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From gut to brain: A network model of intestinal permeability, inflammation, and psychotic symptoms in schizophrenia.

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ABSTRACT

Impaired intestinal permeability has recently been suggested as a possible source of chronic inflammation in schizophrenia, but its association with specific psychopathological features remains uncertain. This study aimed to explore the interaction between intestinal permeability, inflammation, and positive and negative symptoms in schizophrenia using a network analysis approach. The study sample comprised 281 adults with schizophrenia (age 40.29 ± 13.65 years, 63.0 % males), enrolled in a cross-sectional observational study assessing intestinal permeability. We estimated the network with a Gaussian graphical model, incorporating scores from 14 individual items of the Positive and Negative Syndrome Scale (PANSS), along with body mass index (BMI), and plasma C-reactive protein (CRP) and lipopolysaccharide-binding protein (LBP) levels. We calculated strength centrality and expected influence and used bridge centrality statistics to identify the bridge nodes. Distinct but highly interconnected clusters emerged for positive and negative symptoms. The biological variables were closely associated with each other. LBP was positively linked with CRP and BMI, but only indirectly connected to psychopathology. CRP exhibited direct positive relationships with various PANSS items and bridged LBP and BMI with psychopathology. Bridge nodes included Conceptual Disorganisation (P2), Active Social Avoidance (G16), Suspiciousness/Persecution (P6), and CRP. These findings support the role of gut-derived inflammation as a mechanism underlying greater symptom severity in schizophrenia and emphasise the importance of addressing dietary habits not only to enhance physical health but also to contribute to improving psychotic symptoms.

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1. Introduction

Recent biotechnological breakthroughs have created a promising framework for exploring the dynamic interactions between biological, psychological, and environmental factors that underlie mental disorders (Salagre and Vieta, 2021). In this context, there is increased interest in searching for biomarkers in psychiatry along with solid recognition of the need to examine their relationships with individual symptoms, while viewing the body and brain in concert (Dean and Walker, 2023).

Inflammation stands as a primary research domain in the pursuit of biomarkers for schizophrenia, as compelling evidence suggests its role in the pathogenesis of the illness (Khalfallah et al., 2022; Osimo et al., 2021). Consequently, several targets have been explored as potential measures of inflammation in schizophrenia (Mongan et al., 2020). Although disease-specific biomarkers remain elusive, considerable emphasis has recently been placed on C-reactive protein (CRP). Higher blood levels of this accessible and cost-effective biomarker of peripheral inflammation have been linked to the severity of positive symptoms and cognitive impairment (Fond et al., 2018) and seem unrelated to antipsychotic treatment or illness duration (Fernandes et al., 2016). Moreover, CRP has been associated with metabolic syndrome and overall increased cardiovascular risk, frequent comorbidities in psychotic disorders (Fond et al., 2018). However, the mechanisms linking inflammation and schizophrenia have yet to be fully elucidated (Bauer and Teixeira, 2019). Multiple theories have been suggested, and these can be integrated into the framework of a vulnerability-stress-inflammation model (Müller, 2018). These include genetic predisposition in individuals with schizophrenia and exposure to environmental stressors occurring prior to the clinical onset of symptoms, like obstetric complications, childhood trauma, and substance abuse (Khandaker et al., 2015; Mongan et al., 2020). Gut-derived inflammation may also contribute to the aetiology of the disease (Mongan et al., 2020), supported by evidence of the bidirectional neurohumoral communication system between the gut and brain, commonly referred to as the "gut–-brain axis" (Khandaker et al., 2015).

