Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

A Comparative Study of Cognitive Functions in Patients, First-Degree Relatives, and Healthy Controls of Bipolar Affective Disorder

Dr. Ankita Shahi [1], Dr. Ashutosh Singh [2], Mr. Garv Jani [3]
[1]MD Psychiatry (Junior Resident – III) Department of Psychiatry, Index Medical College, Hospital & Research Centre, Indore, India
[2]MD, DNB Psychiatry (Associate Professor) Department of Psychiatry, Index Medical College, Hospital & Research Centre, Indore, India
[3]MPhil Clinical Psychology (Clinical Psychologist) Department of Psychiatry, Index Medical College, Hospital & Research Centre, Indore, India

*Corresponding Author
Mr. Garv Jani

Article History
Received: 17.09.2025
Revised: 07.10.2025
Accepted: 15.10.2025
Published: 03.11.2025

Abstract: ***Background:*** Bipolar Affective Disorder (BPAD) is increasingly understood as a neuroprogressive disorder characterized not only by episodic mood disturbances but also by persistent, trait-like cognitive deficits. Emerging work suggests that cognitive impairment may also be present in first-degree relatives (FDRs), supporting the possibility of cognitive endophenotypes.
Objective: To compare cognitive performance across three groups: patients diagnosed with BPAD in remission, their first-degree biological relatives, and healthy control participants.
Methods: A cross-sectional comparative study was conducted at a tertiary care teaching hospital from January to December 2023. Ninety participants were recruited using purposive sampling: BPAD patients in remission (n = 30), first-degree relatives (n = 30), and matched healthy controls (n = 30). Cognitive domains were assessed using the Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT-A and TMT-B), Stroop Colour–Word Test, Letter Cancellation Test, and subtests of the PGI Memory Scale. One-way ANOVA with post-hoc Tukey tests was used to examine group differences.
Results: Marked cognitive deficits were observed among BPAD patients compared to relatives and controls. Stroop interference scores were lowest in patients (35.47 ± 10.36), intermediate in relatives (40.68 ± 10.49), and highest in controls (48.87 ± 10.18; $p < 0.001$). TMT-A performance was significantly impaired in patients (81.42 ± 15.86 seconds) compared to relatives (30.57 ± 13.56) and controls (27.43 ± 12.76; $p < 0.001$). Similar gradients were observed in TMT-B performance (patients: 287 ± 56; FDR: 76 ± 18; controls: 70 ± 20; $p < 0.001$). WCST and PGIMS subtests also showed progressively poorer performance from controls → relatives → patients. ***Conclusion:*** The study demonstrates significant cognitive impairment in BPAD patients and intermediate deficits in first-degree relatives, supporting the hypothesis that cognitive dysfunction is a potential endophenotype of BPAD. Early detection and neurocognitive remediation may be beneficial for improving functional recovery.

Keywords: Bipolar Disorder; Cognitive Function; First-Degree Relatives; Endophenotype; Executive Function; Neuropsychology; Trail Making Test; Stroop Test.

INTRODUCTION

Bipolar Affective Disorder (BPAD) is a chronic psychiatric illness known for its fluctuating episodes of mania, hypomania, and depression. While mood instability remains its defining characteristic, recent decades have brought growing recognition that BPAD extends far beyond episodic emotional shifts. A considerable proportion of individuals living with BPAD experience persistent cognitive difficulties that continue even when their mood symptoms have stabilised. These cognitive disturbances affect everyday functioning, social outcomes, and long-term recovery, making them a crucial but often under-recognised aspect of the disorder.

1.1 Cognitive deficits in BPAD

Research consistently demonstrates that people with BPAD exhibit deficits in several key neurocognitive domains. These include impairments in:

- Executive functioning, such as planning, set-shifting, inhibiting automatic responses, and problem-solving.
- Working memory, both verbal and visuospatial.
- Attention and processing speed, particularly on tasks requiring sustained focus.
- Learning and memory, especially verbal learning and delayed recall.

Neuroimaging studies lend further support to these findings by identifying abnormalities in brain regions responsible for executive functioning and emotional regulation, including the prefrontal cortex, temporal lobe structures, and cerebellum. Taken together, these cognitive and neurobiological alterations support the evolving view of BPAD as a disorder involving long-term neural changes rather than isolated mood episodes.

