Chapter 91

Neuropsychology Evaluation - Adults

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Neuropsychological impairments are common in many epilepsy syndromes, and are related to clinical factors such as seizure frequency and severity, age of seizure onset, as well as the underlying pathologic substrate. It is beyond the scope of this chapter to provide a comprehensive review of all epilepsy syndromes and their patterns of neuropsychological impairment. However, there are several consistent neuropsychological principles that we will highlight.

As described by Hughlings Jackson, there are significant and independent contributions of both static and dynamic factors that affect brain function, and by extension, neuropsychological abilities. Morphological or structural lesions are associated with relatively non-modifiable neuropsychological deficits. In contrast, EEG discharges, seizures, and epilepsy treatment are associated with more dynamic brain changes that, to varying degrees, are modifiable and are under direct physician management. Depending on epilepsy type (idiopathic vs. symptomatic), the relative contributions of specific factors will differ.

Disentangling the stable and dynamic cognitive influences in epilepsy often poses a major challenge since causes of impaired neuropsychological function are not fully independent of each other. Treatment effects, for example, act upon and interact with morphology and epilepsy. Although altered brain structure and function may result in epilepsy, epilepsy and its underpinnings may also alter functional cerebral organization. Finally, at the highest level, epilepsy related cognitive impairment must be evaluated within the patient's developmental context. Certain seizure syndromes show peaks at specific developmental stages, and etiology is associated with age at seizure onset. Cognitive profiles vary depending on age of seizure onset, with difference apparent depending on whether epilepsy develops in the maturing brain vs. mature brain vs. aging brain. However, age of seizure onset may simply reflect the expression of dysfunctional brain maturation.

Epilepsy is often dichotomized according to whether the EEG abnormalities involve the entire cerebrum (generalized epilepsy) or begin focally (partial epilepsy). Generalized epilepsy includes tonic clonic seizures, juvenile absence epilepsy, and myoclonic epilepsy. Partial epilepsy includes a variety of seizure types including the so called "benign" partial epilepsy (e.g., benign epilepsy with centro-temporal spikes, or BECTS) as well as symptomatic focal epilepsy (e.g., mesial temporal lobe epilepsy and neocortical epilepsy). We will describe disease effects on cognition as a function of epilepsy syndromes, age of onset, and epilepsy course. We will also discuss the complex issue of whether poorly controlled seizures are associated with progressive cognitive decline. For ease of discussion, we will categorize epilepsy subtypes according to whether they are considered to be idiopathic of symptomatic.

Idiopathic epilepsy

Idiopathic epilepsy, including both generalized and partial epilepsy expression, is characterized by a genetic predisposition and the absence of readily identifiable brain lesions. Although not completely silent behaviorally or cognitively, idiopathic epilepsy is generally easy to treat and is associated with less severe cognitive impairments than other seizure types. *Idiopathic generalized epilepsy* (IGE) is characterized by generalized EEG abnormalities involving the entire cerebral cortex whereas *idiopathic partial epilepsy* (IPE) is associated with regional EEG abnormalities (e.g., centro-temporal EEG in rolandic epilepsy).

As would be predicted from generalized EEG abnormalities, diffuse and generalized cognitive impairments is present including deficits in attention, psychomotor speed, visuo-spatial skills, and nonverbal memory. Language and verbal memory, in contrast, appear unaffected (1-3).

The epileptiform discharges and cognition are also closely related. Not only does cognitive impairment vary as a function of seizure activity, but cognition may also induce seizures and seizure discharges (4). Although this relationship has been described in patients with symptomatic temporal lobe epilepsy (5), patients with IGE are particularly likely to show neuropsychological EEG activation. Negative effects of spike-wave bursts exist for sensory and executive functions. Therefore, tasks requiring sustained attention are best suited to detect cognitive effects of EEG changes in IGE (2). Although cumulative attentional effects may ultimately result in diminished level of function when they occur over long periods, decreased IQ is not a primary feature of the disease with developmental delay and retardation developing from interference with cognitive functions over a long period of time. Absence epilepsy developing in early childhood is generally associated with poorer outcome than juvenile absence epilepsy.

Benign childhood epilepsy with centrotemporal spikes (BECTS) is common epilepsy syndrome (10-15%) beginning between 5 and 9 years of age and extending into adolescence. It has a favorable prognosis and most patients become seizure free after puberty. Its neuropsychological prognosis, however, is less benign. During its active phase, neuropsychological deficits may include attention, motor functions, short-term memory, visual and perceptive abilities. Language difficulty relating to the interictal dysfunction of perisylvian language areas, however, is a major characteristic of BECTS (2). Learning disabilities are common in BECTS (6), although they are not progressive in nature. Although children rapidly improve in most areas following seizure remission, minor problems in executive functions and verbal comprehension persist (7, 8). Complete seizure remission is generally needed for a favorable cognitive outcome.

