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Neuroprogression in bipolar disorder: why right is wrong

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Abstract

The controversy on whether bipolar disorder is a neurodevelopmental versus a neuroprogressive illness is still around, despite some reductionistic claims that only one model is right. The current diagnostic classifications are not helpful to address this issue, and there is conflicting evidence in favor and against either model. In practice, though, understanding that many patients may show a progressive cognitive and functional decline which may be correlated with the number and severity of episodes may lead to better outcomes through early intervention strategies.

Invited Commentary

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Strong beliefs may make us comfortable, but they are not facts. Passion does not automatically turn opinion into truth. In science, we can test hypotheses and we can try models, but a model is not a hypothesis. There are plenty of examples of situations where a model is more explanatory than a hypothesis, especially when addressing complex questions that do not have a simple, or a single answer. While hypotheses may be right or wrong, models are better or worse. When trying to understand the nuances of cognitive impairment in bipolar disorder (Samamé, 2024), debating who is wrong, (those who believe in a neurodevelopmental cause, or those who think that it is driven by neuroprogression), leads to a black and white approach that will not solve the question, simply because this is not the question. Neuroprogression and neurodevelopment are not hypotheses, they are models, with their pros and cons. Neither model is proven right or wrong, and depending on the context, one may fit better than the other. There is also a crucial concept in science which is bias. Bias is particularly relevant in epidemiology and especially in observational studies. It is not the same to study the trajectory of certain variables in a sample of patients from a private outpatient clinic than from a representative sample of patients from a given catchment area, and one has always to be mindful of attrition in long-term studies.

Cognitive impairment in bipolar disorder is hugely heterogeneous (Burdick & Millett, 2021). Cluster analysis from cross-sectional studies shows that a subset of patients may show persistent cognitive deficits, while others are apparently cognitively intact; there is also a third group with selective impairments (Lima et al., 2019). Two decades ago, two independent studies reported the impact of manic episodes on cognitive impairment (Cavanagh, Van Beck, Muir, & Blackwood, 2002; Martínez-Arán et al., 2004). Although those were cross-sectional studies, similar cognitive dysfunctions across bipolar mood states, including euthymia, were reported, as well as a correlation between the severity of cognitive impairment and poor functioning. This finding has been replicated several times, the last of which was a large, multicentre study with over 5800 patients, that showed an association with the number of episodes (Burdick et al., 2022), of which the manic ones seem to be the most impairing (Sanchez-Moreno et al., 2018).

The main argument against a neuroprogression model, as argued by Samamé (2024), is the fact that most longitudinal studies do not show cognitive impairment to progress over time. The problem, though, is that most longitudinal studies are very short, and they suffer from selection bias. The main bias is caused by the fact that the most severe and difficult-to-treat patients tend to be lost to follow-up or die. Hence, those patients may be less treatment adherent (Samalin & Belzeaux, 2023) and relapse, and their cognition and functioning may decrease over time, in line with the concept of neuroprograssion. It is not a matter of the type of setting, but the 'survivor' effect, as described by Montejo et al. (2022) in elderly population. In fact, the best longitudinal studies are those that start from premorbid states (supporting indeed a staging model), showing that subjects developing bipolar disorder were, on average, actually even smarter than those who remained healthy (Cannon et al., 1997; Zammit et al., 2004). If the majority of people with bipolar disorder do not show any premorbid cognitive deficits, and the majority of bipolar patients are cognitively impaired in clinical samples, it seems obvious

that something happened in between. But of course, due to heterogeneity, it is likely that a relatively small subset of patients with bipolar disorder may actually have a neurodevelopmental condition (Kjærstad, Søhol, Vinberg, Kessing, & Miskowiak, 2023); those are more likely to have an early onset of disease, and comorbidity with ADHD and other neurodevelopmental problems. One could think of these patients as neurodevelopmental phenocopies of bipolar patients with a neuroprogressive trajectory. Moreover, there is now evidence that not only cognitive dysfunction tends to worsen over time in the most severe and recurring patients, but structural brain changes such as frontocortical thinning are also associated with worse course outcomes and the number of manic episodes (Abé et al., 2022). Importantly, this is a longitudinal study, and the authors conclude that their results yield insights into disease progression in bipolar disorder and highlight the importance of mania prevention in bipolar disorder treatment. While it is true that the cluster analysis studies identified a subset of patients who were apparently cognitively intact, this term may be misleading, because it refers to those patients as having a cognitive performance similar to healthy controls, but in the context of cross-sectional studies, we do not know if those patients worsened with respect to their baseline performance before illness onset. Here, the concept of cognitive reserve comes into play (Sánchez-Torres et al., 2023).

