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Review Article

The Neuropsychology of Frontal Lobe Epilepsy: A Selective Review of 5 Years of Progress

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Abstract

The neuropsychological consequences of Frontal Lobe Epilepsy (FLE) are not as well characterized as those of temporal lobe epilepsy. In the past 5 years though, new advances in behavioral assessment and imaging techniques have begun to more fully elucidate the cognitive, behavioral, and emotional sequelae of these conditions, especially in children. This review summarizes the recent advances in understanding the neuropsychology of FLE, and points out future directions for growth in this rapidly evolving area.

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ABBREVIATIONS

FLE: Frontal Lobe Epilepsy; TLE: Temporal Lobe Epilepsy; TOM: Theory of Mind; AED: Antiepileptic drug; JME: Juvenile Myoclonic Epilepsy; EF: Executive Functioning; NFLE: Nocturnal Frontal Lobe Epilepsy; NIH: National Institutes of Health

INTRODUCTION

The frontal lobe and epilepsy- relatively unexplored territory

Our understanding of the temporal lobes, the nature of memory, and the neuroanatomy of language owes an enormous debt to the willingness of patients with Temporal Lobe Epilepsy (TLE) to participate in research with basic and clinical neuroscientists over the years. Due to its relatively high prevalence and the potential for amelioration with surgical treatments, the neuropsychology of TLE has been well delineated [1,2]. In contrast, the neuropsychology of the Frontal Lobe Epilepsies (FLE) is not as well defined. The enormous functional diversity of the frontal lobes explains some of this lack of clarity. The frontal lobes account for about a third of the cortex and regulate or are implicated in a host of functions: speech production, motor control, motor planning and programming, oculomotor control, problem solving and reasoning, social regulation, motivation/drive regulation, and affective regulation, just to name a few [3]. Furthermore, the frontal lobes have direct and indirect associations with basic sensory, motor, and most other functional brain networks. Epileptic disruptions in the frontal lobes may have varied presentations depending on the networks and connections impacted. Finally, FLEs are not unitary in cause, as they can have an enormous degree of variability in the etiology, developmental course, and genetic factors causing the underlying disorder [4].

Given the variable presentations of patients with these conditions, much has been written in recent years reviewing the individual FLE syndromes from a clinical or epileptology standpoint (see reviews on orbitofrontal and insular epilepsies [5]; epilepsies of the dorsolateral and prefrontal cortex [6]; medial FLE [7]; and more general overviews of the FLE) [8-10]. However, reviews focusing specifically on the neuropsychology of FLE have either predated the rapid expansion of neuroimaging research [11], or focused on particular syndromes such as the neuropsychology of pediatric FLE [12,13]. Thus, to build on these previous works, this paper attempts a selective review on the neuropsychology of FLE across disorders and the lifespan, focusing on advances made in the last 5 years since Patrikelis' comprehensive review [11].

Lessons learned from the neuropsychological phenomenology of frontal lobe epilepsy

Cognition: In recent years, the cognitive difficulties accompanying FLE have been increasingly recognized, particularly in children. For example, in comparing a group of children with mixed seizure etiologies, children with FLE were more likely to have lower IQ's, even after excluding cases with frank intellectual disability, than other seizure groups [14]. While devastating developmental conditions such as autism are not commonly viewed as a direct consequence of FLE in isolation, at least two recent case studies linked subtypes of nocturnal FLE with autism and severe intellectual disabilities [15,16].

Despite trends toward more global impairments in this population, there is enormous heterogeneity in the cognitive outcomes of children with FLE. The risk factors for developing these impairments though are unclear. Luton and colleagues found that more cognitive problems were present in children with an earlier onset of seizures [17]. This in turn implies that the early onset of FLE alters the developmental course of the brain, of which abnormal cognition is one manifestation. As straightforward as this hypothesis is, it is not universally supported by other studies. Braakman undertook a comprehensive neuropsychological study of 71 children with cryptogenic FLE [18]. Across measures, the patients demonstrated a host of cognitive and behavioral impairments. Interestingly though, epilepsy related variables such as duration, seizure frequency, and age of onset had relatively little relationship with the neuropsychological difficulties observed.

