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MICEmi: A method to identify cognitive endophenotypes of mental illnesses

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Abstract

Background. Characterizing neurocognitive endophenotypes of mental illnesses (MIs) could be useful for identifying at-risk individuals, increasing early diagnosis, improving disease subtyping, and proposing therapeutic strategies to reduce the negative effects of the symptoms, in addition to serving as a scientific basis to unravel the physiopathology of the disease. However, a standardized algorithm to determine cognitive endophenotypes has not yet been developed. The main objective of this study was to present a method for the identification of endophenotypes in MI research.

Methods. For this purpose, a 14-expert working group used a scoping review methodology and designed a method that includes a scoring template with five criteria and indicators, a strategy for their verification, and a decision tree.

Conclusions. This work is ongoing since it is necessary to obtain external validation of the applicability of the method in future research.

Introduction

The concept of "endophenotype" was coined in 1966 by Bernard John and Kenneth R. Lewis in a study of the chromosomal and geographical variability of grasshoppers [1]. Later, this term has been used in multiple fields of medicine to clarify the etiology and pathophysiology of various clinical conditions. The endophenotype, also called the intermediate phenotype, has been used in many ways, mostly to refer to a phenotype that is closer to the biological etiology of the disorders than to the signs or symptoms affected by one or more genes associated with the disease [2]. Specifically, in psychiatry, endophenotypes acquired special relevance when they began to be associated with cognitive functioning [2] and were used to help understand the genomics of schizophrenia and other mental illnesses (MIs), becoming an excellent potential tool for multiple studies in neurobiology, neuropsychiatry, neuropsychology, and heritability [3–5]. An increasing number of studies have included this concept as the basis for their research, using neurocognitive evaluations instead of genetic and brain morphology tests to identify cognitive endophenotypes [6–10].

Several criteria have been proposed to establish that a specific characteristic can be considered an endophenotype of pathology. For instance, it must appear concomitantly with the pathology to be studied; that is, it can be considered as an element of the disease in question, although it is not necessarily a requirement of it but has a high probability of manifesting itself [11, 12]. Another criterion that should be taken into account for the determination of an endophenotype is that it should be "measurable" and "temporarily stable"; that is, it should be more of a "trait marker" than a "state marker" of the disease [13, 14]. Moreover, an endophenotype must be observable in subsequent measurements, thus introducing a longitudinal perspective in the search for and verification of endophenotypes [14, 15]. Furthermore, the presence of similar deficits in the unaffected biological relatives of these individuals favors the use of a genetic substrate for them [16–20].

Research Article

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The most commonly used criteria to identify endophenotypes in recent clinical studies are as follows: The phenotype (a) is associated with illness in the population, (b) is heritable, (c) is state-independent (manifests in an individual whether or not the illness is active) but age-normed and might need to be elicited by a challenge, (d) co-segregates with the illness within families, and (e) one of which identified in the proband is found in the unaffected relatives at a higher rate than in the general population [21].

In the case of neurocognitive endophenotypes, various studies using several of these criteria have shown that there are neurocognitive deficits in the broad domains of attention, memory, and executive functions in patients with MIs, such as bipolar disorder (BD) or schizophrenia, as well as in their first-degree relatives (FDRs), although the latter in an attenuated manner [22–26]. Similarly, complex polygenicity with a predominance of the genetic component has been established by studies including twins and FDR, facilitating the search for cognitive endophenotypes linked to MIs. However, the outright neurocognitive endophenotypes associated with MIs remain unclear. Moreover, a consensual and standardized cognitive evaluation and selection procedure that allows identification and a more comprehensive description of the cognitive endophenotypes associated with MIs are not available yet [27–29].

Studies on endophenotypes constitute a cost-effective and easier method to implement when studying the wide range of subclinical characteristics of MIs [16, 23, 30–32]. Characterizing endophenotypic profiles associated with MIs could be useful for identifying individuals at risk, increasing the effectiveness of early diagnosis, improving disease subtyping, and proposing therapeutic strategies to reduce the negative effects of the symptoms, in addition to serving as a scientific basis for the physiopathology of the disease [33–35]. Thus, the identification of suitable cognitive endophenotypes for MIs is a potentially useful strategy to improve the understanding of MIs [36–39].

