Dynamic Resting-State EEG Alpha Connectivity: Quantifying Brain Network State Evolution in Individuals with Psychosis

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Abstract

This study introduces a novel pipeline for investigating brain activity in psychosis using dynamic connectivity from resting-state EEG.
Seventy-eight individuals with psychosis and sixty control subjects were analyzed. Source estimation was performed using eLORETA, and connectivity in the alpha band was assessed with wPLI. A modified k-means algorithm was employed to cluster connectivity matrices into distinct brain network states (BNS), from which several metrics were extracted.
The segmentation revealed five distinct BNS. The control group exhibited significantly higher connectivity power, while the psychosis group showed greater duration dispersion. In the control group, correlations were found between BNS metrics and cognitive scales. Negative correlations were identified between BNS metrics and the SANS scales in the psychosis group.
These results underscore the variability of neural dynamics in individuals with psychosis, as demonstrated by this novel methodology.

Introduction

Psychosis is a multifaceted mental health condition characterized by significant disruptions in an individual's perception of reality, often manifesting through symptoms such as hallucinations, delusions, and disorganized thought processes (1). Research indicates that psychotic disorders profoundly affect brain structure and function, both at rest and during cognitive tasks, altering the typical activity of various brain regions (2).

Despite extensive research, the precise neural mechanisms underlying psychosis remain poorly understood (2,3), hindering the development of targeted diagnostic tools and effective treatments. One major challenge is the significant variability between patients, which limits the effectiveness of current approaches (4). This underscores the need for new paradigms that can define patient-specific profiles.

Among the various neuroimaging techniques, electroencephalography (EEG) has proven to be a valuable tool in the study of psychosis (5–7). EEG allows researchers to observe the brain's intrinsic activity without necessarily requiring task performance, providing a unique window into brain function (8). Previous studies have highlighted alterations in brain activity in psychotic disorders, such as decreased activity in the alpha frequency band (9,10). Over the past decade, EEG analyses have increasingly focused on functional connectivity to understand brain behavior better (11,12). However, traditional static connectivity measures, often combined with graph theory metrics, may not adequately capture the complex, rapidly changing nature of brain activity (13). This limitation can result in a loss of critical information and obscure the underlying neural mechanisms of psychosis.

Recent advancements in dynamic connectivity analysis have begun to address these limitations, offering new insights into the transient states of brain networks (14,15). Indeed, the concept of brain state has become of huge interest in its potential ability to change brain activity patterns and, therefore, characterize neural dynamics in health and disease (16).

Studies using MEG and fMRI data have observed distinct network differences between controls and patients in the alpha band (17,18). However, only a portion of the data presented in (17), specifically the MEG data, has been thoroughly investigated despite the availability of corresponding EEG (19,20).
Based on their promising results in the alpha band on MEG data and the growing evidence supporting dynamic connectivity in EEG studies in Parkinson's disease (21) and postural control (22), we aimed to analyze the public EEG data on the alpha band with a novel methodology. This approach is inspired by classical EEG microstates, which have proven effective in capturing the dynamic aspects of brain electrical activity, particularly in psychosis studies (23,24).

The current work introduces an innovative methodology for analyzing resting-state EEG data by integrating source localization techniques with dynamic functional connectivity and advanced clustering algorithms. This methodology enables the identification and characterization of distinct brain network states (BNS) defined by specific connectivity patterns and temporal properties. Examining these BNS, we aim to delineate the neural signatures associated with psychosis and compare them with those observed in healthy controls.

Our approach not only identifies these unique states but also explores their functional roles and dynamics, providing a deeper understanding of how brain network activity differs in individuals with psychosis. Furthermore, we investigate the potential relationships between these network states and various clinical outcomes, including cognitive performance and psychopathological symptoms.

Methods and Material

We examined the properties of resting-state electroencephalographic (EEG) activity in individuals diagnosed with psychosis and compared them to healthy control subjects, focusing on a dynamic tracking of brain activity. Figure 1 is a graphical abstract of our novel methodology that will be detailed in the following sections.