Impairment of intestinal permeability (IP) refers to loss of intestinal barrier integrity and its normal function. Increased IP, influenced by various endogenous and exogenous (e.g. dietary habits) factors, can facilitate the translocation of bacterial components into the lamina propria and later into the systemic circulation (Seethaler et al., 2021; Vanuytsel et al., 2021). Various endogenous proteins have been studied to measure IP and lipopolysaccharide (LPS) has recently been proposed as a valuable non-invasive biomarker for the assessment of IP (Seethaler et al., 2021). LPS is part of the bacterial wall of Gram-negative bacteria, which, once in the bloodstream, can activate immune cells by binding to lipopolysaccharide-binding protein (LBP) (Bauer and Teixeira, 2019). LBP and its co-receptor sCD14 then interact with TLR-4 receptors on monocytes, macrophages, and microglia, triggering a proinflammatory cascade (Bauer and Teixeira, 2019; Borkent et al., 2022). Disruption of the intestinal barrier has recently been a focus of increased attention because of its proposed associations with multiple health conditions (Seethaler et al., 2021; Vanuytsel et al., 2021), including psychiatric diseases. For example, impaired IP has recently been proposed as a possible source of chronic inflammation in schizophrenia, acting through different pathways (Borkent et al., 2022; Szeligowski et al., 2020). The higher plasma levels of LBP (Gokulakrishnan et al., 2022; Jensen et al., 2023) and sCD14 (Dzikowski et al., 2020; Tanaka et al., 2017) found in patients with schizophrenia compared with healthy controls seem to support this theory.

Elevated body mass index (BMI), a common metabolic feature of schizophrenia, may also influence these pathways due to its association with both IP and chronic low-grade inflammation. This leaves open the question of whether it represents a mere consequence of treatment side effects or it plays a more active role in the aetiology of the disorder (Szeligowski et al., 2020).

However, research exploring the association between IP and inflammation with specific psychopathological features of schizophrenia remains limited. Moreover, studying immune and inflammatory variables in psychiatry poses several methodological challenges, and traditional statistical tools may not be suitable for capturing their complex interactions (Khalfallah et al., 2022). Furthermore, examining individual biomarkers in isolation could lead to divergent findings (Osimo et al., 2021).

This study aimed to explore the interplay between IP, peripheral inflammation, and psychopathology in schizophrenia using a network analysis framework. Based on the existing evidence, we expected that peripheral inflammation would play a pivotal role in connecting impaired IP to psychotic symptoms.

2. Experimental procedures

2.1. Study design and participants

The study sample comprised 281 adults with schizophrenia diagnosed according to DSM-5 criteria who participated in a cross-sectional observational study conducted at four sites in Spain (PI17/00246). This study aimed to assess intestinal permeability in schizophrenia and investigate its clinical consequences. A more detailed description of the rationale, objectives, and protocol of the project can be found elsewhere (Anmella et al., 2023).

Past head trauma resulting in loss of consciousness, organic diseases with mental repercussions, and acute inflammatory events (e.g. fever >38 °C or infection in the two weeks preceding the interview or vaccines in the previous four weeks) were exclusion criteria.

All patients provided written informed consent to participate after receiving information about the purposes and protocol of the study and prior to undergoing any procedures. The local ethics committees of the participating sites approved the study protocol (127/2015).

2.2. Measurements

2.2.1. Clinical assessment

After completing an initial screening visit to evaluate eligibility, baseline data were collected, including sociodemographic variables, illness duration, diagnosis, and anthropometric measurements (weight, height, and body mass index - BMI). The Spanish version of the Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994) was used to assess psychopathology.

2.2.2. Laboratory tests

After a confirmed overnight fast, two 10 mL tubes of peripheral blood were obtained by venipuncture and used to quantify CRP and LBP levels, following the instructions of the kit manufacturer (RayBiotech ELH-LBP Kit).

2.3. Data analyses

First, we performed the descriptive statistics of the sample's sociodemographic characteristics and the psychopathological and biological variables, expressing the results as means, standard deviations (SD), and percentages.

Second, we estimated a Gaussian graphical model (GGM), a detailed description of which can be found elsewhere (Isvoranu et al., 2022). In the resulting undirected network, nodes represent the study variables, and edges represent partial correlation coefficients between them after controlling for all other variables in the network. The scores on the individual items of the PANSS were entered into the model, along with the biological variables (LBP and CRP) and BMI, which was added as a possible confounding factor in light of previous evidence of associations with both IP and peripheral inflammation. Due to the sample size, we selected 14 variables from the PANSS scale: the seven items of the positive subscale and the seven items constituting the negative factor

described by Marder et al. (Marder et al., 1997). We employed the graphical LASSO algorithm to compute the model to limit the number of spurious connections amongst nodes, combined with EBIC model selection. The EBIC tuning parameter was set to 0.50. We used the default layout and the colourblind theme for visualising the network.

