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REVIEW ARTICLE

Brief risk rating scale: A preliminary screening and monitoring tool emphasizing individual differences for better prognosis in Alzheimer's disease

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Abstract

Over the last several decades, significant progress has been made in the diagnostic criteria of Alzheimer's disease (AD) to identify its early stages, including subjective cognitive decline and mild cognitive impairment. However, the previous research rarely took account of individual differences when evaluating AD-spectrum patients at different stages, thereby resulting in similar treatment, which was not only ineffective but also resulted in the missed window of opportunity for intervention. In this review, we propose the Brief Risk Rating Scale (BRRS), which is predominantly based on extant literature concerning AD risk factors and brain alterations, with the aim of providing a preliminary screening and monitoring tool that can facilitate the assessment of individual's risk level, the prediction and tracking of disease progression, as well as precise treatment in a timely manner. Meanwhile, due to its simplicity and ease of use, it can be widely promoted and likewise accessible to clinicians in grassroots clinics. In general, the scale comprises two parts: The original score (O) related to patients' risk factors and the variation score (V) related to brain abnormalities tested by different sequences of magnetic resonance imaging. In addition, the advantages along with its clinical application, such as introducing BRRS into cognitive training and brain stimulation, are also discussed. We conclude that BRRS positively contributes to enhancing the accuracy of clinical diagnosis and the efficiency of personalized treatment in AD-spectrum patients, with individual differences fully considered and little additional burden added. However, the weight coefficient of each item in BRRS should be thoroughly studied in future research.

Keywords: Alzheimer's disease; Guideline; Risk factor; Magnetic resonance imaging

1. Introduction

Alzheimer's disease (AD), the most prevalent cause of dementia in the elderly, is a chronic and age-related neurodegenerative disease that is characterized by progressive declines in cognitive and functional abilities. It has been proven that pathological changes and

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network damage would have had already taken place before clinical symptoms appear[1]. Therefore, there has been a growing interest in subjective cognitive decline (SCD) and mild cognitive impairment (MCI), which are both regarded as the preclinical and prodromal stages of AD[2], in recent years. Compared to MCI, in which irreversible neuronal damage has been observed[3], SCD receives more research interest for the reason that cognitive functioning is still relatively preserved through compensation or restitution of function at this stage, and patients could potentially benefit from timely interventions[4].

However, we find that individual differences, which play a crucial role in disease progression, have rarely been emphasized in the current diagnostic or therapeutic guideline. Research has suggested that not all AD-spectrum patients have structural atrophy[5] or memory impairment[6]. A variation in brain organization, the differences in regional vulnerability, and the pathologic diversity potentially result in complex AD subtypes[7]. Throughout the prolonged course of the disease, different AD subtypes may exhibit different progressing patterns that are inconsistent with the developing order observed in the guideline[5]. Besides, the previous studies have suggested that AD is heterogeneous not only in terms of its clinical manifestations at diagnosis but also with regard to the rate of disease progression[8]. Consequently, there are several limitations in the current diagnostic criteria for a comprehensive evaluation, including the etiology, pattern and speed of progression, as well as the degree of deterioration. Our investigation finds that only a number of studies took both stages and subtypes of AD patients into account when designing the group, whereas most studies considered either of them, of which the results obtained represented the mean characteristic of AD in a normal distribution. Nonetheless, it is in essence more likely to be a skewed distribution due to individual variation among patients.

In addition, despite a significant amount of time and financial expenses invested, effective methods to cure AD remain undiscovered to date; instead, they merely serve to alleviate clinical symptoms or potentially slow the disease progression to some extent[9]. Therefore, conservative medicine or therapies are predominantly used[10]. However, such standardized treatment fails to deal with the differences in clinical features among AD patients; for example, the degree of severity and urgency. Under these circumstances, patients over the mean value are at high risk of being overlooked, thus missing the optimal time window for early intervention, which not only leads to reduced diagnostic accuracy and therapeutic effectiveness but also blocks the progress in the discovery of the pathological mechanisms underlying AD progression and in seeking for curative treatment.