Moving away from broad cognitive constructs such as IQ, other cognitive functions may be more directly impacted by FLE. Though not synonymous with the frontal lobes, Executive Functioning (EF) – the ability to initiate volitional responses, plan, decide, and monitor performance– [19] is one of the most frequently impaired cognitive constructs in FLE. Longo and colleagues compared a host of cognitive abilities in FLE and other seizure groups and found that difficulties with concept formation (an aspect of EF) were uniquely related to FLE, while other problems such as attention and working memory disorders were equally impacted in all patient groups [20]. These difficulties may be present in non-epileptic relatives of FLE patients, suggesting a genetic contribution to the cognitive impairments that is independent of the underlying epilepsy [13].

Outside of EF, other cognitive domains remain relatively unexplored in FLE. For example, the neuropsychology of memory is well demarcated in TLE, as consolidation of memory via mesial temporal lobe structures is relatively well understood [4]. However, the frontal lobes have a critical role to play in a host of memory functions as well, including organization and encoding of information to be learned, memory retrieval, and prospective memory [21]. A well-designed study by Johnson-Markve and colleagues compared a group of 34 FLE and 34 TLE patients on a host of measures, including tasks sensitive to the organizational and meta-aspects of memory [22]. This study generally found equivalent difficulties across standard memory measures in the groups. However, FLE patients had more difficulty with a selective reminding task that requires a clear strategy in addition to more basic recall processes. Thus, memory tasks that focus on strategy of acquisition as well as recall may be particularly helpful in differentiating temporal versus frontal memory problems. The fact that memory is not just a temporal lobe process was also highlighted by Giovagnoli et al who analyzed the various task components necessary to draw items from memory [23]. In this study, the FLE patient's difficulties drawing items from memory were more strongly related to performance on executive function tasks, while the TLE patients demonstrated difficulties more related to semantic memory stores. Again, this study highlights inexorable links between the frontal and temporal lobes in remembering information.

In addition to memory and EF, attention and processing speed difficulties can be found in FLE. Gottlieb and colleagues evaluated children's ability to process information quickly and manipulate information in working memory, tasks measuring a domain of cognition referred to as cognitive proficiency [24]. Children with anterior lesions or right-sided FLE seemed to have more difficulties with these tasks relative to temporal lobe patients, even after accounting for general cognitive abilities and other factors. Thus attention and working memory may represent another important type of cognitive difficulties in FLE.

As can be noted in the above review, continued work is being done on elucidating the basic cognitive manifestations of FLE, with much of that work occurring in children. However, more complex cognitive constructs such as social-behavioral reasoning may be impacted by damage to the frontal lobes [3]. In FLE, only limited work has been done studying these issues. Giovagnoli looked at one aspect of social reasoning, known as Theory Of Mind (TOM) [23]. TOM requires an individual to be able to see the world through another's perspective. For example, evaluating a scene to identify what is appropriate or inappropriate behavior requires individuals to respond from another's cognitive or social perspective. Interestingly, patients with FLE demonstrated subtle difficulties on these tasks, such as having more difficulty identifying social faux pas. This difficulty was related to the duration of epilepsy in these patients.

The cognitive difficulties demonstrated by patients with FLE can be a rich source of data about the brain and its functions. However, an equally important but relatively unexplored question is the extent to which these cognitive difficulties interfere with day-to-day functioning. Cahn-Weiner and colleagues performed a unique study in this regard, evaluating how patients with frontal and temporal lobe epilepsies perform on a host of daily cognitive tasks [25]. While they hypothesized a double dissociation (more difficulties with memory for daily tasks in TLE patients and more difficulties with judgment in FLE patients), this hypothesis was rejected. Instead, regardless of epilepsy type, both groups struggled with most of the aspects of cognitive related daily tasks, suggesting subtle, but measurable functional impairments in both patient groups. Furthermore, in a follow-up to the previously mentioned TOM study, Giovagnoli et al found that TOM difficulties were associated with decreased quality of life and increased mental health concerns [26]. In sum, these studies suggest that cognitive difficulties in FLE patients have real world consequences, and are potential targets for intervention in order to improve daily functioning outside the lab.

