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PERSPECTIVES

Neurocognitive heterogeneity across the spectrum of psychopathology: need for improved approaches to deficit detection and intervention

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Neurocognition is one of the strongest predictors of clinical and functional outcomes across the spectrum of psychopathology, yet there remains a dearth of unified neurocognitive nosology and available neurocognition-targeted interventions. Neurocognitive deficits manifest in a transdiagnostic manner, with no psychiatric disorder uniquely affiliated with one specific deficit. In fact, recent research has identified that essentially all investigated disorders are comprised of 3–4 neurocognitive profiles. This within-disorder neurocognitive heterogeneity has hampered the development of novel, neurocognition-targeted interventions, as only a portion of patients with any given disorder possess neurocognitive deficits that would warrant neurocognitive intervention. The development of criteria and terminology to characterize these neurocognitive deficit syndromes would provide clinicians with the opportunity to more systematically identify and treat their patients and provide researchers the opportunity to develop neurocognition-targeted interventions for patients. This perspective will summarize recent work and discuss possible approaches for neurocognition-focused diagnosis and treatment in psychiatry.

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Neurocognitive deficits have been identified in essentially every psychiatric disorder and reflect one of the most common transdiagnostic features of child, adolescent, and adult psychopathology.[1-3] Neurocognition predicts a host of clinical outcomes in adult psychopathology, including long-term functional recovery,[4,5] overall functioning,[6] quality of life,[7] and social/occupational functioning.[8,9] Furthermore, deficits in child/adolescent neurocognition have been associated with concurrent and future psychopathology, as well as academic, global, social, and functional outcomes.[10–15] Despite the established importance of neurocognition, there is no nosology of neurocognition, and available interventions that specifically target neurocognition are limited (e.g., medication management).

Nearly, every research study to date has identified neurocognitive differences between a given psychiatric disorder and healthy controls, including the many meta-analyses documenting these differences. Despite this, there is limited evidence to suggest there are any neurocognitive differences between specific psychiatric disorders (as opposed to compared with healthy controls). Most recently, in one of the largest studies to date, Doyle et al.[16] examined intelligence, reaction time variability, and executive functioning (EF) in 486 youth referred for neuropsychiatric evaluation. All examined childhood psychiatric disorders (i.e., mood disorders, attention deficit hyperactivity disorder [ADHD], autism spectrum disorder [ASD], and psychosis) were associated with neurocognitive deficits, without significant differences between the diagnostic groupings. Furthermore, this pattern of deficits was not driven by comorbidity. The authors noted that commonly held notions of disorder-specific deficits (e.g., inhibition in ADHD) were not supported, and generally, no deficit was specific to any disorder. Within-disorder neurocognitive impairment also has significant variability: for example, bipolar disorder (adult; 27–93%),[17-19] depression (adult; 23–81%),[17-21] schizophrenia/schizoaffective (adult; 55–84%),[19] anxiety (adult; 18–50%),[18] and ADHD (50–89%).[21,22]

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Related to above, Kofler et al.[22] identified EF deficits in a majority of children with ADHD, yet deficits were divided across EF subdomains: 35% of the sample had only working memory deficits, 16% had only set shifting deficits, 13% had working memory and inhibitory control deficits, 11% had working memory and set shifting deficits, 11% had no deficits, 7% had inhibitory control and set shifting deficits, 4% had only inhibitory control deficits, and 4% had all three deficits. Additionally, a 2015 review paper found no clear neurocognitive impairments in child and adolescent depression,[23] whereas an earlier meta-analysis (2014) did conclude that neurocognitive impairments were evident in depression.[24] This highlights the significant variability that can occur in research methodology, measurement of cognition, and across individuals with the same psychiatric disorders.

The overall aim of this perspective is to discuss potential neurocognition-centric approaches to investigation and clinical care, specifically by: 1) summarizing findings from recent cluster analysis studies and 2) considering how these findings could guide improved neurocognition-focused diagnosis and treatment in psychopathology.