We estimated two inference measures to identify the most central nodes in the network: strength centrality and expected influence (EI). It is noteworthy that, while Strength is calculated using the sum of the absolute weights of the correlations of one node to all other network nodes, EI can assume negative values, which avoids misleading interpretations if negative edges are present.

The stability and accuracy of the network were assessed using nonparametric bootstrapping based on 1000 bootstrap samples.

Finally, we calculated bridge strength and betweenness to identify the bridge nodes. We selected the nodes scoring in the top 20 % for bridge strength as bridge nodes, in keeping with previous research methods (Jones et al., 2021).

We conducted the analyses using R (version 4.1.0) with the *bootnet, qgraph*, and *networktools* packages.

3. Results

3.1. Participants and descriptive statistics

The sociodemographic, clinical, and psychometric characteristics of the sample ($n = 281$) are reported in Table 1, along with the descriptive statistics.

3.2. Network structure

The estimated network (Fig. 1) consisted of 17 nodes, and the model retained 59 non-zero edges out of a possible 136 edges, corresponding to a density of 0.434. Most of the edges were positive.

The positive and negative symptoms items formed distinct but highly interconnected clusters, while the biological variables exhibited close associations with each other and maintained connections with both symptom groups. The LBP node was positively linked with CRP and BMI and only indirectly connected to psychopathology. The BMI node presented positive associations with LBP and CRP, a direct but weak positive connection with Passive/Apathetic Withdrawal (N4), and weak negative links with the Excitement (P4) and Conceptual Disorganisation (P2) nodes. By contrast, CRP showed positive relationships with various PANSS items, including Excitement (P4), Conceptual Disorganisation (P2), Hallucinatory Behaviour (P3), Poor Rapport (N3), and Motor Retardation (G7).

Table 1
Sociodemographic, clinical, anthropometric, and biological data of the sample ($n = 281$). Data are expressed as mean (SD) or n (%).

	Whole sample ($n = 281$)
Age (years)	40.29 (13.65)
Sex, male	177 (63.0%)
Illness duration (years)	13.21 (11.26)
First-episode psychosis	60 (21.4%)
BMI (kg/m^2)	27.81 (5.50)
CRP (mg/L)	5.16 (7.96)
LBP (μg/mL)	17.47 (7.75)
PANSS Positive	12.22 (5.19)
PANSS Negative	19.79 (7.80)
PANSS GP	29.91 (9.35)
PANSS Total Score	61.93 (18.98)

BMI: body mass index; CRP: C-reactive protein; LBP: lipopolysaccharide-binding protein; PANSS: Positive and Negative Syndrome Scale, GP: general psychopathology.

3.3. Centrality measures

Strength centrality and EI results are shown in Fig. 2, while the standardised and raw values can be found in the Supplementary Materials (Table S1).

The most central nodes in terms of strength were Delusions (P1), Poor Rapport (N3), Emotional Withdrawal (N2), Lack of Spontaneity and Flow of Conversation (N6), and Excitement (P4). In terms of EI, the most central nodes were Emotional Withdrawal (N2), Poor Rapport (N3), Delusions (P1), Blunted Affect (N1), and Active Social Avoidance (G16).

3.4. Bridge nodes and bridge centrality measures

Fig. 3 illustrates the bridge centrality statistics, including bridge strength and bridge betweenness.

The top 20 % scoring nodes for bridge strength were: Conceptual Disorganisation (P2), Active Social Avoidance (G16), Suspiciousness/Persecution (P6), and CRP. Active Social Avoidance (G16), Suspiciousness/Persecution (P6), and Conceptual Disorganisation (P2) acted as bridge nodes between the positive and negative symptom groups, with the latter also directly connecting with CRP. On the other hand, CRP emerged as the bridge node linking biological variables with psychopathology.

3.5. Network stability and accuracy analysis

The Supplementary Materials provide the results of the nonparametric bootstrap analysis (Figs. S1-S2), with adequate confidence intervals around the edge weights, denoting an accurate network estimation. Strength centrality and EI estimates exhibited consistency, with correlation stability coefficients of 0.594 and 0.673, respectively. These values exceeded the suggested threshold (not below 0.25 and preferably above 0.50) (Epskamp et al., 2018).