AD is now regarded as a continuum progressing from unnoticeable brain alterations to subsequent memory impairments that are caused by brain alterations and eventually physical disability[11]. Considering the disease as multifactorial and multidirectional (i.e., neuron, structure, and function), it has been recommended that a spectrum may be more suitable than categorical subtypes[6]. A preliminary screening and monitoring tool that can be used in coordination with the current AD guideline to assist in identifying patients who are likely to be overlooked and at a greater risk for disease progression is essential. We, therefore, propose the Brief Risk Rating Scale (BRRS), which allows the quantification of individual risk factors and existing brain alterations, so as to make full use of individual information for the sake of a better assessment of individual's risk level, the prediction and tracking of disease progression, as well as a precise treatment in a timely manner. In parallel with the continuous efforts in discovering the underlying pathological mechanisms, developing advanced diagnostic technology, and designing new pharmacological approaches, BRRS provides an economical, efficient, and accessible way to make progress in achieving the goal of preventing, stopping, and curing AD[12,13].

2. Methods

A recent systematic review and meta-analysis[14] of AD risk factors and interventions has proposed 21 evidence-based suggestions with different levels of evidence (11 with Level A and 10 with Level B) and strengths of suggestions (19 with Class I and two with Class III) on AD prevention. It is hitherto the most comprehensive and large-scale systematic review and meta-analysis, which included a total of 243 observational prospective studies and 153 randomized controlled trials, to evaluate AD risk factors and offer clinicians and stakeholders credible guidance for AD prevention. Hence, the first part of BRRS concerning individual's risk level was formulated primarily on the basis of this excellent review.

With regard to the second part, which focuses on the aberrant structural and functional brain alterations of AD-spectrum patients, PubMed and Web of Science databases were searched for related articles, published from January 2000 to December 2021. Keyword searches were conducted using the following search terms: ([SCD (Title/Abstract)] OR [subjective cognitive impairment (Title/Abstract)] OR [MCI (Title/Abstract)] OR [AD (Title/Abstract)]) AND (AD [Title/Abstract]) AND ([magnetic resonance imaging (MRI)] OR [structural

MRI] OR [functional MRI] OR [DTI]). Initially, 10,608 records were identified after deduplication according to the following inclusion criteria: (1) Studies referring to brain abnormalities at the structural and functional levels in individuals with SCD or MCI due to AD; (2) original research conducted with different MRI sequences; and (3) articles published in English with easy access to full text. After preliminary title and abstract screening and further detailed full-text assessment, 10,409 records were eliminated for reasons as follows: (1) Case reports, clinical trials, study designs, and secondary literature, such as reviews and meta-analysis; (2) research based on animal models rather than population-based data; (3) studies out of topics, that is, studies lacking neuroimaging markers or focused on other neuroimaging techniques rather than MRI (e.g., positron emission tomography, magnetoencephalography, electroencephalography, *etc.*); studies focusing on SCD or MCI caused by conditions other than AD (e.g., cerebrovascular disease, Parkinson's disease, frontotemporal dementia, Lewy body disease, epilepsy, *etc.*); studies focusing on treatment and intervention; and studies focusing on other irrelevant topics. Ultimately, a total of 199 studies were included in the study. The literature selection process is shown in detail in a flowchart (Figure 1).

3. Results

3.1. BRRS

The BRRS comprises two parts: The original score (O) and variation score (V). The sum (S) of O and V is calculated (S = O + V) to evaluate individual clinical performance or features at present and further tracing (i.e., at follow-up or after a treatment) for a better clinical diagnosis, prognosis, and intervention. If the patient's condition corresponds with the statement in the BRRS, each corresponding item is given a score of 100 points (Table 1).

The initial score (S_0) is calculated is to establish the patient's risk level before receiving any medical intervention and to identify those with high risk for deterioration from others diagnosed in the same stage. The accumulated S_n (n = number of scoring time) at follow-up enables precise tracking of disease progression. By calculating the difference between the former and later scores, for instance, S_n–S_{n-1}, the rate of deterioration is reflected, and the effectiveness of the given intervention can be evaluated. It should be noted that to obtain precise group item and total scores, non-tested items must be clearly marked in both the O and V parts.