Due to the discrepancies found in the procedures and criteria used to identify the cognitive endophenotypes of a MI and in the results on what can be considered a stable cognitive endophenotype of a certain MI, we consider that there is a need for a standardized method that provides definite and clear neuroscientific support for cognitive endophenotypic profiling in future research. The main objective of this study was to present a method that includes and refines the procedures used by other researchers for the search and identification of suitable cognitive endophenotypes in MI research, for each individual diagnosis or for identification of common endophenotypes across multiple diagnoses. We propose an inventory of exploration and verification, which in addition to fulfilling its primary objective, could be useful in unifying the results of previous studies in future investigations.

Methods

Scoping review

We conducted a scoping review (PRISMA-ScR) [40], which is the most widely used method for synthesizing research evidence when the subject has not yet been extensively reviewed or is complex or heterogeneous in nature. The method is mostly used when researchers seek, among other things, to identify research gaps in the existing literature and attempt to develop a methodological framework for rigorously and transparently mapping the area being investigated [41], as in our case. The scoping review protocol was accomplished by the members of the research team CB/07/09/0021 of the Center for Biomedical Research in Mental Health Network (CIBERSAM).

The following search string was used on the "Scopus," "Web of Science," and "PubMed/Medline" databases: (endophenotype OR intermediate phenotype) AND (mental disorder OR MI OR psychiatric disorder OR psychiatric illness) AND (cognitive OR neurocognitive) AND (first degree OR relatives). The following main filters were applied at convenience: Full text, article records from inception to July 31, 2022, English, and Humans. The inclusion criteria were original articles that focused on the identification of cognitive or neurocognitive endophenotypes of MIs that include any of the following aspects: (a) Studies on patients with a psychiatric disorder and healthy controls; (b) Studies on patients with a psychiatric disorder and relatives of patients; (c) Studies on patients with a psychiatric disorder, relatives of patients, and healthy controls; (d) Studies on the relatives of patients with a psychiatric disorder and healthy controls; and (e) Studies on patients with different types of psychiatric diseases compared with each other. The exclusion criteria were: (a) Studies focused on different types of endophenotypes, such as genetic, physiological, neurological, brain structure, or other health aspects; (b) Studies where only one or several cognitive functions were evaluated in psychiatric patients, without considering the endophenotypic aspect; and (c) Studies not relevant to the study objective.

Method design

A working team of 14 experts from different Spanish research groups was established to design the cognitive endophenotype identification method in four steps. First, a *criteria list* was established based on the most used criteria found through scoping review. Second, *each criterion was defined* based on its background. Third, *each indicator was established*; that is, the manifest properties by which each criterion can be directly identified and measured. Fourth, based on the know-how of experts, group decisions were made considering the importance of each criterion and indicator. The weight or value that each would have, and the method to rate them and verify the endophenotype were considered to *set up a scoring system* to obtain numerical data. The scoring system can be used to statistically analyze the results in future studies.

To provide content and construct validity, each expert separately evaluated the relevance, coherence, sufficiency, clarity, and weight, of each element of the method based on: general procedure, aspects to consider during the process, criterion, definition, indicator, score, and verification of the criteria, verification of the endophenotype, and the decision tree. Inter-rater reliability was used to score this process.

Results

Scoping review

Following the search string, a total of 5,176 papers were retrieved from the databases (2,114 from PubMed/Medline, 1,763 from Scopus, and 1,299 from Web of Science) as potential papers for inclusion in the study. After applying the filters, removing duplicates, and unifying and refining the searches of each reviewer, 2,620 articles were excluded. The results of the selected 2,556 publications were screened and evaluated, and were further refined based on whether they described the use of a methodology to identify cognitive endophenotypes of psychiatric diseases. Finally, 83 papers were included in this study (Figure 1).