4. Discussion

To our knowledge, this study represents the first attempt to use network analysis techniques to integrate markers of intestinal permeability and inflammation in schizophrenia with psychopathology. The major findings were the absence of a direct association between LBP and psychopathology and that CRP acted as the intermediary between LBP, BMI, and psychotic symptoms.

These findings differ from a recent study where a modest association was observed between LBP levels and PANSS total score after accounting for confounders such as CRP and BMI (Jensen et al., 2023). However, our analysis explored only specific PANSS symptoms, and the association reported by the authors may be explained by items not included in our analysis or a potential sum effect. On the other hand, other studies have observed no significant direct correlations between LBP and psychotic symptoms severity (Gokulakrishnan et al., 2022) or cognition (Scheurink et al., 2023). Nonetheless, these results are challenging to compare because of the limited body of literature on the relationship between markers of IP and psychotic symptoms in schizophrenia, probably due to the novelty of the topic.

The relationships between CRP and various items of the PANSS, including positive symptoms such as Excitement, Conceptual Disorganisation, and Hallucinatory Behaviour, align with the existing literature (Fernandes et al., 2016; Fond et al., 2018). Interestingly, aggressive behaviours have been associated with the Excitement and Hallucinatory Behaviour nodes in a network model (Dal Santo et al., 2022), as well as with significantly elevated CRP, LPS, and sCD14 levels in another study (Wang et al., 2021), suggesting that increased IP may trigger aggressions through a proinflammatory response.

Although our cross-sectional analysis does not allow for causal inference, the finding of CRP as a bridge between LBP and the PANSS

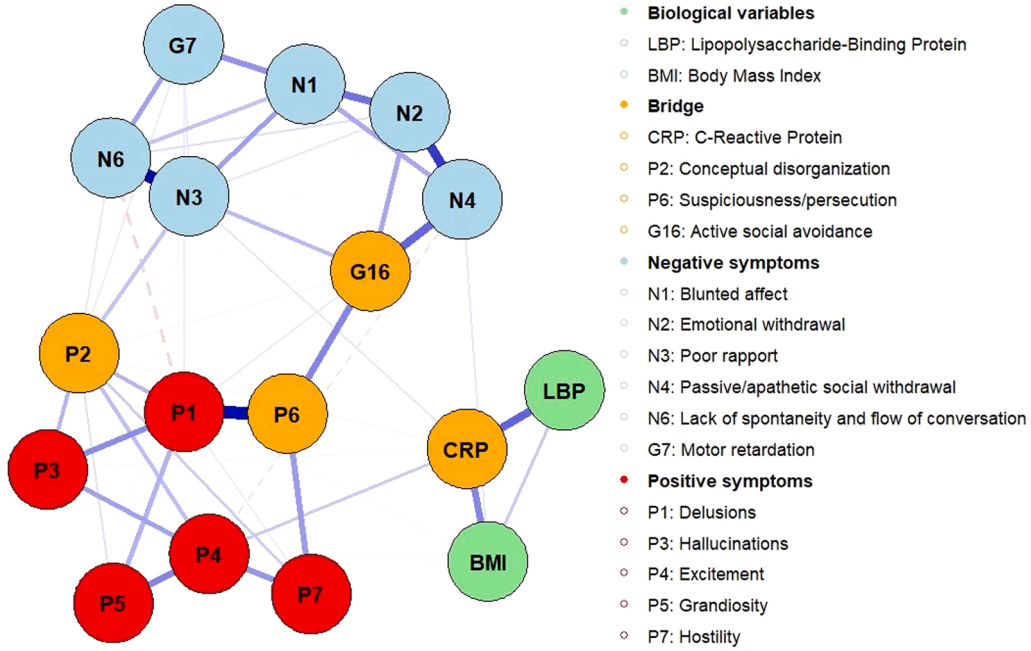

Fig. 1. Estimated network for positive and negative symptoms and biological variables.
Note: P: PANSS positive subscale; N: PANSS negative subscale; G: PANSS general psychopathology subscale. Numbers represent item numbers in the scale; solid blue edges represent positive associations; dashed red edges represent negative associations. The thickness and saturation of edges indicate the strength of these associations.