Neurocognitive Clusters

As noted above, the traditional approach to investigating disorder-specific neurocognitive profiles has significant limitations. An alternative is to take a neurocognition-centric approach by investigating neurocognitive profiles or phenotypes across psychiatric disorders. Such neurocognitive phenotypes may be more closely linked, for example, to underlying pathophysiological pathways and likely do not directly align with current psychiatric diagnostic criteria.[25] The development of neurocognitive phenotype nosology would allow for: 1) improved information on the natural course and outcomes of neurocognitively homogeneous subgroups and 2) development and implementation of novel cognition-targeted treatments. This conceptualization fits well within the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC), which is a framework to investigate the cross-diagnostic mechanisms underlying psychiatric symptomatology. Cognitive systems (i.e., attention, perception, language, memory, and EF) is one of the five major RDoC domains, highlighting the importance of cognition in this approach.[26] Research has already begun investigating neurocognitive phenotypes or homogenous clusters, primarily in adult psychiatric disorders (Table 1).

Adult

The cluster analysis approach has been successfully utilized in adults (13 studies) to detect neurocognitively homogenous subgroups in psychiatric disorders. Studies have examined neurocognitive clusters within specific disorders (i.e., schizophrenia, bipolar disorder, and gambling disorder)[27–31] or more commonly, across psychiatric disorders, such as examining across affective disorders,[32] across psychotic disorders,[33–35] and across the affect-psychosis spectrum.[36–39] The majority of studies identified three to four neurocognitive clusters, including a neurocognitively intact cluster and a globally impaired cluster. In addition to intact/impaired clusters, most studies also identified one or two middle groups, described as either selective impairment, mixed profile, intermediate profile, or mild–moderately impaired groups, depending on the study. Some degree of variability in the affected domain was noted across studies due to the range of assessed neurocognitive domains, although visual memory deficits, psychomotor speed deficits, and executive deficits were specifically identified. Importantly, these distinct subgroups were associated with critical clinical/functional variables, in that generally the more impaired clusters were associated to worse outcomes/variables, such as symptomology,[27,31,32,35,40–43] psychiatric episodes,[30,34] and response to clinical treatment[28] as well as years of education,[32,34] age,[31,34] employment status,[30,31] community functioning,[33] and socioeconomic status.[32]

Youth–young adult

Four studies have examined neurocognitive clusters in adolescents and young adults (12–30 years)[40–42,44] with early or first-episode psychosis. In these young people, three to four clusters were identified, including intact neurocognition, globally impaired neurocognition, and one to two intermediate groups, such as moderately impaired,[42] mixed,[44] or select visual memory and EF deficit groups.[40] In psychiatrically hospitalized adolescents/young adults with affective disorders, two clusters were identified, including one characterized by attention/memory deficits and another characterized by switching deficits.[41] Across studies, these subgroups were associated with estimates of premorbid intelligence,[40,42,44] symptomatology,[40–42] years of education,[40] and overall socioccupational functioning.[42,44] Six additional studies have been conducted in children and adolescents with ADHD,[45,46] learning disorders,[47] bipolar disorder,[43] anorexia nervosa,[48] and affective/psychotic disorders.[49] Three to four clusters were identified in each study, and when most identified the previously described intact and globally impaired subgroups,[43,48,49] there was some variability in the intermediate subgroups. The intermediate group was characterized by a moderate level of impairment in bipolar disorder,[43] a verbal/visual discrepancy in anorexia nervosa,[48] and by both an organization deficit group and memory/inhibition deficit group in hospitalized children with affective or psychotic disorders.[49]

Studies on ADHD and learning disorders obtained more specific findings secondary to a narrowed

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Table 1. Review of cluster analysis studies