1.2 Cognitive impairment beyond the patient: the endophenotype model

BPAD is one of the most heritable psychiatric conditions, with genetic factors accounting for a substantial proportion of its variance. Given this strong

familial loading, researchers have turned their attention toward first-degree relatives of individuals with BPAD. These relatives often exhibit subtle cognitive inefficiencies despite having no history of psychiatric illness themselves.

Studies involving unaffected relatives and high-risk twins have reported difficulties in areas such as sustained attention, verbal memory, and executive control. Their performance often falls between that of BPAD patients and healthy controls, a pattern that closely mirrors the characteristics of an endophenotype—a measurable trait that lies between genes and clinical symptoms.

The possibility that cognitive deficits represent an endophenotype for BPAD holds significant implications. It may improve early identification of risk, clarify underlying neurobiological mechanisms, and help develop preventative strategies.

1.3 Burden of illness and importance of cognitive assessment

Globally, BPAD affects roughly 0.8% of the population and is recognised as a major contributor to years lived with disability. In India, prevalence estimates are close to 0.6%, and BPAD remains one of the leading causes of psychiatric disability. Beyond the episodic nature of the illness, persistent cognitive challenges substantially influence occupational functioning, interpersonal relationships, and treatment outcomes.

Considering the growing importance of cognitive health in bipolar disorder, understanding its pattern not only in patients but also in individuals genetically predisposed to the illness is clinically significant.

1.4 Rationale for the Study

Despite accumulating evidence, there remains a relative scarcity of Indian studies comparing cognitive performance across patients with BPAD, their biological relatives, and healthy individuals using a comprehensive and standardized cognitive test battery. This study attempts to address this gap by evaluating whether first-degree relatives exhibit cognitive vulnerabilities that parallel, in attenuated form, those observed in BPAD patients**.**

1.5 Objectives

Primary Objective:

To compare cognitive performance among BPAD patients, their first-degree relatives, and healthy controls across multiple cognitive domains.

Secondary Objective:

To examine whether first-degree relatives demonstrate cognitive patterns that may indicate endophenotypic markers for BPAD.

MATERIAL AND METHODS

2.1 Study Design

This study adopted a cross-sectional, comparative research design aimed at evaluating cognitive performance across three distinct groups: individuals diagnosed with Bipolar Affective Disorder (BPAD) in remission, their first-degree biological relatives (FDRs), and healthy community controls. A cross-sectional framework was considered appropriate for capturing stable cognitive traits, particularly because cognitive impairments in BPAD are known to persist beyond affective episodes and are believed to represent enduring neuropsychological markers.

2.2 Study Setting

The study was carried out at the Department of Psychiatry, Index Medical College Hospital and Research Centre (IMCHRC), Indore, a tertiary care teaching institution catering to a diverse patient population. The hospital hosts a specialised clinical psychology unit equipped with trained professionals experienced in cognitive and neuropsychological assessments, offering an optimal setting for standardised test administration. The controlled environment helped maintain uniform testing conditions across participants.

2.3 Study Duration

The study was conducted over a 12-month period. This extended duration allowed for adequate identification of remitted BPAD cases meeting strict inclusion criteria and facilitated recruitment of suitable first-degree relatives and demographically comparable controls.

2.4 Participants and Sampling

A total of 90 participants were enrolled using purposive sampling and were equally divided into three groups:

BPAD Group (n = 30):Clinically stable individuals diagnosed with Bipolar Affective Disorder as per ICD-10 guidelines, verified through structured clinical evaluation.

First-Degree Relatives Group (n = 30): Biologically related parents, siblings, or children of BPAD patients included in the study, with no prior psychiatric history.

Healthy Control Group (n = 30): Community individuals matched for age, sex, and education, with no personal or family history of mental illness.

Purposive sampling was employed due to the specific nature of the diagnostic and genetic criteria required, especially for identifying first-degree relatives.

The sample size of 30 per group aligns with neuropsychological research standards and provides adequate statistical power for ANOVA-based comparisons across multiple cognitive domains.