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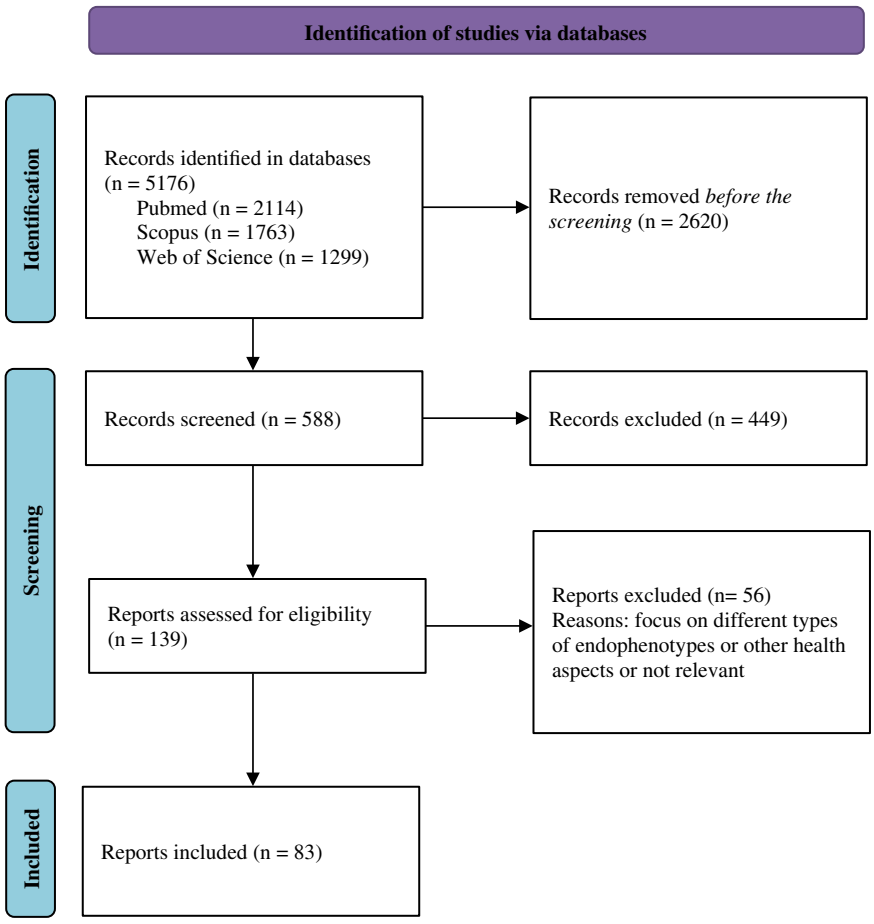

Figure 1. PRISMA-ScR flow diagram [42].

Analyzing the selection criteria of neurocognitive endophenotypes used in the studies, it was found that, the diseases included attention deficit hyperactivity disorder ($k = 11$), anorexia nervosa ($k = 3$), autism spectrum disorder ($k = 2$), BD ($k = 21$), eating disorders ($k = 3$), mood disorders ($k = 6$), obsessive–compulsive disorder ($k = 9$), substance use disorder ($k = 2$), schizophrenia, and psychosis spectrum ($k = 30$), and others. Unaffected relatives in comparison with genetically unrelated controls were included in the 83 studies. Eighty-one of the papers compared a group of patients with healthy controls. At least two repeated measures were included in four studies. Age-normed and clinical variables that could affect the performance were considered in statistical analyses of 55 of the studies.

Based on these findings a list of the "most used criteria" and its "indicators" were configured:

1. Concomitance or association with the disease, high probability of manifestation, and measurability: comparison with other groups.
2. Presence in biological relatives, heritability, or co-segregation with the disease within families: inclusion of unaffected relatives in comparison with genetically unrelated controls in the study.
3. Temporary stability (longitudinal perspective): longitudinal studies with at least two repeated measures.
4. State independence: age-normed and clinical variables that could affect performance considered in statistical analyses.

The 83 articles summarizing the target groups, endophenotypes studied, and selection criteria used, are arranged in chronological order in Table 1.

In summary, most of the articles reviewed and evidenced the existence of endophenotypes in individuals diagnosed with MIs and their FDR compared with healthy controls, fulfilling the first and second criteria. Very few of them included repeated measures regarding the third criterion. As to the fourth criterion, although in most of the articles some sociodemographic and clinical variables were controlled, they did not control the effect of some of them that might have given rise to interpretation biases and reduced the power of the findings. Additionally, none of them considered these a useful criterion for the selection of endophenotypes. Another important aspect is that very few studies corroborated their findings on a certain endophenotype based on the same description of a specific cognitive function and/or with the same measurement instrument or even the same clinical type as in other studies.

The designed method

The final version of the method was obtained after refining each of the four steps through a cross-review among the experts. The consensus included five classification categories or criteria: (a) association, (b) heritability, (c) stability, (d) independence, and (e) reliability of results with corresponding descriptions, each with indicators and corresponding weightage and a particular

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Table 1. Summary of the included articles.