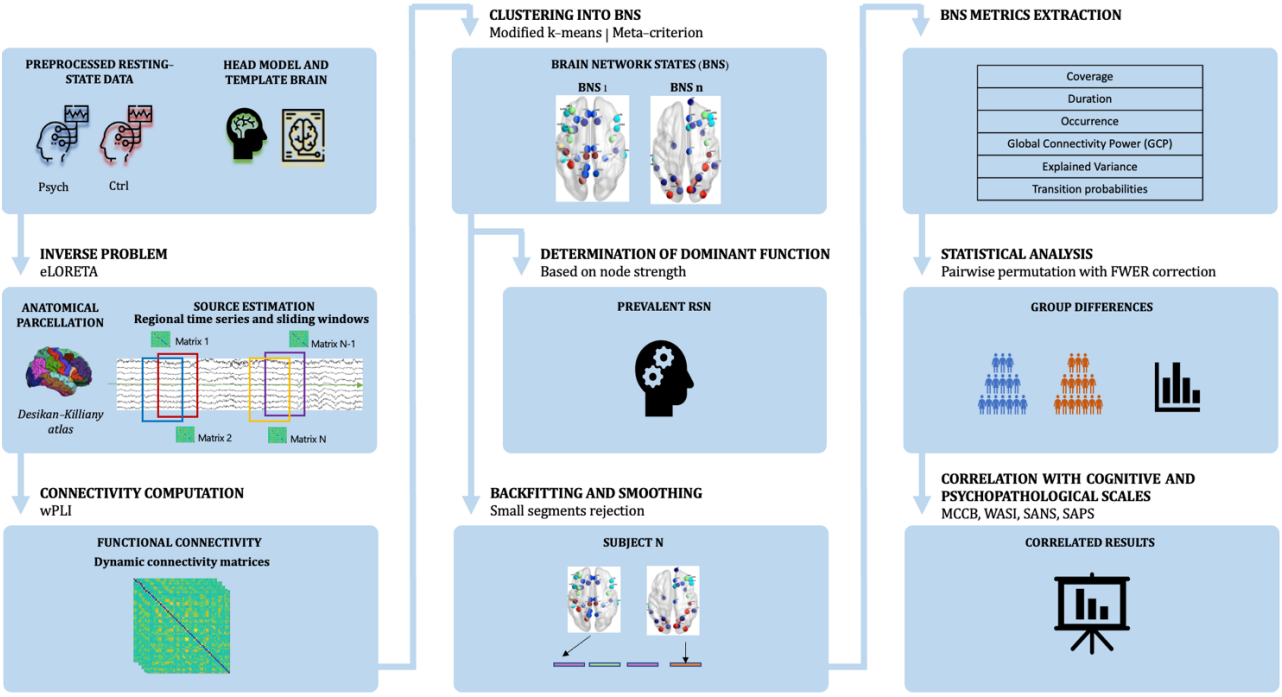

Figure 1 - Graphical abstract

1 - Participants

We utilized a dataset comprising 78 participants with a first episode of psychosis (FEP) (23 female; age, 22.9±4.8 years) and 60 age-matched control subjects (26 female; age: 22.8±4.9) sourced from the OpenNeuro database (19,20). A complete demographics table can be found in the supplementary material (Table S1).

Each participant was subjected to a 5-minute resting-state EEG recording session, during which they were instructed to keep their eyes open. The EEG data were captured using the EEG channels of an Elekta Neuromag Vectorview MEG system. EEG was recorded using a low-impedance 10-10 system 60-channel cap at a sampling frequency of 1000 Hz. Due to two different EEG montages, a complementary analysis is reported in the supplementary material to highlight that the montage did not influence the source spectral activity (Table S2).

2 - Preprocessing

The preprocessing pipeline is detailed in the supplementary material.
The final preprocessed data was used for further analysis.

3 - Source estimation and connectivity computation

For source localization, we employed the exact Low-Resolution Brain Electromagnetic Tomography (eLORETA) algorithm (25). This method allowed us to estimate the cortical sources of the EEG signals with a focus on 68 regions of interest (ROIs) as delineated by the Desikan-Killiany atlas. To perform this operation, we used the Boundary Element Method head model fitted to the ICBM MRI template, which is composed of three layers (scalp, outer skull, and inner skull), using the OpenMEEG (26) plugin from the Brainstorm toolbox (27). The ROIs were estimated based on the average source strength of all voxels contained in each ROI.