3.2. Evaluation standards of BRRS

Part O contains items referring to the evidence-based suggestions proposed in the latest research on AD

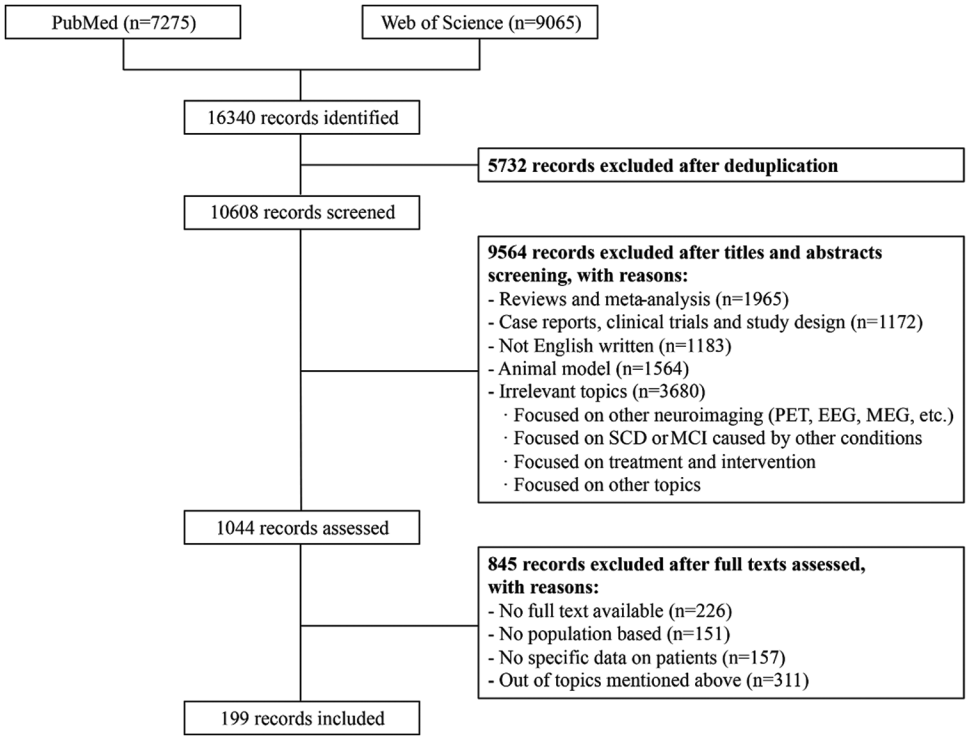

Figure 1. Flowchart of literature selection process. PET, positron emission tomography; EEG, electroencephalography; MEG, magnetoencephalography; SCD, subjective cognitive decline; MCI, mild cognitive impairment.

Table 1. Brief Risk Rating Scale.

Name: **Sex:** **Age:** **Education:** **Date:**				
Original score (O)		**Patient's score**		
		O_0	O_1	O_2
Basic information	Group score:			
	Age: >65 years (add 100 points).			
	Gender: Postmenopausal female (add 100 points).			
	Educational level: <12 years (add 100 points).			
	Pathology: (1) Detected tau protein in CSF or blood (add 100 points).			
	Pathology: (2) Detected Aβ in CSF or blood (add 100 points).			
	AD risk gene: Each gene (add 100 points).			
Lifestyle	Group score:			
	Weight: (1) Adult aged <65 years with BMI not maintained between 18.5 and 24.9 kg/m^2 (add 100 points).			
	Weight: (2) Adult aged ≥65 years with a trend of weight loss or too skinny (add 100 points).			
	History of smoking or living in a smoking environment (add 100 points).			
	Long-term history of insufficient intake of vitamin C (add 100 points).			
	Long-term history of insufficient or poor-quality sleep (add 100 points).			
	Long-term history of frailty (add 100 points).			
	Long-term history of stress (add 100 points).			
Comorbidities	Group score:			
	Diabetes history (add 100 points).			
	Head trauma history (add 100 points).			
	Cerebrovascular disease history (add 100 points).			
	Cardiovascular disease history (i.e., atrial fibrillation, hypertension, orthostatic hypotension, etc.): Each (add 100 points).			
	Depression history (add 100 points).			
	Hyperhomocysteinemia history (add 100 points).			
Variation score (V)		**Patient's score**		
		V_0	V_1	V_2
Limbic region	Group score:			
	Functional damage (add 100 points).			
	Structural damage: White matter (add 100 points).			
	Structural damage: Gray matter (add 100 points).			
	Compensation appears in function (add 100 points).			
	Compensation appears in structure (add 100 points).			
	Decompensation or the previously observed compensation disappears: Each disappearance (add 100 points).			
	WMH (add 100 points).			
Frontal region	Group score:			
	Functional damage (add 100 points).			
	Structural damage: White matter (add 100 points).			
	Structural damage: Gray matter (add 100 points).			
	Compensation appears in function (add 100 points).			
	Compensation appears in structure (add 100 points).			
	Decompensation or the previously observed compensation disappears: Each disappearance (add 100 points).			
	WMH (add 100 points).			