References	Year	Target groups	Cognitive endophenotype	Criteria[a]
Seidman et al. [43]	2000	ADHD	Cognitive performance	1, 2, 4
Dollfus et al. [44]	2002	SZ	Executive functions and attention	1, 2, 4
Myles-Worsley et al. [45]	2002	SZ	Spatial working memory	1, 2, 4
Glahn et al. [46]	2003	SZ	Spatial working memory	1, 2, 4
Tuulio-Henriksson et al. [47]	2003	SZ	Declarative verbal memory and learning	1, 2
Slaats-Willemse et al. [48]	2003	ADHD	Cognitive inhibition	1, 2, 4
Nicol Ferrier et al. [49]	2004	BD	Cognitive performance	1, 2
Wittorf A, Klingberg et al. [50]	2004	SZ	Secondary verbal memory	1–4
Stins et al. [51]	2004	ADHD	Executive functions	1, 2, 4
Kamarajan et al. [52]	2005	SUD	Cognitive inhibition	1, 2
Pirkola et al. [53]	2005	BD, SZ	Spatial working memory	1, 2, 4
Calkins et al. [54]	2005	SZ	Face recognition and visual memory	1, 2
Clark et al. [55]	2005	MD, BD	Executive functions and verbal memory	1, 2
Holliday et al. [56]	2005	AN	Set-shifting	1, 2, 4
Burdick et al. [57]	2006	BD, SZ	Cognitive performance	1, 2, 4
Wang et al. [58]	2007	SZ	Cognitive reaction time	1, 2
Gur et al. [59]	2007	SZ	Cognitive performance	1, 2
Ma et al. [60]	2007	SZ	Cognitive performance	1, 2, 4
Bidwell et al. [61]	2007	ADHD	Executive functions	1, 2, 4
Barrantes-Vidal et al. [62]	2007	SZ	Working memory	1, 2, 4
Menzies et al. [63]	2007	OCD	Cognitive performance	1, 2, 4
Wang et al. [64]	2008	SZ	Prospective memory	1, 2, 4
Robles et al. [65]	2008	SZ	Nonverbal delayed recognition	1, 2, 4
Leppänen et al. [66]	2008	SZ	Facial affect recognition	1, 2
Frantom et al. [67]	2008	BD	Cognitive performance	1, 2, 4
Lopez et al. [68]	2009	ED	Cognitive central coherence	1, 2
Viswanath et al. [69]	2009	OCD	Executive functions	1, 2, 4
Kulkarni et al. [70]	2010	BD	Verbal learning, verbal memory, and executive function	1, 2, 4
Tenconi et al. [71]	2010	AN	Set-shifting and central coherence	1, 2
Chkonia et al. [72]	2010	SZ	Cognitive performance	1, 2
Wang et al. [73]	2010	SZ	Prospective memory	1, 2
Ozan et al. [74]	2010	SZ	Cognitive performance	1, 2
Cavedini et al. [75]	2010	OCD	Executive functions	1, 2, 4
Calkins et al. [76]	2010	SZ	Cognitive performance	1, 2
Ancin et al. [77]	2010	BD	Sustained attention	1, 2
Gau et al. [78]	2010	ADHD	Executive functions	1, 2, 4
Eack et al. [79]	2010	SZ	Social cognition	1, 2
Sumiyoshi et al. [80]	2011	ASD	Verbal learning and executive functions	1, 2
Breton et al. [81]	2011	SZ	Executive control	1, 2, 4
Antila et al. [82]	2011	BD	Processing speed	1, 2, 4
Finke et al. [83]	2011	ADHD	Attention	1, 2
Hu et al. [84]	2011	SZ	Semantic fluency and executive functions	1, 2, 4
Rajender et al. [85]	2011	OCD	Cognitive performance	1, 2, 4
Shang et al. [86]	2011	ADHD	Visual memory	1, 2
Li et al. [87]	2012	OCD	Cognitive performance	1, 2