To assess potential differences between control subjects and individuals with psychosis, we performed a first analysis based on ROIs power spectral density as well as static connectivity analysis based on graph theory

metrics and edgewise analysis, using toolboxes such as Network-Based Statistics (NBS) (28) or Brain Connectivity Toolbox (BCT) (29). This analysis is reported in the supplementary material (figures S1 and S2, table S3).

As our main interest lays in the dynamic functional connectivity within the alpha frequency band (7-13 Hz), we quantify connectivity patterns using the weighted phase lag index (wPLI), a measure robust to the effects of volume conduction and field spread (30). A sliding window approach (window size: 600ms, corresponding to 6 alpha frequency cycles as advised in Lachaux *et al*. (31), with a 50% overlap) was adopted to capture the temporal evolution of connectivity patterns, leading to 999 connectivity matrices per subject.

4 - BNS Clustering

Building upon the classical EEG microstate analysis principles, we conducted a clustering procedure using a modified k-means algorithm (32,33). This technique was chosen due to its ability to identify stable and recurring patterns of brain activity, as it was widely used in classical EEG microstates analyses (34,35) which we will refer to as brain network states (BNS) (21,22).

Diverging from traditional approaches, our clustering was conducted at the group rather than the individual level. A few preliminary steps were performed to prepare the datasets for each subject's data. Dynamic connectivity matrices, being symmetric, were vectorized by extracting only the lower part (resulting in 2278 elements for a 68x68 matrix), creating vectors sized 2278x999 for each subject. These vectors were then concatenated to generate a comprehensive dataset encompassing 138 subjects. This unified vector served as input for the clustering algorithm, following a methodology previously utilized by Duprez *et al*. (15).

Initially, we explored solutions iteratively within a range of 2 to 20, conducting 100 restarts with 1000 iterations each. Subsequently, we narrowed the interval to between 3 and 7 solutions using a data-driven approach, with 200 restarts and 1000 iterations. To identify the optimal number of solutions, we designed a meta-criterion based on 11 clustering criteria (33,36), adapting an approach proposed by Custo *et al*. (37). The list of criteria and the meta-criterion computation is described in the supplementary material (Table S3).

5 - BNS Smoothing and backfitting

Following the identification of distinct BNS, we applied backfitting on each individual based on global map dissimilarity (GMD) (38), which is a distance measure based on the topography of each map and is signal invariant (33).

Then, after the backfitting, we applied labels smoothing based on small segments rejection (33): each BNS lasting less than five consecutive matrices was rejected and relabeled.

6 - BNS metrics and function

From these resulting datasets, we extracted BNS metrics, including global connectivity power (GCP) (i.e., standard deviation of all connectivity indices, as derived from global field power (GFP) (38)), explained variance (GEV), coverage, duration, occurrence, and transition probabilities (34). These metrics provided a comprehensive characterization of the BNS dynamics. Additionally, we utilized graph theory metrics to infer the prevalent function of each BNS, basing it on resting-state networks (RSN) strength (22). Each node was assigned to one of the seven elicited RSN (default mode network (DMN), dorsal attentional network (DAN), salient network (SAN), visual network (VIS), auditory network (AUD), motor network (MOT) and Other)), and the strength of each RSN was added and divided by the number of nodes belonging to this RSN. Among the seven RSNs, the values above mean and standard deviation were considered prevalent. The list of nodes and RSN association is provided in the supplementary material (figure S3).

7 - Statistical analysis

To assess the differences in BNS metrics between the psychosis and control groups, we performed pairwise permutation analyses (10.000 permutations), incorporating family-wise error rate (FWER) correction based on max correction to control for multiple comparisons (39). Furthermore, we conducted a correlation analysis (10.000 permutations) to explore the relationship between BNS metrics and cognitive performance, as measured by the MATRICS Consensus Cognitive Battery (MCCB) and the Wechsler Abbreviated Scale of Intelligence (WASI), as well as psychopathological symptoms, as assessed by the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS) and the Global Assessment Scales (GAS).