(*Cont'd...*)

Table 1. (*Continued*).

Name: **Sex:** **Age:** **Education:** **Date:**			
Original score (O)			**Patient's score**
			O_0 O_1 O_2
Parietal region	Group score:		
	Functional damage (add 100 points).		
	Structural damage: White matter (add 100 points).		
	Structural damage: Gray matter (add 100 points).		
	Compensation appears in function (add 100 points).		
	Compensation appears in structure (add 100 points).		
	Decompensation or the previously observed compensation disappears: Each disappearance (add 100 points).		
	WMH (add 100 points).		
Temporal region	Group score:		
	Functional damage (add 100 points).		
	Structural damage: White matter (add 100 points).		
	Structural damage: Gray matter (add 100 points).		
	Compensation appears in function (add 100 points).		
	Compensation appears in structure (add 100 points).		
	Decompensation or the previously observed compensation disappears: Each disappearance (add 100 points).		
	WMH (add 100 points).		
Occipital region	Group score:		
	Functional damage (add 100 points).		
	Structural damage: White matter (add 100 points).		
	Structural damage: Gray matter (add 100 points).		
	Compensation appears in function (add 100 points).		
	Compensation appears in structure (add 100 points).		
	Decompensation or the previously observed compensation disappears: Each disappearance (add 100 points).		
	WMH (add 100 points).		
Cerebellar region	Group score:		
	Functional damage (add 100 points).		
	Structural damage: White matter (add 100 points).		
	Structural damage: Gray matter (add 100 points).		
	Compensation appears in function (add 100 points).		
	Compensation appears in structure (add 100 points).		
	Decompensation or the previously observed compensation disappears: Each disappearance (add 100 points).		
	WMH (add 100 points).		
Total score			S_0 S_1 S_2
Note			

Aβ, beta-amyloid; BMI, body mass index; CSF, cerebrospinal fluid; WMH, white matter hyperintensity.

prevention[14,15]. It is divided into three groups: Basic information, lifestyle, and comorbidities. The basic information group consists of five items, namely, age[14], sex[16-18], education[14,18,19], AD pathological biomarkers detected in blood or cerebrospinal fluid[20-22], and AD risk genes[23-25]. The lifestyle group comprises six items that are associated with weight, diet, living environment, and sleep. The last group relates to comorbidities, such as diabetes, head trauma, cerebrovascular disease, cardiovascular disease, depression, and hyperhomocysteinemia[14]. Except for the weight item and items that have not been tested or scored points previously, there are often not too many changes in the assessment of the original score. With regard to the items that have originally scored points, despite the

improvement in the patient's condition, for example, a patient under 65 years old who scored in the weight item in S_0 but whose body mass index (BMI) has returned to normal at present, the improvement can only help to potentially slow down the rate of disease deterioration, making no difference to the reduction of the high AD risk level that has resulted from the former morbid state. Consequently, the S_n assessment of the weight items in the aforementioned case should be as follows: (1) If <65 years old but with normal BMI, no extra points will be added or deducted; (2) if over 65 years old, the weight item will be graded according to the over 65-year-old standard. As far as other items are concerned, for the same reason, once any item in O has scored points, there is no need to reappraise it at further tracing, that is, points should not be deducted, and the score should remain unchanged. Due to the minimal change in the original score regardless of whether the patient's condition becomes better or worse, it can be said to be a reliable index to assess the baseline risk level of AD patients.

