows that stressful life events are encoded in the brain’s intrinsic activity (ie, neural activity that is continuously ongoing in the brain independent of whether a particular stimulus or task is processed).1 This intrinsic activity in the brain is established by measuring neural activity during a resting state in which the person closes his or her eyes and does not receive any specific stimuli or need to perform a task. Although the intrinsic activity of the brain is continuous—no matter the stimuli—it does not mean that it is not affected by certain life events. Findings from recent research suggest that the brain’s intrinsic activity encodes information about stressful life events.2 Stressful life events and especially their environmental context seem to leave their traces in the brain’s intrinsic activity. Life events shape the way different brain regions and their neural activity relate to each other during the resting state. The relationship between regions and networks (ie, their functional connectivity) may thus reflect, to some yet unclear degree, a person’s life history.

What are the initial symptoms of depression in our patient? She has the feeling that things have changed. She later recounts that the most painful aspect is her emotional disconnect from her husband and children. She sees how much they care and are concerned about her, but she cannot feel anything. She has difficulty in getting up in the morning, her mood is dark, and she sleeps badly (she stays awake most of the night and finally falls asleep for 1 or 2 hours in the early morning). During depressive episodes, patients withdraw into themselves. They experience themselves as detached from the environment and are no longer able to properly relate to and connect with their environment. It has been shown that depressed patients no longer neuronally process exteroceptive stimuli in the same way that healthy persons do.3,4 This shifts the balance between interoceptive and exteroceptive stimuli toward the interoceptive stimuli at the expense of the exteroceptive stimuli.5 Decreased processing ofexteroceptive stimuli
Many depressed patients report a strong feeling of disconnectedness from the environment, especially in the early stages. There is decreased awareness of the environment (ie, a decreased environmental focus) and, consequently, the subjective experience of disconnectedness from the environment (eg, persons, events, objects) independent of the self and the one’s emotions.5,7 The objects, events, or other persons in the environment are no longer experienced as meaningful.
Self-awareness of this lack of feelings makes it even more painful. Recent studies in healthy persons have shown that during the resting state, intrinsic activity shifts back and forth between different neural networks. One of the main neural networks is the task-negative network. This default-mode network occupies much of the medial regions in the brain—the cortical midline structure (CMS). The other neural network is the task-positive network, which includes much of the lateral prefrontal and parietal cortex. Vanhaudenhuyse and colleagues showed that there is a change in the direction of our awareness about every 20 to 30 seconds. While lying in the MRI scanner during a resting state (eyes closed, sans specific stimuli or task), subjects had to indicate whether they experienced inner (own thoughts) or outer (perceptions) contents in their mental states. When experiencing inner contents, activation in the CMS—the task-negative network—was much stronger than activation in the lateral regions—the task-positive network. This pattern was reversed during outer contents, when the lateral network’s activity dominated over the CMS’s activity. The same activation pattern has been established during stimulus-induced or task-related activity in the brain. While performing certain tasks related to working memory, our awareness may nevertheless slip inward—mind wandering. Imaging studies in healthy persons show that mind wandering leads to increased neural activity, especially in the midline regions, with a rebalancing between midline and lateral regions. The brain encodes the balance between inner and outer awareness into its neural activity during the resting state and stimulus-induced activity. Because of the abnormal shift from outer to inner awareness, one would expect a corresponding shift from lateral to midline neural networks in depression. Findings indicate an abnormal balance between the midline and lateral networks in depression: there is increased neural activity, especially in the anterior midline regions, such as the anterior cingulated cortex, and decreased activity in the lateral prefrontal cortex. This abnormal midline-lateral balance is consistent with findings in animal models of depression in which the same kind of changes can be observed in homologous regions.

There is, however, much more to depression than a decreased focus on environment. The most painful aspect seems to be that all thoughts and concerns revolve around oneself. As the patient withdraws more and more from loved ones, the focus becomes more and more centered on oneself, with thoughts of “I am guilty,” “I am not worth it,” and so on. These feelings of worthlessness are subjective, and they can be further aggravated by objective difficulties (e.g., money problems, relationship problems, job loss) throughout the course of the disorder, especially when the patient suffers from multiple episodes or chronic depression. The focus on oneself is like an inner force that pulls the patient deeper and deeper inside: She sat by the window, looking inward rather than looking out. Her thoughts were consumed with her sadness. She viewed her life as a broken one, and yet she could not place her finger on the exact moment it fell apart. “How did I get to feel this way?” she repeatedly asked herself. By asking, she hoped to transcend her depressed state; through understanding, she hoped to repair it. Instead, her questions led her deeper and deeper inside herself—further away from the path that would lead to her recovery.

Underlying mechanisms of increased self-focus
Increased self-focus is closely related to its sibling, decreased environment focus: the more the focus is on content related to oneself, the less the focus is directed toward environmental content not related to oneself. As long as perceptions, cognitions, and attention are abnormally directed toward oneself, the patient is unable to detach from her own contents and view the world in an objective (rather than subjective) way. Increased self-focus goes hand in hand with predominantly negative emotions rather than positive emotions. The increased self-focus may also be accompanied by an increased focus on one’s body. The patient experiences and perceives her body in a most hypersensitive way. This, in turn, can lead to various somatic symptoms.