Emotional: While mood disturbances have long been recognized in patients with epilepsy [4], there has been relatively limited work in recent years to further elucidate their causes, consequences, or treatment options in FLE. Within the pediatric literature, externalizing and behavioral disorders have been identified as more common in children with FLE [18]. From a neurological standpoint, it is noteworthy that while these disorders were common, they were not strongly related to epilepsy factors such as duration. Researchers note that searching for the underlying cause of emotional or behavioral disturbance will require evaluating the interaction of cognitive, biological, seizure, genetic, and environmental factors that influence the manifestation of these disorders.

In adults, while depression has garnered the bulk of the research [27], anxiety is also a prominent and treatable emotional condition. In 2012, Tang and colleagues found that when compared to a generalized epilepsy group, FLE patients experienced more anxiety. This anxiety was related to a host of different epilepsy factors including seizure frequency and the numbers of anticonvulsants being utilized [28]. However, there remain many questions to be answered about the development and maintenance of mood disorders in patients with FLE.

Behavior: Unusual behaviors are not uncommon in FLE, and can make differential diagnosis quite challenging. Thus, case studies of behavioral manifestations of FLE can provide important insights into the underlying neurobiology of behavior, as well as important clues for distinguishing between neurological and psychiatric conditions. For example, the majority of automatisms in FLE occurs during the ictal state and is stereotypic: chewing, lip smacking, clapping, handshaking, kissing, sucking and other simple movements. However, less commonly, complex movements can be seen. Jahodova reported a case of an automatism described as a "wet dog shakes", marked by complicated shuttering attacks [29]. Carota reported a case of utilization behavior where, during the ictal state, their patient would incorrectly use her cell phone, dialing wrong numbers with a confused look on her face and talking into the phone to nobody [30]. Other less common examples include ictal singing [31], gelastic laughing without mirth [32], palilalia & echolalia [33], stuttering, and aphemia [34].

As noted above, behavioral manifestations of FLE can be quite varied and complex. Triggers of FLE seizures can also be quite complex. For example, eating epilepsy was reported by Patel, who described a case where FLE seizures were provoked by movements or senses associated with the act of eating (chewing, swallowing, and eating a particular type of food) which suggested involvement of the olfactory and gustatory system [35].

Moving beyond ictal behavior, interictal behavioral conditions appear to be fairly common in FLE. Such conditions can include obsessions and compulsions, personality disorders, depression, attention deficit hyperactivity disorders, and other psychiatric condition [4]. Differences between FLE and TLE in these manifestations have been well documented. Pizzi noted that FLE patients reported more behavioral difficulties such as emotional distress and unstable behavior relative to TLE patients, though groups were similar in their level of depression [36]. Thus, while some degree of emotional overlap is shared between these conditions (i.e. difficulty coping with a chronic medical condition) the involvement of the frontal lobes in FLE may lead to increased behavioral dysfunction. Attention deficit hyperactivity disorder (ADHD) can be more common in children with FLE. Zhang noted that as many as 59% of children in their series would meet diagnostic criteria for ADHD [37]. The author hypothesized that these behavior difficulties may be related to epilepsy itself, with complications arising from the underlying cause of the FLE, from AED treatment, or a combination of the above factors. In the extreme, anti-social behavior can be observed in FLE. Though uncommon, Trebuchon reported a case series of a pattern of antisocial behaviors stemming from FLE [38]. Notably, these patients' behavior improved following surgery, suggesting that addressing the underlying epileptic cause may lead to improved behavioral outcomes.