First author and Year	Age/Sex	Recruitment site(s)	Sample size and diagnoses	Methods	Neurocognitive domains/tests	Country
Bora et al., 2016[37]	≥18; 65 Male	Outpatient	*N* =; 124: 97 Scz and BP, 27 HC	Latent class analysis =; four clusters: intact, severe global impairment, and two clusters of mixed cognitive profiles	ToM, EF	Turkey
Burdick et al., 2014[30]	18–65; 151 Males	Outpatient	*N* =; 284: 136 BP, 148 HC	Hierarchical cluster analyses =; three clusters: intact, selective impairment with moderate deficits, global with severe deficits	MATRICS consensus cognitive battery	USA
Cotrena et al., 2017[32]	≥18; 93 Female	Outpatient	*N* =; 153: 66 HC, 29 BP-1, 25 BP-2, 33 MDD	Hierarchical cluster analysis =; three3 clusters: intact, VF deficits, severe inhibition / flexibility impairments	WAIS-III, MMSE, five cognitive domains: three EFs, verbal fluency and divided attention	Brazil
Crouse et al., 2018[44]	12–30; 51 Female	Outpatient	*N* =; 135: psychosis-spectrum	Hierarchical cluster analysis =; three clusters: normal, mixed, grossly-impaired	Premorbid intelligence (predicted IQ); psychomotor speed; mental flexibility; verbal, learning, memory, fluency; EF	Australia
Fair et al., 2012[45]	6–17; 254 Male	Community	*N* =; 498: HC =; 213; ADHD =285	Confirmatory factor analysis, graph theory, community detection	WISC-IV, working memory, response inhibition, response variability, temporal information processing, arousal and activation, interference control, and response speed	USA
Frias et al., 2017[43]	7–17; 79 Male	Outpatient, inpatient units, community, referral	*N* =; 135: BP	Latent class growth analysis adjusted for cofounders =; three longitudinal clusters: high, moderate, and low	CANTAB	USA
Gilbert et al., 2014[28]	20–55; 81 Male	Outpatient	*N* =; 112: Scz	Cluster analysis =; three clusters: intact, global, memory/speed	Broad NP eval, but only memory, speed, WM in clustering	Canada
Hermens et al., 2011[39]	16–30; 54 Female	Outpatient	*N* =; 109: anxiety disorder, MDD, BP, or first-episode psychosis with current depressive symptoms	Hierarchical cluster analysis and discriminant function analysis =; three clusters: poor memory, poor flexibility, impaired attention/ memory	Premorbid intelligence (predicted IQ); psychomotor speed; mental flexibility; verbal, learning, memory, fluency; EF; CANTAB	Australia
Kavanaugh et al., 2016[49]	6–12; 74 Male	Inpatient	*N* =; 106: affective or psychotic disorders	Hierarchical cluster analysis =; four clusters: intact; global; organization; inhibit/memory	Standard cognitive battery	USA
Lee et al., 2017[36]	30–55; 62 Female	Community	*N* =; 143: 68 BP; 39 Scz; 36 HC	K-means cluster analysis =; two clusters: high and low	Perception, non-social cognition, social cognition	USA
Lewandowski et al., 2014[35]	18–55; 86 Female	Inpatient	*N* =; 167: 41 Scz; 53 Schizo-Affective; 73 Bipolar w Psychosis	K-means cluster analysis =; four clusters: intact, global, two mixed	Cognitive and clinical measures	USA
Lewandowski et al., 2018[33]	18–65; 56 Female	Hospital based: inpatient, outpatient, community	*N* =; 151: 120 Psychosis, 31 HC	K-means cluster analysis =four clusters: intact, global, 2 mixed	Premorbid IQ; MATRICS consensus cognitive battery	USA
Mallorqui-Bague et al., 2018[31]	18–65; 145 Male	Hospital	*N* =; 145: Gambling disorder	Twostep-clustering-component =; two clusters: mild EF deficits, severe EF deficits	Standard EF	Spain

(*Continued*)

Table 1 (*Continued*)

