been hypothesized that mood symptoms could be attributed to dysregulation of neuroendocrine signaling instead of an autoimmune basis.[5]

Overall, this case report supports, as a clinical rule of thumb, that organic pathology should be actively investigated when facing first manic episodes at advanced ages.

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Not only pharmacodynamic: the role of brain circuits in improving the treatment of suicidal thoughts and behaviors

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Recently, Watts et al.[1] published a letter in which they argue for the importance of understanding the underlying pharmacodynamic mechanisms of Ketamine in order to personalize its use and to help develop novel drugs designed for specific targets in both depression and suicidality, which they called "the dawn of precision psychiatry." Nevertheless, it is no less important to understand and specify different brain circuits underlying or associated with suicidality to determine the different clinical profiles for which each drug intervention might be more clinically effective.

Schmaal et al.[2] conducted a comprehensive review on the neurocircuitry of suicidal thoughts and behaviors, in which a wide body of evidence suggested that different brain circuits might be involved in each aspect (thoughts vs. behaviors) of suicidality. Suicidal thoughts are more linked with alterations in brain areas involved in regulating positive and negative emotions, such as the medial ventral prefrontal cortex, insula, amygdala, hippocampus, lateral temporal regions, posterior midline structures (posterior cingulate cortex and precuneus), dorsal anterior cingulate cortex, ventral striatum, thalamus, and cerebellum. Suicidal behaviors are more associated with dysfunction in regions involved in cognitive-behavioral control, such as the dorsal prefrontal cortex, inferior frontal gyrus, rostral prefrontal cortex, and dorsal anterior cingulate cortex. Even though there is a clear overlap among these areas, an understanding of these structures and their patterns of connectivity might orient specific circuit-based treatment interventions that can more precisely target different clinical profiles of suicidality.

In practice, there is still debate concerning whether the severity of depressive symptoms independently predicts more suicidal thoughts and behaviors.[3] Of note, improvement in suicidal thoughts after ketamine infusion might be independent of reductions in depressive symptoms,[4] which suggests independent underlying brain mechanisms. Recently, Ballard et al.[5] found that after a single ketamine infusion, reduced suicidal ideation was correlated with reduced activation of the infralimbic cortex (Broadmann area 25). Interestingly, this finding was not supported by overall mood scores, such as depressive symptoms in general.

All this debate might help clinicians more precisely comprehend each clinical profile associated with depression and/or suicidality, as well as encourage future research on therapeutics for each clinical profile, including new pharmacological (e.g., brexanolone, cannabidiol, glutamatergic agents) or neuromodulatory treatments, such as transcranial magnetic stimulation, among others. Previous studies have already stressed the importance of understanding neural circuit biotypes in order to better predict treatment-response for each neurophysiological subtype of psychiatric disorders.[6-8] Regarding suicidality, these clinical phenotypes might include: a) depression without suicidal thoughts, b) depression with suicidal thoughts, c) suicidal thoughts in absence of depression, d) depression without suicidal behaviors, e) depression with suicidal behaviors, f) suicidal behaviors in absence of depression. We hope that this knowledge could drive clinicians and researchers toward a more personalized psychiatric treatment.

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