Results

1.1 Clustering Results

After applying the modified k-means algorithm to the EEG connectivity matrices, we identified five distinct brain network states (BNS). Notably, BNS 2, 4, and 5 were characterized by a predominance of visual regions. Besides this visual prevalence, BNS 4 revealed a stronger activity in ROIs within the left hemisphere. In contrast, BNS 5 showed stronger activity in the right hemisphere, particularly for DAN and SAN. BNS 2 shows a balanced and almost symmetric activity on both hemispheres, mostly DAN and SAN.

BNS 1 and 3 were marked by a higher representation of the DMN. On top of its DMN prevalence, BNS1 has more present activity in the left hemisphere, especially in the SAN and MOT networks, whereas the DAN activity is symmetric. For BNS 3, we observe a more present activity in the "Other" RSNs in the right hemisphere but a symmetric activity in the DAN and SAN.

Figure 2A shows a representation of the BNS and their prevalent function.

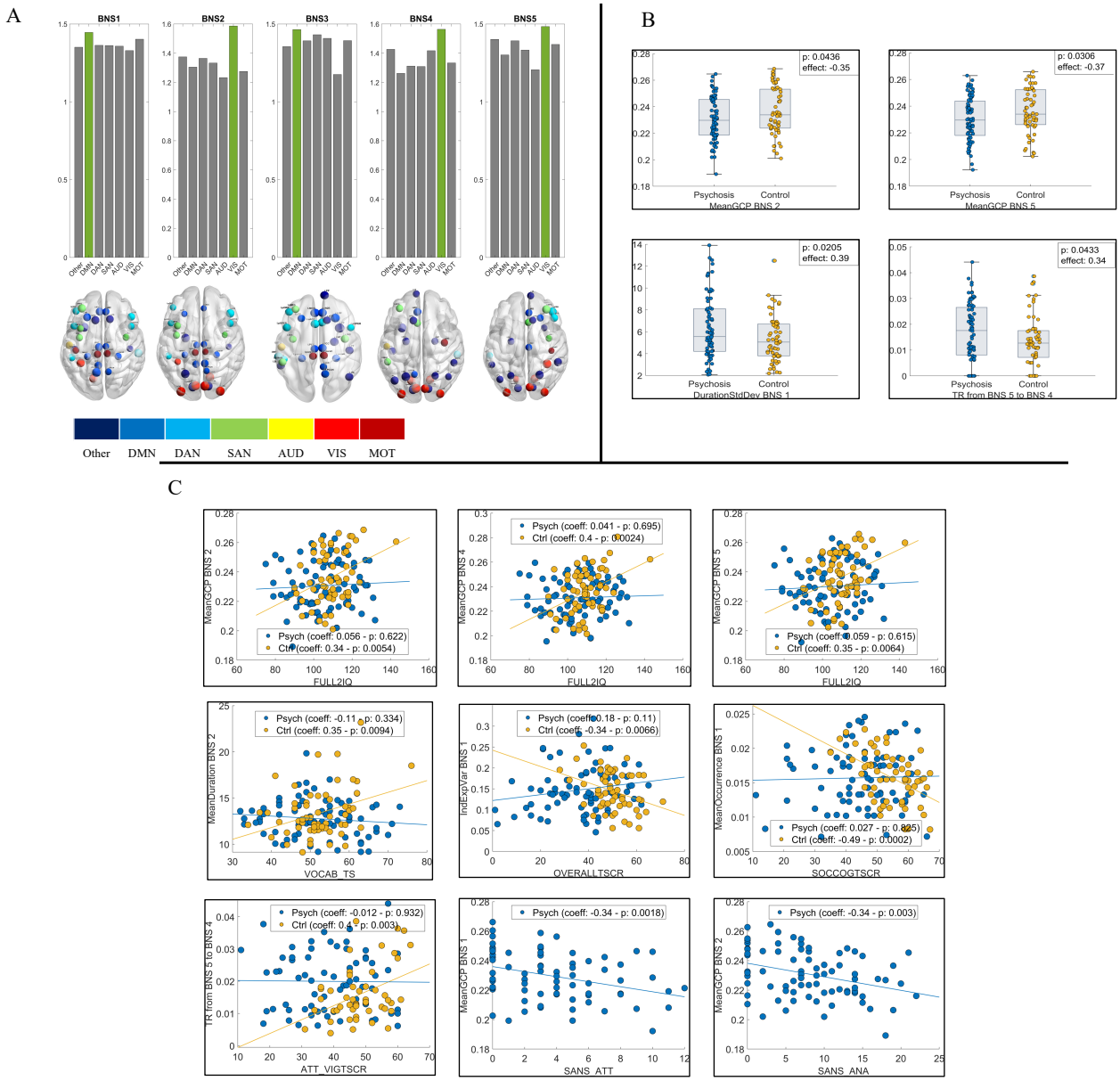

Figure 2 - Clustering results. A) the resulting BNS with their prevalent function and node distribution based on strength. B) the statistically significant (p<0.05) differences in BNS metrics between Psychosis and Control individuals. C) significant (p<0.01) correlations between BNS metrics and the different scales.

1.2 Pairwise Comparisons

Upon comparing the BNS metrics between the control and psychosis groups, several significant differences emerged, as highlighted in Figure 2B. Specifically, BNS 2 and 5 exhibited a higher global connectivity power (GCP) in the control group, indicating more robust functional connectivity within these states. In contrast, BNS 1 showed greater variability in duration among participants with psychosis, suggesting altered temporal dynamics in this state. Additionally, transitions from BNS 5 to BNS 4 occurred more frequently in the psychosis group, which may reflect altered patterns of neural communication.

1.3 Correlation Analysis

Significant correlations were observed between BNS metrics and cognitive performance only in the control group, as highlighted in Figure 2C. Only correlations with a p-value lower than the 0.01 threshold are reported in the figure.