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Table 1. *Continued*

References	Year	Target groups	Cognitive endophenotype	Criteria[a]
Daban et al. [88]	2012	BD	Processing speed	1, 2, 4
MacAllister et al. [89]	2012	ADHD	Cognitive performance	1, 2
Gierski et al. [90]	2013	SUD	Executive functions	1, 2
Kanakam et al. [91]	2013	ED	Set-shifting and central coherence	1, 2, 4
Roberts et al. [92]	2013	ED	Attention	1, 2, 4
Gau et al. [93]	2014	ADHD	Visual information processing	1, 2, 4
Park et al. [94]	2014	SZ	Working memory	1, 2, 4
Talbot et al. [95]	2015	AN	Cognitive performance	1, 2
Hıdıroğlu et al. [96]	2015	BD	Response inhibition and interference control	1, 2, 4
Kim et al. [6]	2015	BD, SZ	Cognitive performance	1, 2, 4
Kosger et al. [97]	2015	BD	Executive functions	1, 2
Vierck et al. [98]	2015	BD	Facial cognitive recognition	1, 2
Papmeyer et al. [99]	2015	MD	Verbal memory and executive functions	1, 2, 4
Zhang et al. [100]	2015	OCD	Cognitive decision	1, 2, 4
Georgiades et al. [17]	2016	BD	Verbal episodic and spatial working memory	2
Liang et al. [101]	2016	SZ	Verbal fluency	1, 2, 4
Sharma et al. [102]	2016	BD	Spatial memory and executive functions	1, 2, 4
Volkert et al. [103]	2016	BD	Cognitive performance	1, 2, 4
Correa-Ghisays et al. [104]	2017	BD	Manual motor speed	1–4
Gkintoni et al. [105]	2017	BD	Cognitive performance	1, 2, 4
Merikangas et al. [106]	2017	MD	Executive functions	1, 2, 4
Tezcan et al. [107]	2017	OCD	Reversal learning	1, 2
Van Eylen et al. [108]	2017	ASD	Executive functions and verbal fluency	1, 2
Eddy et al. [109]	2017	ADHD	Set-shifting	1, 2, 4
Bey et al. [110]	2018	OCD	Executive functions	1, 2, 4
Calafiore et al. [111]	2018	BD	Cognitive performance	1, 2, 4
Fish et al. [112]	2018	SZ	Cognitive reaction time	1, 2, 4
McCarthy et al. [113]	2018	SZ	Cognitive performance	1, 2, 4
Miskowiak et al. [114]	2018	MD	Self-referent negative memory	1, 2, 4
Boxhoorn et al. [115]	2019	ADHD	Attention	2, 4
Correa-Ghisays et al. [116]	2019	BD	Visual memory	1–4
Meluken et al. [117]	2019	MD	Affective condition	2, 4
Grover et al. [118]	2019	SZ	Social cognitive	1, 2, 4
Tikka et al. [119]	2019	SZ	Social cognitive	1–4
Luperdi et al. [120]	2021	BD	Processing speed	1–3
Liu et al. [121]	2021	MD	Executive functions	1, 2, 4
Abramovitch et al. [122]	2021	OCD	Cognitive performance	1, 2, 4
Rodríguez-Martínez et al. [123]	2021	SZ	Working memory	1, 2, 4

Abbreviations: ADHD, attention deficit hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; ED, eating disorders; MD, mood disorders; OCD, obsessive–compulsive disorder; SUD, substance use disorder; SZ, schizophrenia and psychosis spectrum.
[a]Most used criteria: 1 = Concomitance or association with the disease, high probability of manifesting itself, and measurability; 2 = Presence in biological relatives, heritability, or co-segregation with the disease within families; 3 = Temporary stability (longitudinal perspective); 4 = State independence.

verification system. Although these five categories include the previously used criteria, some modifications were made in terms of their definition and indicators that identify them. For example, the "heritability" criterion synthesizes the following: the endophenotype is heritable, co-segregates within families, and can be seen in unaffected relatives. This criterion also includes a new indicator—the profile or an intermediate pattern of family members' performance compared with individuals with particular MI and healthy controls [6, 67, 124]. We also added a new criterion, "reliability of results," referring to corroboration of the findings

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Table 2. MICEmi scoring template.