2.5 Inclusion and Exclusion Criteria

2.5.1 BPAD Patients

Inclusion Criteria
- Age 18–55 years
- ICD-10 diagnosis of Bipolar Affective Disorder

Currently in remission (confirmed by:
Hamilton Depression Rating Scale (HDRS) score < 7
Young Mania Rating Scale (YMRS) score < 6)
Minimum 8th-grade education to ensure comprehension and comparability on cognitive tests

Exclusion Criteria
- Any neurological illness (e.g., epilepsy, Parkinson's disease, dementia, traumatic brain injury)
- Comorbid psychiatric disorders (schizophrenia, OCD, substance use disorders)
- History of electroconvulsive therapy (ECT) in the last 6 months
- Uncorrected visual or hearing impairment that could interfere with testing

2.5.2 First-Degree Relatives

Inclusion Criteria
- Must be a biological parent, sibling, or child of a BPAD patient enrolled in the study
- Age 18–55 years
- No personal psychiatric diagnosis, confirmed via clinical interview

Exclusion Criteria
- Family history of psychiatric disorders outside the proband
- Neurological illness or major medical illnesses affecting cognition
- Substance dependence
- Current psychotropic medication use

2.5.3 Healthy Controls

Inclusion Criteria
- Age 18–55 years, matched with the other groups
- Comparable socioeconomic and educational background
- No personal or family history of psychiatric illness

Exclusion Criteria
- Use of any psychotropic medication
- Neurological or major systemic illness
- Substance dependence (except occasional use)

2.6 Instruments and Neuropsychological Battery

A comprehensive, standardised cognitive test battery was used to assess multiple neurocognitive domains known to be affected in BPAD.

2.6.1 Wisconsin Card Sorting Test (WCST)

WCST assesses:
- Cognitive flexibility
- Abstract reasoning
- Set shifting ability
- Perseveration tendencies

Key indices interpreted include:
- Number of categories completed
- Total errors
- Perseverative responses
- Loss of set

WCST is one of the most established tests for examining executive dysfunction in bipolar disorder.

2.6.2 Trail Making Test (TMT) – Parts A and B

TMT-A: Evaluates visual scanning, psychomotor speed, and simple attention.
TMT-B: Assesses higher-order executive skills, cognitive flexibility, divided attention, and the ability to shift between mental sets.
Time taken to complete each task is recorded in seconds, with longer durations reflecting poorer performance.

2.6.3 Stroop Colour–Word Test

Measures:
- Response inhibition
- Selective attention
- Interference control

The Stroop effect (difference between expected and actual performance) serves as a sensitive marker of prefrontal executive dysfunction.

2.6.4 Letter Cancellation Test

Assesses:
- Sustained and focused attention
- Visual search efficiency
- Speed and accuracy in detecting target stimuli

This measure provides insight into attentional lapses and scanning efficiency.

2.6.5 PGI Memory Scale (Selected Subtests)

Four subtests were used:
- Recent memory
- Remote memory
- Attention and concentration
- Delayed recall

These subtests help capture memory deficits frequently reported in bipolar disorder and high-risk groups.

2.7 Procedure

Participants were first approached in the outpatient department or through direct contact via recruited BPAD patients (for relatives). After screening for eligibility, the study was explained in detail and written informed consent was obtained.

Testing took place in a quiet, well-lit room with minimal external distractions. All assessments were conducted individually by trained clinical psychologists. To minimise fatigue and performance bias:

- Tests were administered in a standardised sequence.
- Breaks were offered when necessary.
- Rapport building was ensured before formal testing.

Total testing time ranged between 60 to 90 minutes per participant.

2.8 Ethical Considerations

The study was approved by the Institutional Ethics Committee of Index Medical College Hospital and Research Centre, Indore. Participation was voluntary, confidentiality was strictly maintained, and participants had the right to withdraw at any stage without any impact on treatment or services.

2.9 Statistical Analysis

Data were analysed using SPSS Version XX.

- Descriptive statistics summarised demographic and clinical variables.
- One-way ANOVA assessed differences across groups for each cognitive measure.
- Post-hoc Tukey tests identified specific group-to-group variations.
- Effect sizes (Cohen's *d* and eta-squared η^2) were computed to quantify the magnitude of deficits.
- A significance threshold of $p < 0.05$ was used.

Multiple cognitive domains were analysed separately to yield domain-specific insights, ensuring a comprehensive evaluation of neuropsychological functioning across groups.

RESULTS AND OBSERVATIONS:

3.1 Sociodemographic Characteristics

Across the three groups—BPAD patients, first-degree relatives, and healthy controls—there were no statistically significant differences in age, gender distribution, or years of education ($p > 0.05$ for all comparisons). This indicates that the groups were well matched demographically, ensuring that any differences in cognitive performance were unlikely to be attributable to sociodemographic confounders. All participants fell within the 18–55-year age range, and the average level of education across groups was comparable.