It is unfortunate that currently there is no pharmacological treatment for cognitive dysfunction in the context of bipolar disorder, schizophrenia, or depression (Miskowiak et al., 2022). In fact, medication is a confounder as many of the drugs used to treat bipolar illness can actually harm cognition (Ilzarbe & Vieta, 2023; Vidal et al., 2023). The same applies to comorbidity (Miguel, Marquez-Arrico, Jodar, Navarro, & Adan, 2023). There are, however, effective treatments based on psychological interventions. Some meta-analyses mistakenly pool cognitive remediation trials with functional remediation ones, causing again heterogeneity and mixing apples and oranges (Samamé, Durante, Cattaneo, Aprahamian, & Strejilevich, 2023). Cognitive remediation improves cognition (Lewandowski et al., 2017), and functional remediation improves functioning (Torrent et al., 2013). Those trials were positive on their primary outcomes, even if they failed on some secondary outcomes.

In summary, in my opinion, there is enough information to say that cognitive impairment in bipolar disorder mostly fits into a neuroprogression model, although there is some heterogeneity and a subset of patients may better fit into a neurodevelopmental model, with premorbid deficits, early age of onset and complex comorbidities, and a course closer to schizoaffective disorder or schizophrenia. It may make sense to try to adjust staging models to this reality and try to tailor effective prevention and treatment strategies accordingly, aiming at personalized, precision psychiatry (Vieta, 2015). If bipolar disorder is mostly neuroprogressive, albeit heterogeneous, treatment and prevention programs should focus on effective prevention of relapse, early diagnosis and treatment, and enhancement of cognitive reserve and resilience.

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References

Abé, C., Ching, C. R. K., Liberg, B., Lebedev, A. V., Agartz, I., Akudjedu, T. N., … Landén. M., ENIGMA Bipolar Disorder Working Group (2022). Longitudinal structural brain changes in bipolar disorder: A multicenter neuroimaging study of 1232 individuals by the ENIGMA bipolar disorder working group. *Biological Psychiatry*, *91*(6), 582–592. https://doi.org/10.1016/j.biopsych.2021.09.008

Burdick, K. E., & Millett, C. E. (2021). Cognitive heterogeneity is a key predictor of differential functional outcome in patients with bipolar disorder. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *53*, 4–6. https://doi.org/10.1016/j.euroneuro.2021.06.008

Burdick, K. E., Millett, C. E., Yocum, A. K., Altimus, C. M., Andreassen, O. A., Aubin, V., … McInnis, M. G. (2022). Predictors of functional impairment in bipolar disorder: Results from 13 cohorts from seven countries by the global bipolar cohort collaborative. *Bipolar Disorders*, *24*(7), 709–719. https://doi.org/10.1111/bdi.13208

Cannon, M., Jones, P., Gilvarry, C., Rifkin, L., McKenzie, K., Foerster, A., … Murray, R. M. (1997). Premorbid social functioning in schizophrenia and bipolar disorder: Similarities and differences. *The American Journal of Psychiatry*, *154*(11), 1544–1550. https://doi.org/10.1176/ajp.154.11.1544

Cavanagh, J. T., Van Beck, M., Muir, W., & Blackwood, D. H. (2002). Case-control study of neurocognitive function in euthymic patients with bipolar disorder: An association with mania. *The British Journal of Psychiatry: the Journal of Mental Science*, *180*, 320–326. https://doi.org/10.1192/bjp.180.4.320

Ilzarbe, L., & Vieta, E. (2023). The elephant in the room: Medication as confounder. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *71*, 6–8. https://doi.org/10.1016/j.euroneuro.2023.03.001

Kjærstad, H. L., Søhol, K., Vinberg, M., Kessing, L. V., & Miskowiak, K. W. (2023). The trajectory of emotional and non-emotional cognitive function in newly diagnosed patients with bipolar disorder and their unaffected relatives: A 16-month follow-up study. *European Neuropsychopharmacology*, *67*, 4–21. doi: 10.1016/j.euroneuro.2022.11.004

Lewandowski, K. E., Sperry, S. H., Cohen, B. M., Norris, L. A., Fitzmaurice, G. M., Ongur, D., … Keshavan, M. S. (2017). Treatment to enhance cognition in bipolar disorder (TREC-BD): Efficacy of a randomized controlled trial of cognitive remediation versus active control. *The Journal of Clinical Psychiatry*, *78*(9), e1242–e1249. https://doi.org/10.4088/JCP.17m11476

Lima, F., Rabelo-da-Ponte, F. D., Bücker, J., Czepielewski, L., Hasse-Sousa, M., Telesca, R., … Rosa, A. R. (2019). Identifying cognitive subgroups in bipolar disorder: A cluster analysis. *Journal of Affective Disorders*, *246*, 252–261. https://doi.org/10.1016/j.jad.2018.12.044

Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., … Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *The American Journal of Psychiatry*, *161*(2), 262–270. https://doi.org/10.1176/appi.ajp.161.2.262

Miguel, N., Marquez-Arrico, J. E., Jodar, M., Navarro, J. F., & Adan, A. (2023). Neuropsychological functioning of patients with major depression or bipolar disorder comorbid to substance use disorders: A systematic review. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *75*, 41–58. https://doi.org/10.1016/j.euroneuro.2023.06.006

Miskowiak, K. W., Seeberg, I., Jensen, M. B., Balanzá-Martínez, V., Del Mar Bonnin, C., Bowie, C. R., … Vieta, E. (2022). Randomised controlled cognition trials in remitted patients with mood disorders published between 2015 and 2021: A systematic review by the International Society for Bipolar Disorders Targeting Cognition Task Force. *Bipolar Disorders*, *24*(4), 354–374. doi: 10.1111/bdi.13193

Montejo, L., Torrent, C., Jiménez, E., Martínez-Arán, A., Blumberg, H. P., Burdick, K. E., … Vieta, E., International Society for Bipolar Disorders (ISBD) Older Adults with Bipolar Disorder (OABD) Task Force (2022). Cognition in older adults with bipolar disorder: An ISBD task force systematic review and meta-analysis based on a comprehensive neuropsychological

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assessment. *Bipolar Disorders*, *24*(2), 115–136. https://doi.org/10.1111/bdi.13175

Samalin, L., & Belzeaux, R. (2023). Why does non-adherence to treatment remain a leading cause of relapse in patients with bipolar disorder?. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *73*, 16–18. Advance online publication. https://doi.org/10.1016/j.euroneuro.2023.04.012

Samamé, C. (2024). What do psychiatrists do with hypotheses proven false? The case of neuroprogression in bipolar disorders. *Psychological Medicine*, *54*, 41–42.

Samamé, C., Durante, P., Cattaneo, B., Aprahamian, I., & Strejilevich, S. (2023). Efficacy of cognitive remediation in bipolar disorder: Systematic review and meta-analysis of randomized controlled 7 trials. *Psychological Medicine*, *53*, 1–13. Advance online publication. https://doi.org/10.1017/S0033291723001897

Sanchez-Moreno, J., Bonnin, C. M., González-Pinto, A., Amann, B. L., Solé, B., Balanzá-Martinez, V., … Vieta, E., CIBERSAM Functional Remediation Group (2018). Factors associated with poor functional outcome in bipolar disorder: Sociodemographic, clinical, and neurocognitive variables. *Acta Psychiatrica Scandinavica*, *138*(2), 145–154. https://doi.org/10.1111/acps.12894

Sánchez-Torres, A. M., Amoretti, S., Enguita-Germán, M., Mezquida, G., Moreno-Izco, L., Panadero-Gómez, R., … Cuesta, M.J., 2EPs group (2023). Relapse, cognitive reserve, and their relationship with cognition in first episode schizophrenia: A 3–year follow-up study. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *67*, 53–65. https://doi.org/10.1016/j.euroneuro.2022.11.011

Torrent, C., Bonnin, C.delM., Martínez-Arán, A., Valle, J., Amann, B. L., González-Pinto, A., … Vieta, E. (2013). Efficacy of functional remediation in bipolar disorder: A multicenter randomized controlled study. *The American Journal of Psychiatry*, *170*(8), 852–859. https://doi.org/10.1176/appi.ajp.2012.12070971

Vidal, N., Brunet-Gouet, E., Frileux, S., Aouizerate, B., Aubin, V., Belzeaux, R., … Roux, P. (2023). Comparative analysis of anticholinergic burden scales to explain iatrogenic cognitive impairment and self-reported side effects in the euthymic phase of bipolar disorders: Results from the FACE-BD cohort. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *77*, 67–79. Advance online publication. https://doi.org/10.1016/j.euroneuro.2023.08.502

Vieta, E. (2015). La medicina personalizada aplicada a la salud mental: la psiquiatría de precisión [Personalised medicine applied to mental health: Precision psychiatry]. *Revista De Psiquiatria Y Salud Mental.*; *8*(3):117–118. Spanish. doi:10.1016/j.rpsm.2015.03.003

Zammit, S., Allebeck, P., David, A. S., Dalman, C., Hemmingsson, T., Lundberg, I., … Lewis, G. (2004). A longitudinal study of premorbid IQ Score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry*, *61*(4), 354–360. https://doi.org/10.1001/archpsyc.61.4.354