General procedure
The data obtained by research on the identification of a cognitive endophenotype of a mental illness are reviewed to determine whether the criteria are met, verifying and scoring each of its indicators using this template as indicated below. Then, the "decision tree" (Figure 2) may be used to determine the next step of the investigation.
Aspects to consider during the process
Target groups: people with a Psychiatric Disease diagnosis (PD); Healthy Controls or people without psychiatric diseases (HC); people with Other Diseases, including diagnosis of another psychiatric disease (OD); unaffected Relatives (uR); patients with Relatives affected by Psychiatric Diseases (PDaR); stable Psychiatric Disease cases or at clinical remission at the time of assessment (sPD); non-stable Psychiatric Disease cases or in acute phase at the time of assessment (nsPD).
Tests or measuring instruments used in the study to assess the cognitive function of interest.
Results of or scores/performance in cognitive assessments.
Statistical comparison of the data.
The terms used to name each criterion are not based on the traditional statistical terminology but on scientific literature related to the identification of endophenotypes.
Regarding "significant differences," even if there is a direct reference to a statistical concept, the criterion or method will depend on the statistical technique used.
The numbers in parentheses of the indicator scores represent the relative weight of each one with respect to the criterion. The numbers in parentheses of the criteria scores represent the relative weight of each one with respect to the total scores.
The "Score" of each indicator or criterion is presented as numbers in parentheses (#/#). The first number signifies the relative weight of each of the items and the second number is the total value of each item or overall.
Criterion 1—ASSOCIATION
Definition: The presence of cognitive deficits associated with the studied condition. Concomitant appearance with pathology. Although not a requirement, the phenotype has a high probability of manifesting itself as a concrete element of the disease.
Indicator 1.1: Significant differences between PDs and HCs (PD < HC).
Score: If the performance of PDs is significantly worse than that of HCs, the score is 12; otherwise, the score is 0 (12/20).
Indicator 1.2: Significant differences between PDs and ODs (PD $\neq$ OD).
Score: If the performance of PDs is significantly different from that of ODs, the score is 8; otherwise, the score is 0 (8/20).
Criterion 1 Total Score (20/100)
Criterion 2—HERITABILITY
Definition: The presence of cognitive deficits in first-degree unaffected relatives (parents, brothers–sisters, sons–daughters) without psychiatric illness. Indications of family co-segregation, aggregation, or a possible genetic cause of the cognitive deficit.
Indicator 2.1: Significant differences between uRs and HCs (uR < HC).
Score: If the performance uR is significantly worse than that of HCs, the score is 8; otherwise, the score is 0 (8/20).
Indicator 2.2: There are no significant differences between uRs and PDs (uR = PD).
Score: If there are no significant differences between uRs and PDs, the score is 6; otherwise, the score is 0 (6/20).
Indicator 2.3: Intermediate profiles of uRs: the average relative score between patients and controls, with or without significant differences (PD $\leq$ uR $\leq$ HC).
Score: If there are no significant differences between uRs and PDs but the performance of uRs is significantly worse than that of HCs, the score is 3 (PD = uR < HC). If the performance of PDs is significantly worse than that of uRs and the performance of uRs is significantly worse than that of HCs, the score is 2 (PD < uR < HC). If there are no significant differences between uRs and the other two groups but their average score is between PDs and HC, the score is 1. If there are no significant differences between relatives of the other two groups and there is no intermediate profile, the score is 0 (3/20).
Indicator 2.4: Significant differences between patients without and with affected relatives, family history of mental illness (in first-degree relatives) (PDaR < PD).
Score: If the performance of PDs is significantly worse than that of PDaRs, the score is 3; otherwise, the score is 0 (3/20).
Criterion 2 Total Score (20/100)
Criterion 3—STABILITY
Definition: The presence of cognitive deficits in any clinical state or evolutionary phase of the disease. It occurs in both acute and clinical remission phases. The deficit is temporarily stable and measurable longitudinally, appearing more as a marker of the "trait" than a marker of the "state" of the disease.
Indicator 3.1: Significant differences between PDs and HCs are maintained in different assessments during the follow-up period (Ass1: PD < HC, Ass2: PD < HC, etc.).
Score: If the performance of PDs is significantly worse than that of HCs and these differences are maintained throughout the follow-up, the score is 7; otherwise, the score is 0 (7/20).
Indicator 3.2: Significant differences between sPDs or in clinical remission and HCs (sPD < HC).
Score: If the performance of sPDs is significantly worse than that of HCs, the score is 7; otherwise, the score is 0 (7/20).
Indicator 3.3: There are no significant differences between sPDs and nsPDs (sPD = nsPD).
Score: If there are no significant differences between sPDs and nsPDs, the score is 6; otherwise, the score is 0 (6/20).