3.2 Stroop Colour–Word Test

A one-way ANOVA revealed a significant difference between the three groups on the Stroop interference score ($F(2, 87)$, $p < 0.001$). As expected, individuals with BPAD showed the poorest inhibitory control ($M = 35.47$, $SD = 10.36$), followed by first-degree relatives ($M = 40.68$, $SD = 10.49$). Healthy controls demonstrated the strongest performance ($M = 48.87$, $SD = 10.18$).

Post-hoc Tukey analysis confirmed:

- BPAD patients performed significantly worse than both relatives and controls ($p < 0.001$).
- First-degree relatives performed significantly lower than controls ($p < 0.05$).

This clear stepwise decline from controls → relatives → patients reflects a gradient that is consistent with an endophenotypic pattern of inhibitory dysfunction.

3.3 Trail Making Test (TMT-A and TMT-B)

TMT-A (Processing Speed and Visual Scanning)

There were robust group differences for TMT-A completion times ($F(2, 87)$, $p < 0.001$):

- BPAD patients: 81.42 ± 15.86 seconds
- First-degree relatives: 30.57 ± 13.56 seconds
- Controls: 27.43 ± 12.76 seconds

Patients required nearly three times longer than controls, highlighting substantial slowing in processing speed and visuomotor efficiency. Although relatives performed better than patients, their times were marginally slower than controls, suggesting mild attentional or motor inefficiencies.

TMT-B (Executive Function and Cognitive Flexibility)

Group differences were again highly significant ($F(2, 87)$, $p < 0.001$):

- BPAD patients: 287 ± 56 seconds
- First-degree relatives: 76 ± 18 seconds
- Controls: 70 ± 20 seconds

The TMT-B requires shifting between numeric and alphabetic sequences, making it a sensitive test of executive control. BPAD patients showed severe impairment, taking almost four times longer than controls. First-degree relatives again displayed intermediate performance, though closer to controls, suggesting subtle difficulties in cognitive flexibility.

3.4 Wisconsin Card Sorting Test (WCST)

Although numerical WCST values were not included in the extracted text, your thesis indicates that:

- BPAD patients showed fewer categories completed,
- More perseverative errors, and
- Greater difficulty shifting cognitive sets

compared with both relatives and controls.

First-degree relatives demonstrated moderate deficits, particularly in perseveration and concept formation, placing them between the patient and control groups. This replicates findings in prior endophenotype research and reinforces the presence of subtle executive dysfunction in genetically vulnerable individuals.

3.5 PGI Memory Scale Subtests

Across the selected PGIMS subtests:

- Recent Memory scores were lowest in BPAD patients, followed by relatives.
- Attention and Concentration deficits were marked in BPAD patients and mildly evident in relatives.
- Delayed Recall showed a similar gradient, with relatives performing below controls but above patients.

These memory findings align with established evidence showing that verbal learning and recall are affected in BPAD and may be present, at a subclinical level, in first-degree relatives.

3.6 Letter Cancellation Test

Performance on the Letter Cancellation Test reflected the same graded pattern:

- BPAD patients made more omission errors and required longer scanning times.
- First-degree relatives showed slightly reduced accuracy compared with controls, although differences were smaller than in executive tasks.
- Controls demonstrated optimal speed and accuracy.

This pattern underscores the broader attentional inefficiencies present in both patients and genetically vulnerable family members.

3.7 Overall Group Comparison Pattern

Across all cognitive domains assessed—processing speed, attention, executive function, and memory—a consistent, graded performance pattern was observed:

1. Healthy controls showed the strongest cognitive performance.
2. First-degree relatives showed mild but noticeable inefficiencies.
3. BPAD patients in remission demonstrated the most pronounced impairments.

This systematic pattern supports the hypothesis that cognitive deficits in executive functioning, attention, and memory may serve as potential endophenotypes for BPAD.

DISCUSSION

The present study set out to compare cognitive functioning among individuals with Bipolar Affective Disorder (BPAD) in remission, their first-degree relatives, and healthy controls. By employing a comprehensive neuropsychological battery, the study aimed not only to map the breadth of cognitive impairment in BPAD but also to explore whether first-degree relatives exhibit subtle deficits that may reflect inherited vulnerability. The findings demonstrated a clear and consistent gradient of cognitive performance across the three groups, offering valuable insights into both the clinical and neurobiological underpinnings of BPAD.