Sleep is also a complex neurobehavioral construct that can be disturbed in some forms of epilepsy. For example, Nocturnal Frontal Lobe Epilepsy (NFLE) is a specific form of FLE that can be quite difficult to diagnosis given the similarity in appearance of more traditional parasomnias and a tendency to have a normal EEG. However, Elmi notes differences between the behavioral presentation of NFLE and non-epileptic parasomnia [39]. NFLE causes stereotypic events occurring multiple times per night lasting approximately 90 seconds. It occurs during earlier sleep stages, and is associated with bedwetting and kicking. Conversely, non-epileptic parasomnias tend to occur once a night in the deep stages of non-REM sleep, may last up to 30 minutes, and are usually not seen after the age of 10. Clearly, the complex involvement of the frontal lobes in sleep and the behavioral manifestations of sleep associated difficulties merits further study.

Given the myriad and complex motor and psychiatric manifestations that a disturbance in the frontal lobes can produce, diagnosis of FLE can be quite complex. Riggio suggests that the degree of stereotypy can be helpful in identifying FLE related behavioral problems [40]. Combining such careful observation with our knowledge of the neuropsychology of the frontal lobes can lead to better localization and diagnosis.

Beyond the "What": Understanding the "Why" of Cognitive and Behavioral Difficulties in FLE

In recent decades, the rapid expansion of neuroimaging has led to unprecedented insights, confirmations, and controversies in understanding neuropsychology in normal and clinical populations [41]. It is encouraging that these techniques have, in recent years, expanded our knowledge of the basic biological mechanisms underlying cognitive and behavioral dysfunction in FLE patient groups, particularly children. Here, we review the imaging correlates of cognitive, behavioral, and emotional phenomena in FLE patients.

Structural Imaging: From a structural standpoint, the evolution of volumetric techniques has allowed for quantification of particular brain regions of interest in patients with FLE. One of the most active research areas for this type of work has understood the relationship between frontal lobe volume and the executive and behavioral disorders which are increasingly recognized in Juvenile Myoclonic Epilepsy (JME). Indeed, Pulsipher's lab demonstrated that EF and behavior problems in children with JME correlate with frontal lobe gray matter and thalamic volumes, implicating this fronto-subcortical loop in behavioral dysfunction in these patients [42]. However, an attempt at replicating these findings in an independent sample failed as Roebling did not find volumetric differences in JME patients and controls, and did not see differences in an fMRI working memory paradigm [43]. Behaviorally however, JME patients in this study performed slightly worse than controls on some measures, but the neuroanatomical and functional correlates were absent. Thus, the authors of this study conclude that other factors such as the genetic diversity of JME conditions or the cognitive effects of AED need to be considered when

drawing conclusions about the underlying causes of behavioral difficulties in these conditions.

Outside of JME, work in other FLE conditions has revealed volumetric differences associated with neuropsychological difficulties. Idiopathic generalized epilepsy is associated with reduced frontal lobe volumes at baseline, and a reduced expansion of white matter development over time, thus implicating changes in brain development in this condition [44]. The functional or cognitive consequences of this abnormality were not studied; and indeed, as noted above, the relationship between cognition and imaging findings is not always clear-cut. For example, patients with childhood absence epilepsy had smaller gray matter volumes in the left orbitofrontal gyrus and both temporal lobes compared to age and gender matched children without epilepsy [45]. However, these volumes were related to demographic and pregnancy complications, not IQ and psychopathology variables in patients; in the control group gray matter volume was associated with IQ. This highlights the complexity of deducing the causes of behavioral difficulties and, highlights the need for a developmental approach to such studies, systematically addressing the host of medical, seizure, and cognitive variables which might be related to obtained imaging data.