First author and Year	Age/Sex	Recruitment site(s)	Sample size and diagnoses	Methods	Neurocognitive domains/tests	Country
Poletti et al., 2018[47]	7–13; 132 Male	Referred for neuropsychological assessment	*N* =; 205: Specific learning disorder (SLD)	Hierarchical cluster analysis =; four clusters: low verbal, low coding, low EF, low reasoning/EF	WISC	Italy
Potter et al., 2010[27]	17–55; 105 Male	Outpatient and Community (HC)	*N* =; 73 Scz and 74 Matched HC	K-means cluster analysis =; three clusters: intact, global but average reading, global	IQ	USA
Reser et al., 2015[40]	15–25; 86 Male	Early Psychosis Prevention and Intervention Centre	*N* =; 128: First-episode psychosis	Hierarchical cluster analysis =; four clusters: intact, low, visual memory, EF	Clinical and cognitive battery: Memory, EF, speed, language, visuospatial	Australia
Rose et al., 2016[48]	9–18; 253 Female	Outpatient and Secondary schools (HC)	*N* =; 423: 253 Anorexia (AN) disorder; 170 HC	K-means cluster analysis =; three clusters in AN: low average to average, verbally strong all intact, verbal/vs discrepancy	Standardized neuropsychological assessment battery	United Kingdom, Norway, Germany, Switzerland
Russo et al., 2017[29]	18–65; 111 Female	Hospital	*N* =; 180: 60 BP; 49 unaffected siblings; 71 HC	Cluster analysis =; three clusters: global, intact, selective	Attention and processing speed, verbal learning and memory, EF, premorbid IQ	USA
Sauve et al., 2018[34]	17–50; 149 Male	Early Psychosis Prevention and Intervention Centre: emergency department, inpatient, self, family member	*N* =; 201: Psychosis 80 first-episode of psychosis; 121 multiple episodes of psychosis; 55 HC	K-means cluster analysis =; three clusters: normal, generalized< intermediate	CogStateSchizophrenia Battery	Canada
Tickell et al., 2019[41]	16–30; 38 Female	Inpatient	*N* =; 50 inpatients with affective disorder	Hierarchical cluster analysis =; two clusters: attention/memory; switching	Demographics, clinical features, cognition	Australia
Uren et al., 2017[42]	15–25; 88 Male	Early Psychosis Prevention and Intervention Centre	*N* =; 133: first-episode of psychosis; 46 HC	K-means cluster analysis =; three clusters: global; intact; moderately impaired	Social cognition, processing speed, attention and working memory, visual organization and memory, verbal comprehension	Australia
Banaschewski et al., 2012[60]	5–17; 362 Male	Prior studies: Random population cohort study, Endophenotype Research, and clinical ASD-ADHD genetic study	*N* =; 644: 109 ADHD, and 58 ASD_ADHD, 59 ADHD_ASD and 418 non-affected siblings	Latent class analysis =; five classes: two without behavioral problems, one with only ADHD behavior, and two with both clinical symptom levels of ASD and ADHD but with one domain more prominent than the other (ADHD[_ASD] and ASD[_ADHD])	Comorbid symptoms and cognitive profiles of motor speed and variability, EF, attention, emotion recognition, and detail-focused processing style.	The Netherlands
van Hulst et al., 2015[46]	6–25; 52 Female	Outpatient	*N* =; 217: 96 ADHD and 121 HC	Latent class model =; three subgroups	Cognitive control, timing and reward	The Netherlands
van Rheenen et al., 2017[38]	18–65; clinical sample 617 Male	Four prior studies examining cognition in psychiatric illness	*N*= 1541: 564 Scz; 402 BP; 575 HC	Hierarchical clustering analyses =; three clusters: severely impaired; mild–moderately impaired; relatively intact	MATRICS consensus cognitive battery	Australia and USA

ToM =; Theory of mind; EF =; Executive functioning; HC =; Healthy control; MDD =; Major depressive disorder; BP =; Bipolar disorder; Scz =; Schizophrenia; CANTAB =; Cambridge Neuropsychological Test Automated Battery; MATRICS =; Measurement and Treatment Research to Improve Cognition in Schizophrenia; VF: Verbal Fluency; NP: Neuropsychological; WM: Working Memory.

neurocognitive focus. In learning disorders, identified subgroups were characterized by low verbal functions, low processing speed, low EF, and low reasoning/EF subgroups.[47] In one ADHD study, subgroups were characterized by attentional variability, low EF (two sub-subgroups), low processing speed, and low arousal (two sub-subgroups),[45] whereas in another, subgroups included intact neurocognition, low cognitive control, and variable response timing.[46] Only in bipolar, ADHD and affective/psychotic disorders were these subgroups associated with clinical/demographic variables, such as symptomatology, overall functioning, and medication status.[43,46,49] When collapsed into two subgroups in one study (i.e., nonmild impairment vs moderate–high impairment), additional differences were detected in number of diagnoses/medications, age, and length of hospital stay.[49] As exemplified here, the variability in utilized measures resulted in greater degree of inconsistency in child/adolescent studies compared with young adult/adult studies.