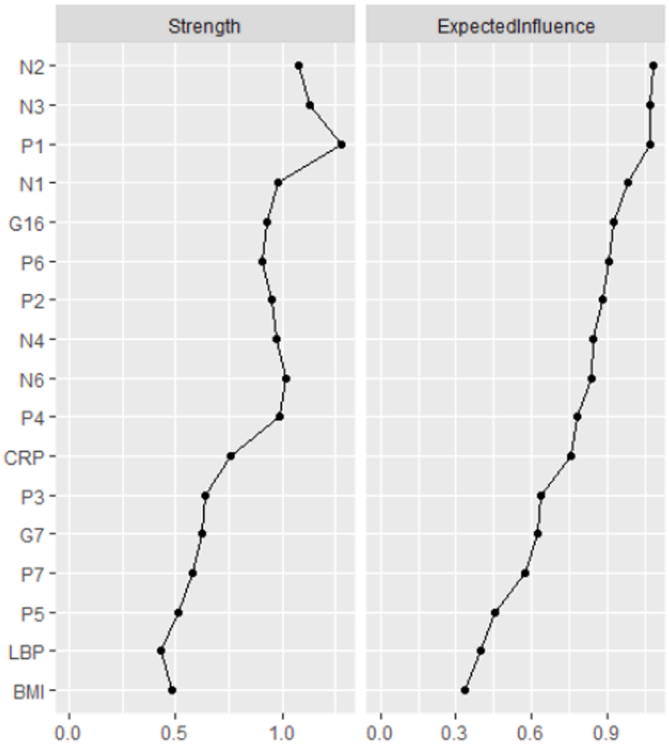

Fig. 2. Inference measures of the estimated network.
Note: BMI: body mass index; CRP: C-reactive protein; LBP: lipopolysaccharide-binding protein; P: PANSS positive subscale; N: PANSS negative subscale; G: PANSS general psychopathology subscale. Numbers represent item numbers in the scale.

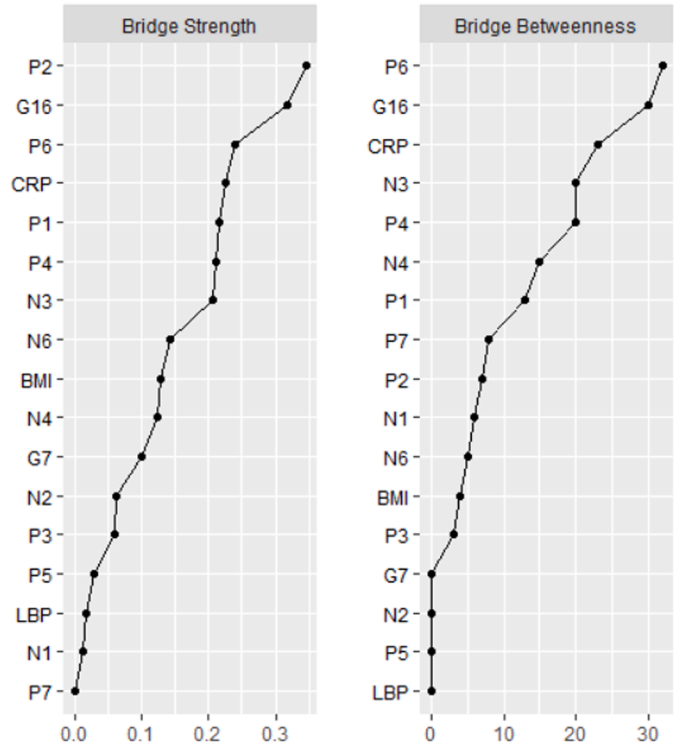

Fig. 3. Bridge centrality measures of the estimated network.
Note: BMI: body mass index; CRP: C-reactive protein; LBP: lipopolysaccharide-binding protein; P: PANSS positive subscale; N: PANSS negative subscale; G: PANSS general psychopathology subscale. Numbers represent item numbers in the scale.

nodes seems to support previous theories suggesting a continuum between impaired intestinal permeability, chronic inflammation, and the clinical features of schizophrenia (Borkent et al., 2022; Szeligowski et al., 2020). Furthermore, from a translational perspective, as LBP reacts exclusively to the LPS endotoxin (Severance and Yolken, 2020), we suggest that the joint determination of LBP and CRP levels could aid in differentiating gut-derived inflammation from other medical conditions. This could thereby enhance the utility of CRP as a biomarker in schizophrenia, especially when considering its limitations as a stand-alone biomarker due to its low specificity and its associations with various chronic illnesses. However, the reader should be mindful that elevated LBP levels may indicate not only LPS translocation from the intestine but could also result from concurrent acute bacterial infections (Seethaler et al., 2021), which should be ruled out as a preliminary step, as in the current study.