One example of this type of work is Kanemura's group who has used volumetric analyses to study longitudinal changes in brain volume over the course of treatment for FLE. This group found reduced frontal lobe volume in a child with continuous slow wave sleep epileptiform discharges in comparison to controls and 2 children with other epilepsies [46]. Interestingly, the volume improved with AED treatment and resolution of the seizures. However, such a hopeful outcome was not found in all of their case studies. In a child with Benign Childhood Epilepsy with Centrotemporal Spikes (BCETS), reduced brain volume and behavioral problems remained even after resolution of the seizure disorder [46]. Using larger samples and techniques, Kanemura found a similar pattern; patients with BCETS who demonstrated baseline cognitive and behavioral abnormalities showed reduced frontal lobe volumes, which tended not to improve over time unless the years of seizure disorder was well controlled [47]. Similarly, in a case series of patients with FLE, a pattern of reduced frontal lobe volume was found in those who had behavioral difficulties; and, patients without behavioral disturbance showed a pattern of growth in the frontal lobes that mirrored controls over time [48].

While structural changes in the frontal lobes have garnered a great deal of research attention in FLE, Widjaja hypothesized that the rich cortico-cortico connections implicated in FLE could lead to cortical thinning in extra-frontal regions as well [49]. Their findings supported this, with widespread thinning in in the parietal, temporal, and frontal lobes of FLE patients, consistent with the notion that frontal lobe seizures may have widespread impacts on the cortex. What this study did not include were cognitive measures, so the functional correlate of this finding remains unexplored.

Diffusion Tensor Studies: In addition to brain volumes, diffusion tensor imaging (DTI) studies have allowed for exploration of white matter abnormalities in FLE. Holt found that children with drug resistant epilepsy had abnormalities in the superior longitudinal fasciculus relative to controls [50]. Differential patterns in corpus callosum integrity, volume, and diffusivity have been demonstrated in FLE and TLE, with thinning in areas connecting the frontal lobes in FLE and temporal lobes in TLE. Decreased whole brain white matter integrity has been described in children with FLE relative to controls, which did not correlate with seizure characteristics [51]. Given this finding, it may be that the white matter abnormalities are associated more with a maturational differences than injuries from the seizures per se.

Similar to the findings in the gray matter literature, white matter differences appear to have neuropsychological significance. Braakman demonstrated that cognitively impaired children with FLE showed increased posterior white matter abnormalities [52]. Similarly, Wang et al found that in adults with FLE and diffuse frontal lobe white matter changes, the left frontal lobe white matter in particular was associated with global cognitive status [53]. However, the correlation between white matter changes and behavior is also not always supported. For example, Kim and colleagues showed evidence of diffuse white matter abnormalities and behavior problems in JME patients [54]. Interestingly, the degree of white matter changes correlated with frequency of seizures, not the cognitive or behavioral variables.

While much work remains to be done in understanding the functional significance of white matter changes in FLE, these studies hold the tantalizing prospect of explaining many phenomenological peculiarities in these conditions. For example, patients with JME have a tendency to have myoclonic jerks in association with cognitive activity. An elegantly designed study of white matter in JME revealed a pattern of abnormalities that may explain this phenomenom [55]. In this study, JME patients had increased connectivity between cognitive and motor regions in the frontal lobes relative to controls, but reduced connectivity between anterior regions (presupplementary motor area and orbitofrontal regions). Thus, cognitive activity may hyperactivate motor systems, but cognitive regions may be relatively disconnected. Finally, the hyperconnectivity of the frontal and occipital lobes was also identified, thus suggesting a possible pathway, which allows for photic stimulation to elicit these seizures.

Functional neuroimaging: In addition to structural techniques, functional neuroimaging has begun to offer new insights into the mechanisms by which cognition is impaired in FLE. Centeno used fMRI to demonstrate that patients with FLE had to activate a broader network of frontal lobe areas when encoding new information relative to controls [56]. Thus, the processes underlying encoding of information were impacted by the condition. Another study by Chaudhary and colleagues evaluated both EEG and fMRI during a working memory paradigm [57]. This study found that as task complexity increased, so did epileptic discharges in FLE patients. This in turn seemed to modify hemodynamic response to the task as quantified by fMRI. Thus, fMRI studies hold the potential to explain the underlying functional system abnormalities that may lead to impaired cognition.