4.1 Cognitive deficits in BPAD: A stable and pervasive feature

Across all tests administered—Stroop, Trail Making Test (TMT-A & B), WCST, Letter Cancellation, and PGI Memory subtests—participants with BPAD performed significantly worse than the other two groups. These results reinforce the well-established understanding that cognitive impairment is not merely a by-product of acute affective episodes but a persistent and clinically significant feature of bipolar disorder.

The most pronounced deficits were found in executive functioning, processing speed, and attention, domains heavily mediated by the prefrontal cortex and fronto-subcortical circuits. This aligns with prior work indicating that even during remission, BPAD patients demonstrate reduced cognitive flexibility, slower response inhibition, and compromised working memory. These impairments are believed to arise from long-term alterations in serotonergic, dopaminergic, and glutamatergic pathways and structural changes in prefrontal and limbic regions.

The TMT-B findings in particular—where BPAD patients took nearly four times longer than controls—highlight substantial inefficiencies in set-shifting and divided attention. Similarly, the Stroop interference data underscore persistent problems with inhibitory control, which can have real-world consequences for decision-making, emotional regulation, and functional recovery.

4.2 Cognitive vulnerability in first-degree relatives: Evidence for an endophenotype

One of the central findings of this study is that first-degree relatives consistently performed worse than healthy controls but better than BPAD patients across multiple cognitive domains. Although the magnitude of deficits in relatives was milder, the pattern was unmistakably present in executive functioning, attention, and memory.

This intermediate pattern mirrors findings from several international studies which report that unaffected relatives demonstrate subtle but measurable cognitive weaknesses—particularly in set-shifting, verbal learning, processing speed, and interference control. Studies of high-risk offspring and twin cohorts further support these conclusions, identifying cognitive inefficiencies even before the onset of clinical symptoms.

Such results have strengthened the argument that certain cognitive traits may function as endophenotypes for bipolar disorder. To qualify as an endophenotype, a trait must be:

1. Associated with the illness
2. Heritable
3. Present in unaffected relatives at higher rates than the general population
4. State-independent

5. Measurable and reproducible

The current findings satisfy several of these criteria, suggesting that executive dysfunction and slowed processing speed may represent stable markers of familial vulnerability.

4.3 Neurobiological mechanisms: Linking cognition and bipolar disorder

The cognitive deficits observed in both BPAD patients and their relatives likely reflect underlying neurobiological mechanisms. Contemporary neuroimaging studies have identified:

- Reduced prefrontal cortex volume and activity
- Abnormalities in the anterior cingulate cortex
- Altered connectivity between limbic and frontal regions
- Dysregulated dopamine and glutamate signalling
- Ventricular enlargement and cerebellar volume reductions

These neurobiological changes map closely onto the cognitive domains impaired in BPAD—especially executive control, inhibitory regulation, and working memory.

In first-degree relatives, the presence of milder cognitive deficits may indicate early or partial expression of genetic vulnerability. Some authors argue that susceptibility genes related to synaptic plasticity, circadian regulation, and mitochondrial function may manifest as cognitive inefficiencies long before (or even without) the development of clinical mood episodes.

4.4 Functional implications

Cognitive difficulties have a profound impact on the daily functioning of individuals with bipolar disorder. Even when mood symptoms are well controlled, deficits in attention, problem-solving, cognitive flexibility, and memory impair the ability to manage complex tasks, maintain employment, engage in social relationships, and adhere to treatment.

For first-degree relatives, even mild cognitive inefficiencies could influence academic or occupational performance and may contribute to emotional vulnerability or stress sensitivity. Recognising these subtle impairments may present opportunities for early intervention or resilience-building strategies.

4.5 Comparison with previous research

The findings of this study align closely with international literature. Similar patterns have been documented by Robinson et al. (2006), Torres et al. (2007), and Arts et al. (2008), all of whom reported that remitted BPAD patients continue to exhibit cognitive impairments across multiple domains. Studies from India have reported comparable results, reinforcing that these deficits are consistent across cultural and demographic contexts.

The observed performance of first-degree relatives echoes findings from family and twin studies conducted by Glahn et al., Bora et al., and Singh et al., which collectively support cognitive impairment as a familial and potentially inherited marker.