Diagnostic Consideration

In clinical practice, knowing the patient's specific psychiatric diagnosis provides very limited information on his/her neurocognitive status, as the patient may theoretically possess one of the three to four possible neurocognitive phenotypes of psychopathology. Even when the psychiatrist, psychologist, or other mental health provider has results from the clinical neuropsychological evaluation, the lack of neurocognitive diagnostic nosology leaves clinicians dependent on qualitative interpretations of neurocognitive strengths and weaknesses. The field is moving toward improved quantitative interpretation of evaluation, but qualitative differences between neuropsychologists remain.[50] A unified nosology for neurocognitive status in psychopathology is needed for improved assessment and care of neurocognitive deficits, although how this classification will manifest is still unclear.

The development of a formal nosology for psychopathology-related neurocognitive impairment should focus on characterizing the neurocognitive status of the patient, independent of the specific psychiatric disorder(s). As described by Schoenberg et al.,[50] non-neuropsychologists prefer to see neuropsychological results as one of the three categories to most clearly communicate important findings: abnormal (and related to brain dysfunction), normal, or equivocal (may be mild impairment or normal variability). Too many (e.g., mildly-to-moderately impaired, moderately impaired, etc.) or too few (i.e., abnormal or normal) categories are reportedly undesirable to referring clinicians.[50] To build upon clinical classifier and cluster analysis work, the field may benefit from clinical care and research studies universally classifying each patient/participant into one of the three to four categories: 1) intact neurocognition, 2) globally or definitively impaired, 3) mixed, intermediate or mild impairment, and 4) equivocal as to whether findings reflect normal variability or mild/early impairment.

Arguing for a universally administered battery of neuropsychological tests is beyond the scope of this article. However, universal reporting of domain composite scores and an overall composite (regardless of the preferred clinical tests) would provide a wealth of information in clinical/research work. The global deficit score (GDS) by Heaton and colleagues utilizes a well-defined, 5-point scale to categorize performance from intact (0) to severe impairment (5)[51] for each test performance. This is then averaged to create the composite GDS score. A GDS cutoff score of ≥0.5 has been long utilized in HIV research to accurately detect neurocognitive impairment.[51] More recently, the GDS has been paired with measurement of activities of daily living (ADL) to accurately classify HIV affected adults with and without HIV-associated neurocognitive disorder, including HIV-associated dementia (i.e., GDS ≥ 1.5 with severe ADL decline), asymptomatic neurocognitive impairment (i.e., GDS ≥ 0.5 without ADL decline), and minor neurocognitive disorder (i.e., GDS ≥ 0.5 with ADL decline).[52] The approach Heaton and colleagues have taken in their work with HIV populations is the exemplar of classifying neurocognitive impairment with neuropsychological rigor in a digestible and generalizable manner. Calculating the GDS for a given battery of tests and utilizing 0–0.5 to indicate intact, 0.5–1.5 to indicate mild/intermediate impairment, and 1.5+ to indicate global or definitive impairment could be a promising approach in work with psychiatric populations.

Continued work is needed to investigate the prevalence of neurocognitively homogenous syndromes, and their associated clinical, functional, and neurobiological characteristics. Eventually, neurocognitive status could be listed as a specifier with the diagnosis, broken down into the previously described, empirically based three or four categories (with specific deficits then listed). This could be similar to currently available neurocognitive symptom codes within ICD-10, for example, EF deficit (R41.844), psychomotor deficit (R41.843), visuospatial deficit (R41.842). Alternatively, within the current DSM-5, mild and major neurocognitive disorders are currently utilized to capture the neurocognitive deficits that occur in a host of medical/neurological disorders. Currently, major neurocognitive disorder requires deficits to be two standard deviations below the mean, whereas minor neurocognitive disorder requires deficits to be one to two standard deviations below the mean. At present, neurocognitive deficits secondary to psychiatric disorders are a rule-out in these neurocognitive disorders, and thus, this diagnostic entity cannot currently be applied to psychopathology. As such, inclusion of psychopathology as an etiological entity for

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neurocognitive disorder (in the same manner as current medical/neurological etiologies) could provide a comprehensive nosology that would improve identification and subsequent treatment of psychopathology-related neurocognitive deficits.