Outside of the memory domain, impulsivity may be associated with an abnormal activation in the frontal lobes in individuals

with JME. Abnormalities in the resting state network activation of children with FLE were associated with executive dysfunction [51]. Similarly, Wandschneider and colleagues demonstrated that patients with JME demonstrated less learning from previous experiences on a gambling task [13]. This impairment in learning was correlated with a more diffuse pattern of fMRI activation during a working memory task. The authors suggested that even interictally, JME patients' abnormalities in frontal lobe function were related to their difficulties learning from previous experience.

Functional imaging has also allowed scientists to evaluate not just how networks activate during cognitive processing in FLE, but how these networks are organized [58]. In this study, children with FLE showed very similar patterns of activation during a visual search task relative to controls. However, their networks showed stronger modularity than controls. This finding suggests that while the individual cognitive centers control and FLE children utilized in this task were similar, the individual modules did not "talk" to each other as efficiently. In turn, this degree of modularity was associated with reduced performance on the task. In contrast and using different methodologies, JME was associated with increased motor and cognitive linkage during cognitively demanding tasks, suggesting that increased seizure frequency while under cognitive demand may be explained by too much activation and communication among brain regions during these tasks leading to symptoms [59]. While still preliminary, such studies highlight the ways in which combining structural and functional information is necessary to explain the heterogeneity of cognitive performances in patients with FLE.

Other methods of imaging have not been utilized as often in studying cognition in FLE, though they may provide useful insights. We found only one study of magnetic resonance spectroscopy in an FLE neuropsychological study in recent years [60]. This study revealed that patients with JME and behavioral or personality difficulties had a higher N-acetyl-aspartate/creatine ratio in the left frontal lobe, as well as an increase in glutatmate ratio relative to the above. De Araújo Filho et al hypothesized that this may be a biomarker of these behavioral difficulties in JME patients [60]. Again, such research is very preliminary and not frequently utilized in this patient population.

Genetics: In recent years, the genetic contributions to epilepsy have garnered increasing research attention [61]; but, the behavioral and cognitive influence of genetics and epilepsy have not been as thoroughly studied. Iqbal and colleagues studied the neuropsychological functioning of children with JME, and their siblings [62]. They found neuropsychological dysfunction in both patients and unaffected siblings. Their hypothesis was that JME was just one manifestation of an underlying genetically linked fronto-subcortical dysfunction. While this is an intriguing hypothesis, further research is clearly needed. Another avenue of genetic and behavioral interactions in FLE stems from studies of cohorts with genetic linked nicotinic receptor abnormalities, which are associated with nocturnal FLE. Interestingly, families who share these genotypes also seem to have greater than expected cognitive dysfunction, particularly executive and memory dysfunction [63].

Neuropsychological outcomes or treatments for frontal lobe epilepsy

Medication: Little additional work has evaluated the interaction of frontal lobe epilepsy and medication effects, despite the possibility of an interaction between the pathological process of epilepsy and AED effects on cognition [64]. For example, topiramate has been shown to be associated with cognitive difficulties, particularly language dysfunction in patients and controls alike [65]. In FLE patients, Yasuda et al demonstrated that the addition of topiramate when combined with other agents was associated with increased abnormalities in the default mode network, which in turn seemed to be associated with reduced verbal fluency [66].

Surgery: Resective surgery for TLE tends to have a more favorable prognosis relative to extratemporal resective surgeries, including those performed for FLE [67]. However, moving beyond seizure outcomes, there remain many unanswered questions about neuropsychological outcomes from frontal lobe resective surgeries.

As noted above, in the developing brain, longer duration of seizures may be associated with more cognitive and behavioral difficulties. When considering neuropsychological outcomes of frontal lobe resections, children who wait longer to undergo surgery may be at increased risk for cognitive difficulties, which precede and continue after surgery [68]. Simasathein and Pinheiro-Martins both stress the importance of earlier intervention to maximize both epileptic and neuropsychological outcomes [69,70]. Even in cases with a good outcome from a seizure standpoint, there is a risk of cognitive decline post surgically. Chieffo reported a case series of children undergoing frontal or temporal lobe surgeries. The FLE group showed improvements in both behavior and seizure control, but also slight declines IQ and EF [71]. Changes in children's' behavioral functioning post FLE surgery is complex as well. Colonnelli reported variable results in the psychiatric outcome of children undergoing extratemporal resections: some children improved, some stayed the same, and others developed new problems [72].