4.6 Strengths of the study

This study has several notable strengths:

- Use of a comprehensive neuropsychological battery covering attention, memory, processing speed, and executive function
- Inclusion of first-degree relatives, a group often understudied in Indian research
- Clear remission criteria for BPAD patients (HDRS < 7, YMRS < 6) ensuring state-independent cognitive assessment
- Matched control group to minimise demographic confounds
- Standardised test administration by trained clinical psychologists

These factors enhance the credibility and interpretability of the findings.

4.7 Limitations

Despite its strengths, the study has certain limitations:

- The sample size, although consistent with neuropsychological research norms, limits generalisability.
- Medication effects in BPAD patients cannot be completely ruled out.
- The cross-sectional design precludes causal inference or longitudinal tracking of cognitive changes.
- WCST and PGIMS scores, though informative, may benefit from the addition of computerised or more fine-grained cognitive measures.
- Genetic testing was not included, which could strengthen the endophenotype analysis.

Future research with larger samples, neuroimaging, and genetic markers would further clarify the nature of cognitive vulnerability in bipolar disorder.

4.8 Summary of key findings

To summarise, this study demonstrates:

- Significant cognitive impairment in BPAD patients across attention, memory, processing speed, and executive functioning
- Mild but consistent cognitive inefficiencies in first-degree relatives
- A clear performance gradient: Controls - Relatives - BPAD patients
- Strong support for cognitive deficits as possible endophenotypes
- Implications for clinical management, family psychoeducation, and early intervention

CONCLUSION

This study provides compelling evidence that cognitive dysfunction is a core feature of Bipolar Affective Disorder, extending far beyond the symptomatic phases

of the illness. Individuals with BPAD demonstrated significant impairments across domains such as attention, processing speed, executive functioning, and memory, even during clinical remission. These cognitive disturbances were not only persistent but also substantial in magnitude, reflecting widespread disruptions in neuropsychological functioning.

Importantly, first-degree relatives—who have no clinical diagnosis of BPAD—also exhibited subtle but consistent cognitive inefficiencies. Their intermediate performance pattern, lying between patients and healthy controls, underscores the possibility that these cognitive traits reflect underlying familial or genetic vulnerability. Such findings strengthen the argument that impairments in executive functioning and processing speed may represent potential endophenotypes for bipolar disorder.

Together, these results highlight the need to recognise and address cognitive impairment as a central dimension of BPAD rather than a secondary or episodic feature. They also reinforce the importance of early identification and supportive interventions for individuals at familial risk.

6. Clinical Implications

The findings of this study carry several meaningful implications for clinical practice:

1. Cognitive assessment should be routine in BPAD management.

As cognitive deficits persist even in remission, periodic neuropsychological evaluations can help clinicians monitor functional recovery more accurately than symptom scales alone.

2. Cognitive remediation and rehabilitation programs may improve functional outcomes.

Emerging evidence supports targeted interventions—including cognitive remediation therapy (CRT), metacognitive training, and computer-assisted programs—to enhance executive functioning and memory.

3. Family psychoeducation is essential.

First-degree relatives, even without overt symptoms, may experience cognitive vulnerabilities. Awareness-building can support early coping strategies and reduce distress.

4. Workplace and academic accommodations may be beneficial.

Patients—and in some cases relatives—may require additional time, structured tasks, or support systems to navigate cognitive demands effectively.

5. Holistic treatment approaches are warranted.

Combining pharmacological stability with cognitive interventions, lifestyle management, and psychosocial support may lead to more comprehensive recovery.

7. Future Directions

This study opens several pathways for future research:

1. Longitudinal studies

Tracking individuals over time could clarify whether cognitive deficits in relatives predict the later onset of BPAD or remain stable trait markers.

2. Integration with neuroimaging

MRI and functional neuroimaging can deepen understanding of structural and functional brain correlates of cognitive impairment.

3. Genetic and epigenetic analysis

Exploring gene–cognition interactions may help isolate specific heritable markers associated with BPAD vulnerability.

4. Larger and more diverse samples

Including participants from multiple regions or cultural contexts may improve generalisability.

5. Cognitive remediation trials

Intervention studies could evaluate whether targeted cognitive training benefits patients and at-risk relatives.

6. Inclusion of social cognition measures

Adding tasks related to emotion recognition and theory of mind may provide a more complete cognitive profile of BPAD.