Part V consists of items related to the aberrant brain alterations of AD-spectrum patients who are detected by neuroimaging techniques. As a brief scale for ease of use and promotion, we choose MRI, the most commonly used imaging modality for AD patients in current clinical practice, of difference sequences (*i.e.*, sMRI, fMRI, and diffusion tensor imaging [DTI]) for evaluation at the structural and functional levels. The evaluation standard is based on the MRI features of AD that has been comprehensively summarized from the previous studies (additional information can be found in Tables S1-S3). It has been proven that different network types and functions may exist in the same region of the brain whose alterations are not linear across the AD continuum[5,20]. Besides, the stimulation of non-invasive techniques, such as repetitive transcranial magnetic stimulation and transcranial pulse stimulation (TPS), targets the surface area of the brain and is unable to differentiate between gray and white matters or between network modules or types[13,26]. Therefore, part V focuses on six brain regions, including the limbic, frontal, parietal, temporal, and occipital regions as well as the cerebellum. Neural plasticity, which represents the adaptability and flexibility of the brain, contributes to a compensatory phenomenon against impairment in the AD spectrum, including the abnormal hyperactivation or increased connectivity in multiple brain regions[27]. This compensatory phenomenon can be viewed as a process of brain reconstruction or function remodeling to sustain optimal network functioning[28,29]; on the other hand, it can also be explained as a pathological state that may lead to further brain damage as a result of neuronal excitotoxicity[30,31]. With the progression of the disease, the compensatory ability deteriorates and eventually reaches a point of exhaustion due to extensive neurodegeneration[32]. Based on these findings, we suggest scoring each brain region by assessing the functional connectivity, structural connectivity, and compensation patterns as follows: (1) Functional damage (add 100 points); (2) structural damage of white matter (add 100 points); structural damage of gray matter (add 100 points); (3) functional compensation (add 100 points); structural compensation (add 100 points); and (4) decompensation or the disappearance of previously observed compensation (add 100 points for each disappearance). The gray and white matters are evaluated separately because there is no causal relationship in the damages between the two in AD. Meanwhile, white matter hyperintensity (WMH), which represents vascular pathology and decreasing blood flow and is considered a manifestation of cerebral small vessel disease[33,34], is associated with an increased risk of developing AD[35]. Hence, if WMH is observed, add 100 points. In every S_n evaluation, score the changes as follows: (1) Grade all changes in each brain region based on the standard and (2) no extra points added or deducted with the disappearance of WMH that was previously observed.

It is known that the development of a disease is influenced by the interactions among various factors and the modifiable network of interlocking feedback loops[12,36,37]. However, the intention of introducing the BRRS is to provide a preliminary screening and monitoring tool that can be conveniently and effectively applied in clinical settings with little additional burden added and time consumed. Therefore, we propose a method with similar items but a larger value for each item to ensure the ability to distinguish patients with a higher risk of AD progression, thus serving as a replacement for the extremely complex weighted coefficient in the interactions.

4. Discussion

4.1. Advantages and characteristic of BRRS

The BRRS may be used as a supplementary method for diagnosing AD with the following advantages: (1) Enabling objective quantification of individual differences in terms of AD risk factors and neuroimaging abnormalities; (2) enabling early identification of patients at increased risk of rapid deterioration from those diagnosed in the same stage; (3) enabling individually tailored intervention based on individual's respective scored items; (4) enabling convenient monitoring and assessment of individual's trajectories of brain changes, disease development, and therapeutic effect at follow-up; (5) reducing the time consumed and errors in calculation with the same but larger valued items, and enabling efficient judgment from

both total and individual group scores; and (6) adding insignificant burden to the diagnostic process with the ease of widespread promotion under the current AD guideline.

We recommend applying the BRRS to the AD clinical guideline in pursuit of a better understanding of AD patients. For instance, (1) if patients are in the same stage but with different S_0, more attention should be paid to those with higher scores, that is, those who are prone to deterioration; (2) if patients are in the same stage and with the same S_0, it is necessary to compare the items in each group and determine the most appropriate intervention for each patient; (3) if patients are in different stages but with the same S_0, it indicates that the patients may share similar AD risk factors and brain damage patterns despite the varying degrees of severity at the moment; the network impairment in SCD, compared with MCI and AD, is still reversible at the neuronal level; therefore, we advise implementing intensive training for SCD patients to prolong and preserve cognitive function and moderate training for MCI and AD patients in case of fluctuations in dynamic compensatory neural processes and the acceleration of the exhaustion of compensation in brain functional networks due to excessive brain activity[38]; and (4) if patients are diagnosed with different stages and S_0, both the stage and score should be considered when formulating an individually tailored intervention plan; after all, an SCD patient who scores 3000 points has a higher risk of disease progression and rapid deterioration than an AD patient who scores 100 in S_0.