In adults, cognitive difficulties following FLE surgery can take various forms. Sarkis noted risk factors for reduced verbal fluency included poor seizure control, dominant hemisphere lesion, and higher pre-surgical verbal fluency scores [73]. Dulay demonstrated that patients who showed symptoms of depression pre-surgically were more likely to have more executive dysfunction postsurgically [74]. It was theorized that this may be secondary to depressed patients having a decreased cognitive reserve.

In terms of maximizing surgical outcomes, a frontal lobe lesion that is well demarcated is associated with better surgical outcome. For example, a visible lesion on MRI [70], as well as a localizing EEG are associated with better outcomes in terms of seizure freedom [67]. Whether these same factors predict cognitive outcomes post-surgically remains to be seen.

Future directions for neuropsychological research in frontal lobe epilepsy

The last 5 years have resulted in an enormous expansion

of our knowledge about the neuropsychology of frontal lobe epilepsy, particularly in children. Behavioral studies have clarified the cognitive phenotypes in these conditions, imaging studies have elucidated the underlying structural and functional correlates of observed cognitive and behavioral difficulties, and work elucidating the cognitive outcomes of common treatments for FLE has continued. These advances are quite encouraging, but clearly, there is more work to be done.

One issue which has long-confronted neuropsychologists studying executive dysfunction in most conditions, including FLE, is the significant differences in tasks and terminology used to define and measure the underlying cognitive processes [11]. Helping to ameliorate these differences will be, at least for researchers in the United States, the recent initiatives from the National Institute of Health (NIH) creating a common and core set of behavioral and cognitive measures. Known as the NIH PROMIS initiative, this work represents a standardized set of symptom report scales and cognitive measures with a goal to create common metrics across populations and the life span [75]. More specifically for measurement of executive dysfunction, the NIH EXAMINER battery has been also created [76]. This is a specific series of theory driven and psychometrically robust instruments designed to characterize the breadth of cognitive constructs associated with EF across studies. By using these two methodologies, it will be easier to define the difficulties series of patients is having, and increase comparability across study samples.

From a behavioral standpoint, future studies should move from understanding cognitive difficulties in the lab to understanding their real world correlates. Cahn-Weiner and Giovagnoli are examples of such work, [25,26] but further research incorporating real world functional outcomes improves our ability to treat patients and improve daily functioning. Furthermore, identifying how self-monitoring and insight, two aspects of EF that may be impaired in patients with FLE, influence common tasks as self-report of seizure characteristics and medication compliance may help to improve care for these patients.

When studying the neuropsychology of FLE, it is important to recognize that neural substrates interact with cultural norms to shape behavior. A cross-cultural approach to understanding the social-cognitive features of FLE is important in understanding disparities in results across centers and sites. Similarly, the above literature has shown a preponderance of studies in FLE focusing on childhood. Understanding FLE across the developmental span, from earliest development to late life, is important in meeting the needs of these patients and understanding how the frontal lobes in FLE develop and change over time.

Imaging work has provided exciting new insights into the neurobiology of FLE in recent years. Expanding this work in adults, and evaluating the influence of different treatments on these biological markers, is important. Taking a multi-modal network approach, linking white matter, gray matter, functional, and behavioral aspects should also help to more fully elucidate the complex interactions between these systems.

From a treatment standpoint, studying the interaction of pharmacological variables with the baseline cognitive difficulties in FLE is important to minimize adverse side effects and discern which symptoms are attributable to which variable. Furthermore, more work is needed to understand the neuropsychological outcome of FLE surgery.

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