In the control group, the metrics associated with the visually-dominant BNS (BNS 2, 4, and 5) positively correlated with full IQ and Vocabulary scores on the WASI, implying a relationship between visual processing efficiency and general cognitive ability. Furthermore, the metrics of BNS 1 were negatively correlated with social cognition and overall performance on the MCCB, suggesting that the dynamics of this network state may be inversely related to these cognitive domains. The transition metrics, particularly from the right to the left hemisphere (BNS 5 to BNS 4), were positively correlated with attention and vigilance scores on the MCCB, indicating that these transitions may play a role in sustained attention. Conversely, in the psychosis group, no significant correlations were found between BNS metrics and cognitive domain scores. However, a negative correlation was identified between the GCP of BNS 1 and BNS 2 and the Attention and Anhedonia – Asociality scales of the SANS, indicating that alterations in connectivity within these BNS may be associated with specific psychopathological symptoms in psychosis.

No significant correlations were observed between BNS metrics and the GAS scales.

Discussion

The current study proposes a new methodology based on dynamic connectivity from EEG resting-state data, to improve the description of the neural mechanisms in psychosis. The presented results confirm the interest of exploring new approaches, leaning towards the obtention of concrete and exploitable findings, in the functional and clinical aspect.

1. *Interpretation of the Identified Brain Network States (BNS)*

The identification of distinct BNS provides crucial insights into the neural correlates of psychosis. BNS 2, 4, and 5, which are associated with visual regions, suggest a significant role of visual processing in brain network activity. This was expected, the recording paradigm being eyes open. However, the hemispheric differences observed in BNS 4 and BNS 5, with stronger left and right hemisphere activities, highlight brain function lateralization. BNS 1 and 3, marked by a higher representation of the default mode network (DMN), confirm the involvement of internally focused thought processes in the resting-state.

2. *Group Differences in BNS Metrics*

The observed differences in global connectivity power (GCP), duration variability, and transition probabilities between the psychosis and control groups are noteworthy. The higher GCP in BNS 2 and 5 in controls indicates more robust functional connectivity, suggesting that these states may be less stable in individuals with psychosis. The greater variability in the duration of BNS 1 in the psychosis group points to altered temporal dynamics, which may reflect disruptions in maintaining consistent brain states. Additionally, the increased frequency of transitions from BNS 5 to BNS 4 in the psychosis group suggests stronger neural communication patterns from the right to the left hemisphere.