Concerning BMI, our network highlights its dual correlation with both LBP and CRP, which also accords with earlier observations. While the association of obesity and chronic low-grade inflammatory state is well-documented, less is known about the relationship between impaired IP and elevated BMI (Szeligowski et al., 2020). Notably, one study found that LBP correlated with BMI in individuals with schizophrenia but not bipolar disorder (Severance et al., 2013), suggesting that disease-specific metabolic changes may be involved. From a clinical perspective, the self-reinforcing loop of IP, inflammation, and elevated BMI that emerges in our model highlights the importance of a multimodal approach in individuals with schizophrenia, where promoting healthy lifestyles should receive special attention. For example, interventions targeting poor dietary habits could address not only the medical implications of elevated BMI, but also contribute to improving specific symptoms by mitigating the effects of impaired intestinal permeability and obesity-related inflammation.

Finally, the findings of this study align with those of a previous study in a first-episode psychosis sample, where Active Social Avoidance and Conceptual Disorganisation were identified as bridges between the positive and negative symptom groups (Dal Santo et al., 2022). This highlights the significance of also targeting such symptoms in established schizophrenia to prevent inter-symptom activation and comorbidity.

4.1. Strengths and limitations

The strengths of this study include its multicentre design and the implementation of innovative network analysis techniques, such as bridge centrality statistics, that enhance the reliability of our findings by transcending a mere visual inspection. Moreover, we computed the network model using individual symptoms as nodes and included biomarkers of both IP and inflammation.

Nonetheless, certain limitations must be acknowledged. The sample size did not allow us to simultaneously examine all the PANSS general psychopathology items along with the psychotic symptoms, which may have restricted the scope of our analysis. For the same reason, a specific comparison of groups by sex and age was not feasible. Furthermore, the cross-sectional design precludes the inference of causal relationships between the variables and the detection of dynamic changes over time.

5. Conclusions

Network analysis represents a promising methodology for developing comprehensive models of schizophrenia by integrating biomarkers with psychopathological features. Our model supports the theory of gut-derived inflammation as a mechanism underpinning greater symptom severity in schizophrenia and supports the potential of joint determination of LBP and PCR levels for identifying and understanding these pathways. Finally, from a clinical standpoint, our findings emphasise the importance of addressing dietary habits in individuals with schizophrenia, as they can enhance not only physical health, but also contribute to the improvement of psychotic symptoms.

CRediT authorship contribution statement

Conceptualisation: **Dal Santo, García-Portilla, Arranz**. Data curation: **Alfonso, Hernández, Sanchez-Autet, Anmella, Amoretti, Marín Alcaraz**. Formal analysis: **Dal Santo, González-Blanco, García-Portilla**. Data visualisation: **Dal Santo, Sanchez-Autet, Anmella**. Writing – original draft: **Dal Santo, González-Blanco, García-Portilla, Arranz**. Writing – review & editing: **Alfonso, Hernández, Sanchez-Autet, Bernardo, Anmella, Amoretti, Safont, Marín Alcaraz**. Study supervision: **García-Portilla, Bernardo, Safont, Arranz**. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

FDS has received grants from the Spanish Foundation of Psychiatry and Mental Health and the European Psychiatric Association.

LGB has been a consultant to and/or has received honoraria/grants from the Spanish Foundation of Psychiatry and Mental Health, European Psychiatric Association, Otsuka, Lundbeck, Janssen-Cilag and Pfizer.

MPGP has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer.

MB has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda.

GA has received continuing medical education (CME)–related honoraria or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck and Otsuka, and Angelini.

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All other authors declare that they have no conflicts of interest related to the current work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.10.004.

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