Functional imaging can be used to investigate that relationship between self and negative emotions. We used functional imaging to gauge the degree of self-relatedness of subjects. In accordance with clinical symptoms, depressed patients attributed increased degrees of self-relatedness to especially negative emotional pictures: the more negative the emotions, the higher the degree of self-relatedness attributed to it. This, in contrast, was not the case in healthy cohorts, who related increased degrees of self-relatedness to increased degrees of positivity in the emotional pictures. The imaging data show altered neural activity in the anterior midline regions, such as the anterior cingulate cortex and the ventromedial and dorsomedial prefrontal cortex, during the self-relatedness when subjects were shown pictures with emotional content (Figure). Emotion-inducing
pictures that have a high degree of personal relevance to the viewer (i.e., self-relatedness) stimulate activity changes in the midline regions. In contrast, emotional pictures that remain rather irrelevant to the person do not induce a strong activity in the midline region. This suggests that the increased resting state activity in these regions is directly related to increased self-focus. This is further underlined by findings in healthy subjects in whom neural overlap can be observed in the anterior midline regions.\textsuperscript{21-23}

(Figure): Cortical midline structures and the self

(A) Distinction between self and non-self: cortical midline structures and domain independence. The figure on the left depicts all the imaging studies on the self as plotted in their obtained location on one brain. This includes self-referential stimuli in various domains or functions, such as memory, social, and spatial, as indicated by the colors. On the right, 3 different coordinates (x, y, z) are shown that determine the direction (medial-lateral, inferior-superior) of the location in the brain. All studies locate in the midline regions of the brain (left image) as seen in the x-coordinate that describes the medial-lateral location (right image).

(B) Cortical midline structures: anatomical definition.

MOPFC, medial orbital prefrontal cortex; PACC, perigenual anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; SACC, supragenual anterior cingulate cortex; PCC, posterior cingulate cortex; MPC, medial parietal cortex; RSC, retrosplenial cortex.

What about the increased body focus? Interceptive stimuli are processed in the insula, a region on the outer surface where interoceptive and exteroceptive stimuli from body and environment converge and are integrated. We studied depressed patients during awareness of their body (heart beat counting) and during exteroceptive awareness (tone presentation).\textsuperscript{3,4} The Body Perception Questionnaire (BPQ) was used to measure awareness of the body. Patients with depression showed significantly higher values in the BPQ, indicating higher degrees of body awareness. This is compatible with the assumption of an increased body focus.

Neural activity
Patients with depression show increased resting state activity in the insula. This, in turn, leads to decreased neural differentiation between interoceptive and exteroceptive stimuli in the insula. Exteroceptive stimuli are processed more or less in the same way as interoceptive stimuli. Because of the lack of interoceptive-exteroceptive differentiation, exteroceptive stimuli are experienced in terms of the body rather than as environmental stimuli that are distinct from the body. Awareness is shifted toward one’s body, which can explain at least in part the increased body focus. If exteroceptive stimuli are less strongly processed in the brain, interoceptive stimuli are more strongly represented in the neural activity of the brain. Such a shift in the balance between interoceptive and exteroceptive stimulus processing may be manifested in an analogous shift in the contents of our awareness and attention. The body becomes the primary content of our awareness, and attention toward environmental content is reduced. Ultimately, this results in an increased focus on the body rather than the environment.

**Therapeutic implications**

A study of patients in the acute state of depression and patients with depression in remission found that the activity changes in the insula reversed and normalized during remission. This means that the abnormal insula activity may be considered a predictive marker of therapeutic effects and thus of possible remission. However, additional studies are needed to support these results.

What is the biochemical level that is relevant for pharmacological treatment? The neural activity in the brain is generated on the basis of neural excitation and inhibition. There are 2 biochemical substances that generate neural excitation and inhibition. Glutamate is the main transmitter that mediates neural excitation, while γ-aminobutyric acid (GABA) induces neural inhibition that results in an excitation-inhibition balance. GABA, induced by specific stimuli, is also related to neural activity in particular regions.

Wiebking and colleagues have shown that the neurotransmitter GABA plays a central role in both the anterior cingulate cortex and the insula: GABA mediates exteroceptive awareness in the pregenual anterior cingulate cortex; it also mediates the neural activity during specifically interoceptive awareness in the insula. This is compatible with the initial therapeutic effects of benzodiazepines such as lorazepam, which provide some initial relief of depression symptoms (although they do not improve the mood itself).

**Conclusion**

Novel and more specific psychotherapeutic approaches that target increased self-focus and body focus and decreased environment focus can be developed as we gain more insights into the pathophysiological basis in the subcortical and cortical midline regions and their exact underlying neural mechanisms. Psychotherapeutic approaches that train the patient to shift his awareness from the internal to the external might also improve patient outcomes. In the future, imaging studies may be used to see how these interventions affect neural activity in the insula and the midline regions.


19. Grimm S, Ernst J, Boesiger P, et al. Reduced negative BOLD responses in the default-mode...


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