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Table 2. *Continued*

General procedure
Criterion 3 Total Score (20/100)
Criterion 4—INDEPENDENCE
Definition: The presence of cognitive deficits without the influence of other factors or covariates.
Indicator 4.1: Cognitive deficit is independent of the traditional sociodemographic variables, such as sex, age, educational level, and so forth.
Score: If these variables represent no significant differences in performance, or if differences disappear after controlling for them, the score is 8; otherwise, the score is 0 (8/20).
Indicator 4.2: Cognitive deficit is independent of clinical or evolutionary variables of the disease, such as the age of onset, illness duration, number of episodes, number of hospitalizations, or pharmacological treatment (number, type, dose, adhesion), and so forth.
Score: If these variables represent no significant differences in performance, or if differences disappear after controlling for them, the score is 8; otherwise, the score is 0 (8/20).
Indicator 4.3: Cognitive deficit is independent of other factors recognized as deficit enhancers, such as comorbidity, nutrition, sedentarism, obesity, and so forth.
Score: If these variables represent no significant differences in performance, or if differences disappear after controlling for them, the score is 4; otherwise, the score is 0 (4/20).
Criterion 4 Total Score (20/100)
Criterion 5—RELIABILITY
Definition: Corroboration of findings by the results of previous studies.
For the score of this criterion, each study reviewed should check for:
(a) The same type of cases: For example, when investigating a cognitive endophenotype of type I bipolar disorder (TB-I), previous studies should include a generic similarity (TB + schizophrenia as a single group), include similar groups in some aspects (TB without differentiating between TB-I and TB-II), or include the same group in all aspects (TB-I vs. TB-II or TB-I vs. other groups), and so forth.
(b) The same cognitive function: For example, when investigating deficits in immediate visual memory as a cognitive endophenotype, previous studies should include the construct "memory" at the generic level, include similar functions in some aspects (immediate memory), or include the same function in all aspects (immediate visual memory).
(c) The same test: For example, when investigating processing speed deficit assessed with a "Stroop test," previous studies should assess that function with "digit symbol," or when investigating learning with TAVEC, previous studies should use the same instrument to assess other cognitive functions, such as "memory," "verbal memory," and so forth.
Indicator 5.1: Previous findings corroborating the results of the present study.
Score: If there are no previous study, the number and their level of similarity in aspects (a), (b), and (c) are valued and scored at the discretion on a scale of 1 to 10, where 1 represents that similarity is scarce and/or has a very low level, and 10 represents equality or high similarity. If there are previous studies, none of which has contradictory findings, the reliability of the results is justified at some level. If there are no studies that corroborate or contradict the results of the present study, the score is 5, justifying the novelty of the study (10/20).
Indicator 5.2: Previous findings contradicting the results of the present study.
Score: If there are previous studies that corroborate the results of the present study and there are previous studies that contradict the results, the number and their level of similarity in aspects (a), (b), and (c) are valued and scored at the discretion on a scale of 10 to 1, where 10 represents that similarity is scarce and/or has a very low level, and 1 represents equality or high similarity. If there are studies that contradict the results and there are no studies that corroborate the results, the score is 0. If there are no studies that corroborate or contradict the results, the score is 5, justifying the novelty of the study (10/20).
Criterion 5 Total Score (20/100)
Verification of the criteria
To determine that a criterion is met, at least one of its indicators must be checked with its minimum score. A higher total score of the criterion will give greater weight to the internal validity of the findings.
Indicator and criteria scores may be used to test the results and present the findings. A higher total score will give greater weight to the validity of the endophenotype. By publishing the results of the study, the values may be used to provide a better explanation of the findings.
Verification of the endophenotype
IDENTIFIED ENDOPHENOTYPE: • All criteria must be validated to consider a cognitive deficit as a definitive endophenotype of the disease. • When publishing the results of the study, it can be concluded that the cognitive endophenotype is validated to be included within the definitive profile of the disease.
POTENTIAL ENDOPHENOTYPE: • If one to four of the criteria are validated, especially the first three (as these are the most commonly used traditionally), a cognitive deficit could be considered a potential endophenotype of the disease. • When publishing the results of the study, it can be recommended that further research is needed using the same method so that the endophenotype can be definitively validated or discarded.
INDETERMINATE ENDOPHENOTYPE: • Criteria are not met. • Negative results of the study may be published.