Treatment

It is important to obtain data on neurocognitive deficits in specific psychiatric disorders as well as their association to symptom severity. However, the field must continue to develop an alternative, parallel pathway that takes a (transdiagnostic) neurocognition-centric approach. This approach is consistent with the NIMH's new call for examination of constructs in heterogeneous populations. For example, instead of studying a specific diagnosis (e.g., ADHD), investigations could study a specific neurocognitive deficit (e.g., response inhibition deficit) in a range of participants, from healthy controls to those with a range of psychiatric disorders. Furthermore, intervention studies would only recruit those with documented neurocognitive deficits in a specific domain and randomize participants to active/sham intervention conditions (and thus, only treat those in need of intervention). Reduced reliance on diagnosis may create initial challenges in recruitment/enrollment, as our clinical referral sources have patients with diagnoses, but do not as often have patients with identified neurocognitive deficits.

The lack of unified neurocognitive nosology to be used in conjunction with psychiatric disorder classification has limited the development and implementation of novel neurocognition-targeted interventions. As has been described above, not everyone with a given psychiatric disorder will have neurocognitive deficits, and therefore, not everyone with a psychiatric disorder will need or respond to a specific neurocognitive intervention. For example, repetitive transcranial magnetic stimulation (rTMS), which is an evidence-based, clinically available treatment for treatment-resistant depression, may have an effect on neurocognition. Its effects have been examined as a secondary variable, not as the target of an intervention, in prior research and has been limited and/or inconsistent in neuropsychiatric conditions.[53] However, when studies have more specifically targeted underlying brain activity (e.g., oscillations) and a clearly defined neurocognitive function (e.g., working memory), preliminary results have been promising. Studies have found that rTMS (compared to sham) at the dorsolateral prefrontal cortex has led to enhanced frontoparietal gamma and theta oscillations during working memory demands and subsequently improved working memory performance.[54,55]

For cognitive training (CT), clinical results in ADHD have found a select effect on neurocognition but not a corresponding improvement in clinical symptomatology.[56] However, in other work, theta[57] and gamma power[58] oscillations increased after CT within frontoparietal regions during cognitive demands.[57,58] Such oscillatory changes were associated with enhanced cognitive control performance.[58] Consistent with the foundational principle that those with deficits will be the ones to respond to cognitive interventions,[59] one reason for limited outcomes of neurocognitive interventions (e.g., TMS/CT) could be due to the fact that many of the patients had an intact neurocognitive profile at baseline, with limited room to improve, that is, there was a ceiling effect.

Conclusions

Neurocognitive deficits are one of the most significant predictors of outcomes in child/adolescent and adult psychopathology. There is no consistent evidence of significant across disorder neurocognitive deficits, yet there is a significant degree of within-disorder variability in the rate of neurocognitive impairment. A novel approach to investigating psychopathology-related neurocognition is to identify the neurocognitively homogenous clusters or phenotypes. A wealth of adult research has consistently identified intact neurocognition, globally impaired neurocognition, and mixed/intermediate impairment phenotypes, with these phenotypes associated with distinct clinical/functional variables. Recent clinical work has similarly recommended classification into intact, impaired/abnormal, or equivocal labels. Importantly, no studies have identified a direct association between a specific diagnosis and a specific neurocognitive subgroup; neurocognitive subgroups often consist of individuals with a range of different diagnoses as well as healthy control participants. Thus, these subgroups are not merely a reflection of the already established psychiatric diagnostic classification, but alternatively, reflect their own neurocognitively homogenous subgroups of patients. Preliminary work in child/adolescent psychiatry has been consistent with adult findings, but further work is needed.

These findings have critical implications for neurocognitive assessment, research, and treatment. The field would benefit from more formalized terminology or classification of these within-disorder neurocognitive phenotypes. Universal utilization of indicators such as intact, impaired, mixed, or equivocal for clinical evaluations could move the field forward, whereas research could subsequently examine clinical and/or neurobiological characteristics of these subgroups. Future work might include providing a specifier in the psychiatric diagnosis. Finally, we must begin to develop and test possible neurocognition-targeted treatments in neurocognitively impaired phenotypes (such as the utilization of rTMS for EF) in order to improve long-term clinical and functional outcomes of these patients.

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