3. *Relationship between BNS Metrics and Clinical assessment*

a. *Relationship Between BNS Metrics and Cognitive Performance*

In the control group, the positive correlations between metrics of visually-dominant BNS (2, 4, and 5) and cognitive performance, including IQ and vocabulary scores, indicate that efficient visual processing is linked to better general cognitive abilities. The negative correlations of BNS 1 metrics with social cognition and overall MCCB performance suggest that more pronounced DMN activity may hinder these cognitive domains. The transition metrics' positive correlation with attention and vigilance scores implies that specific brain state transitions are crucial for sustained attention. The lack of significant correlations in the psychosis group may be due to the disrupted connectivity patterns affecting cognitive integration. It can also be explained by the FEP heterogeneity, as mentioned before (4). A division into subgroups could be interesting to observe more specific discrimination between BNS metrics, cognitive performance, and clinical phenotype.

b. *Association Between BNS Metrics and Psychopathological Symptoms*

The negative correlations between GCP in BNS 1 and BNS 2 with attention and anhedonia-asociality scales in the psychosis group indicate that altered connectivity within these BNS is associated with specific psychopathological symptoms. These findings suggest that disruptions in particular brain states may underlie specific negative symptoms of psychosis, providing a potential target for therapeutic interventions.

4. *Advantages of BNS approach*

The results presented in the supplementary material highlighted a difference between control and patients with psychosis using traditional methods, associated with an alpha decrease in patients. Thus, even if our approach also discriminated patients and healthy subjects based on some BNS metrics, its benefits might not be obvious. While our dynamic BNS approach also discriminated patients and healthy subjects based on some BNS metrics, its benefits are more pronounced in the strong correlations between extracted metrics and cognitive scores. From the resulting BNS sequence, on top of the current usual metrics derived from classical microstates (34), new metrics can be extracted based on complexity measures (40) and have already shown their potential in the observed dataset (17). Thus, our approach can offer an extensive set of metrics that correlate well with cognitive and clinical scales, describing the dynamics of the brain in a resting-state but also potentially task-related paradigms. Those metrics could be input for future machine learning and classification work, which would help to establish a patient-specific profile.

5. *Methodological Considerations and Limitations*

Our study employs advanced source localization and clustering techniques, which offer a detailed analysis of brain network dynamics. However, several limitations should be noted. A strong variability can be observed depending on the inverse solution used, the connectivity technique approach, as well as the clustering algorithm. Moreover, while advantageous for identifying common patterns, the group-level clustering approach may overlook individual variability. Additionally, potential confounding factors such as medication effects were not fully controlled, which could influence the findings. In future works, some steps of the methodology can be tuned to increase the granularity of our proposed approach: a stronger group and subgroup definition and individual-level *vs*. group-level clustering. Furthermore, combining EEG with normative modeling appears to be highly promising for developing patient-specific approaches (41).

6. *Future Directions and Clinical Implications*

The approach proposed in this study needs to be explored and validated with different datasets. Replicating our results and refining the methodology could lead to significant advancements in the field of psychosis. Similar to the classical microstate approach, defining BNS templates could facilitate easier categorization of resting-state brain activity and enable more global and comparable analyses between datasets.

Future research should also consider longitudinal studies and multimodal neuroimaging approaches to validate and extend our findings.

Investigating the stability of BNS over time and their relationship with treatment responses could provide valuable insights. The overall brain state field could be key in addressing the relationship between neural dynamics, physiological changes, and phenotypes (16).

Clinically, our findings have the potential to enhance diagnostic accuracy and guide the development of personalized interventions based on specific brain network disruptions in psychosis. Identifying reliable biomarkers of psychosis through EEG could significantly impact the management and treatment of this complex disorder, thereby improving patient outcomes.

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Disclosures

The authors reported no biomedical financial interests or potential conflicts of interest.

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