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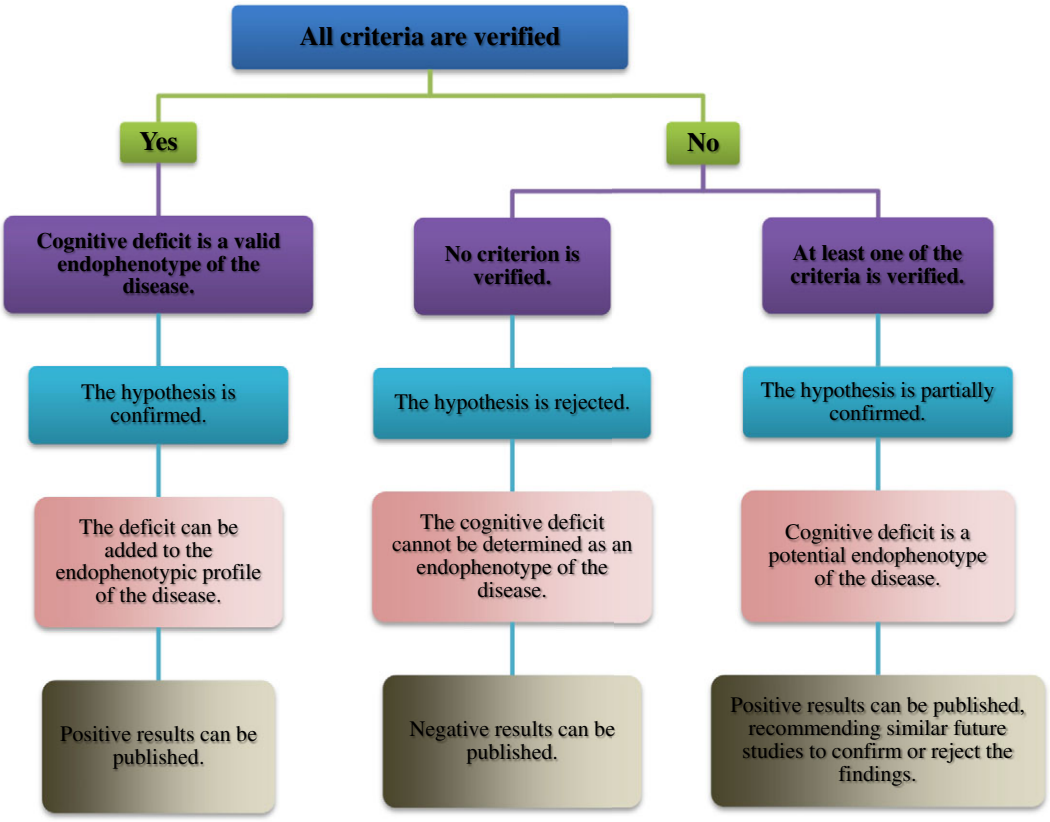

Figure 2. Decision tree.

with those of previous studies because although these criteria are generally reflected in studies of this type, they are not specifically referred to as selection criteria.

Finally, the method with five deliveries was generated: (a) a general procedure and aspects to consider; (b) a reclassification of five criteria, each with its own definition, indicators, and scoring system; (c) verification of the criteria; (d) verification of the endophenotype (Table 2); and (e) a decision tree (Figure 2).

Discussion

In recent years, the interest in cognitive endophenotypes related to MI has increased, causing a change from the previous paradigm—which considers the alterations in MIs as irreversible and that treatments are exclusively curative—toward a new paradigm that focuses on the prevention of those impairments. However, its application is hampered by the lack of a consensus, standardized cognitive evaluation, and selection procedure that allows the identification and a more comprehensive description of the cognitive factors associated with MIs. The use of a method to verify specific criteria to study cognitive endophenotypes in a population with MIs can provide some valuable advantages for researchers, such as systematization, replicability, convergence between different clinical findings, and the delimitation of cognitive endophenotypes for each disease.

The proposed method in this study offers a systematic way of identifying and replicating endophenotypes and therefore should be interpreted as a starting point where the primary goal is the exchange of points of view and subsequent contributions to enrich this field of knowledge and to approach the complexity of reality in a more structured way.

In future research, in addition to the criteria that have already been used to identify cognitive endophenotypes in MIs, it is necessary to add other aspects to the analyses that have not always been studied for further improvement. First, to avoid possible misinterpretations of what is being measured, the same test should be performed to measure each cognitive function, or the results of different tests should be comparable in the most valid and reliable way possible. Second, a greater number of repeated measurements should be made with intermediate time intervals, not so close that they generate a training or learning effect but not so distant that they cause a significant decrease in the sample number. Third, whenever possible, three study groups should be included, including patients with MI, relatives, and controls. Fourth, the maximum number of sociodemographic, psychosocial, clinical, and biological factors should be included to rule out any other possible influences on the cognitive function evaluated other than the biological and genetic factors themselves. Lastly, as we propose in our method as the fifth criterion, "reliability of results," the findings should be corroborated by previous studies.

This work is ongoing, because it is necessary to obtain external validation of the applicability of the method in future research.

Author Contribution. P C-G: had the original idea; conception and design of the study; co-direct the work team; co-coordinated the scoping review; acquisition and analysis of data for the scoping review; drafting the manuscript and figures. JV S-O: conception and design of the study; co-coordinated the scoping review; acquisition and analysis of data for the scoping review; drafting the

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manuscript and figures. R T-S; V B-M: co-direct the work team; drafting the manuscript and figures. I F-D, A M-A, JC R-R, G S-V, J V-F, D M-SG, C S-M, R A-A: work team member; drafting the manuscript and figures. L R-B, P C-E: acquisition and analysis of data for the scoping review. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement. The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

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Conflicts of Interest. The authors declare none.

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