4.2. Clinical application of BRRS

Although precise standards of the intensity and course of clinical treatment such as TMS, TPS, and cognitive training are still under investigation, the previous studies have proven their modulation of cortical areas or networks for compensation in the AD spectrum[39]. As a novelty, these therapeutic strategies implemented now are still in the light of the results of the previous studies and clinical experience. When designing a specialized treatment plan for individual patients with the assistance of BRRS, the total score S and the group score must not be overlooked, especially in part V. To ensure the effectiveness of treatment and prevent unnecessary intervention, the predicted improvement before every implementation must be greater than the altered S_n. With quantitative data, BRRS provides a reference for clinicians not only to set a targeted treatment protocol for patients in advance but also to evaluate the curative effect following clinical interventions. Here, we discuss the further application of BRRS in cognitive training and brain stimulation.

Cognitive training has been clinically put into practice for a period of time. It should be emphasized that cognitive differences play a key role when designing the training pattern and determining the training intensity. For example, for a patient with only memory deficits, memory training and early targeted intervention of specific brain regions are more beneficial and effective than the same standardized treatment, which can also be given to those with significant impairment in other cognitive domains. Moreover, evidence has demonstrated that trainings with higher levels of difficulty are more advantageous to patients with better performance of executive function, whereas trainings that are less challenging are more suitable for patients with poor executive performance[38]. BRRS can also help in objectively estimating patients' executive functioning.

It has been verified that high-frequency brain stimulation increases the cortical excitability of the targeted brain region, whereas low-frequency brain stimulation suppresses it[40]; additionally, there is no significant difference in the clinical effects between single stimulation and complex stimulation of multiple regions in relation to AD's known brain-affected areas[39]. Cognitive, behavioral, and functional measures can be significantly enhanced with the stimulation of the targeted brain region at a certain frequency. Consequently, we suggest formulating individual stimulation protocol based on each group score in part V of the BRRS: (1) if patients are diagnosed with only damage without any compensations in the brain region (i.e., no score in compensation items), non-excessive, effective frequency may help improve functional performance and prevent the exhaustion of compensation ability; (2) if patients have scored in compensation items (but not in decompensation), it is urgent to control the successively developing compensation with a high- or low-frequency protocol in case of exhaustion that will lead to further deterioration; (3) if patients have scored in both damage and compensation items, including structure and network (but not in decompensation), clinicians must pay close attention to the appearance of any critical patterns (e.g., brain regions continuously lose their flexibility to disease damage when modules between relevant networks gradually cluster together)[41], which indicate a high potential for decompensation; and (4) long-term intensive high-frequency stimulation has been suggested as a promising and efficient approach to rescuing the remaining well-performed function following decompensation[42,43].

4.3. Limitations of BRRS

There are still some limitations of BRRS. First, it is beyond the scope of this review to explore the weight coefficient of each item, which may to some extent affect the accuracy or credibility of BRRS. Consistent with our findings, a review has concluded that there is a preferential vulnerability of

highly selected brain regions that are primarily impaired in AD-spectrum patients, including the hippocampus, medial temporal lobe, precuneus, and temporoparietal regions[44]. Nevertheless, despite the fact that there are extensive studies on respective AD risk factors, the scarcity in comprehensive research focusing on the weight of the impact of each AD risk factor until recently makes it impractical for further discussions in this review, requiring further research to solve this in the future. In addition, although the BRRS can provide diagnostic and therapeutic guidance based on the patients' clinical performance, individual AD development rate cannot be evaluated in the early stage of application but only by means of accumulated data from the patients' total scores. Last but not least, neuropsychological testing, which we suggest to employ in conjunction with BRRS, is not included due to our consideration that it has already been widely used in clinical staging.

5. Conclusions

In this review, we propose the BRRS, a promising preliminary screening and monitoring tool based on AD risk factors and brain alteration, which can be used in parallel with the current AD guideline, with individual differences fully considered and little additional burden added. Due to its simplicity of use, the BRRS is accessible to clinicians in grassroots clinics and can be widely promoted. It has major diagnostic and therapeutic implications as it significantly contributes to realizing early and accurate identification of AD, the tracking and prognosis of AD-spectrum patients, as well as the design of individually tailored treatment in a timely manner. Furthermore, we strongly recommend that the weight coefficient of each item in BRRS be extensively studied in future research for the sake of a precise and formal application of the scale in clinical settings as soon as possible.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Ping-Hsuan Wei and Qiujie Shan
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Writing – review & editing: Feng Bai and Yun Xu

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