Juvenile myoclonus epilepsy (JME) generally begins between 12 - 18 years of age, and is characterized by neuropsychological and behavioral features associated with frontal dysexecutive impairment such as reasoning difficulty, poor concept formation,

and decreased mental speed and flexibility (2, 9-12). Of course, frontal lobe dysfunction is not specific for JME. Whether frontal lobe cognitive dysfunction together with personality change (e.g., limited self-control, suggestibility, indifference, rapid mood changes) form a syndrome characteristic of JME merits further study (10). The presence of more focal impairments in addition to generalized slowing are consistent with the view that IGE should no longer be considered purely a "generalized" epilepsy. EEG, histological, structural and functional imaging studies suggest a specific involvement of frontal lobes, thalamus, and thalamo-cortical loops in IGE (13-17).

In conclusion, a wide range of rather mild impairments may be associated with idiopathic generalized or idiopathic partial epilepsy. Mild generalized impairment and learning difficultly have been observed. These are best understood from the close relationship between active epileptic processes interfering with cognitive networks of lower order functions, on perceptive and executive functions, and on the interference of epilepsy with critical periods of cognitive development (i.e., before, during, or after language acquisition, or at the time before or when frontal executive functions are developing). Frontal/executive functions are the last to fully develop and therefore may represent a common endpoint for impairments seen in idiopathic epilepsy. Following epilepsy remission, neuropsychological recovery from active epilepsy driven impairment can be observed. However, some long-term residual deficits may persist, particularly when epilepsy has significantly interfered with cognitive development.

Focal symptomatic epilepsy

In contrast to idiopathic epilepsy, the cognitive profiles of with symptomatic epilepsy are more strongly related to epilepsy location and etiology. The temporal lobes and temporo-mesial structures are particularly vulnerable to seizure development, and temporal lobe epilepsy (TLE) accounts for approximately 70% of chronic symptomatic

epilepsy. Approximately half of TLE patients have hippocampal sclerosis or hippocampal atrophy, although whether mesial TLE represents a distinct nosological entity or a syndrome is still a matter of debate (18). Mesial TLE is characterized by impaired declarative memory (19). Patients with earlier seizure onset tend to have lower IQs, reflecting the interference of seizures and perhaps its treatment with antiepileptic medications with normal cognitive and brain development (20). Accompanying the IQ with earlier seizure onset is a reduction of total brain volume, including both grey and white matter (20). Memory impairment occurs independent of the age of seizure onset, although the nature of the memory impairment depends on when seizures begin. A more generalized memory impairment with earlier seizure onset, whereas a more focal and material-specific memory impairment that varies according to seizure onset laterality is seen with later seizure onset (21).

With later seizure development, left temporal/left temporo-mesial epilepsy is associated with material-specific impairment of verbal learning and memory. Mesial and neocortical structures differentially contribute to verbal memory, with mesial structures subserving consolidation and retrieval and neocortical structures more associated with content processing. Thus, impaired delayed recall is more indicative of mesial rather than neocortical temporal lobe damage (22). Impairment of verbal learning, short-term memory, and naming (i.e., semantic memory) are less specific but also may reflect left infero-temporal or temporo-lateral lesions (23-27). Naming impaired is associated with hippocampal volume (28) and also related to functional activity reflected by spectroscopy (29). Like memory, the magnitude of naming impairment is strongly associated with seizure onset age.

In contrast to left TLE, right TLE tends affect performance on figural or non-verbal memory tasks (30). However, this relationship is less consistent than that between left TLE and verbal memory (31), an effect that has been attributed to

nonverbal memory networks being more bilaterally distributed than verbal memory, covert verbalization during task performance, or the type of the test and test materials (abstractness, complexity). Consequently, using figural memory tests to infer mesial temporal dysfunction will often falsely lateralize seizure onset. However, false lateralizing figural memory impairment in left TLE may also reflect atypical language dominance or sex differences (21).

Even though the area of seizure onset in focal TLE is limited, neuropsychological impairment often extends beyond the seizure onset zone (32, 33). These "frontal" deficits imply impaired functional connectivity that is disrupted with a temporal lobe focus, and may be considered to reflect "nociferous cortex" effects in which the negative effects associated with ongoing seizure discharge impair brain function at some distance away from the active seizure focus (34). However, MRI volumetrics have demonstrated prominent disruption in ipsilateral hippocampus and neural connectivity (i.e., white matter volume loss) that extends beyond the temporal lobe, affecting both ipsilateral and contralateral hemispheres (35). TLE patients with secondary generalized seizures are at higher risk of additional general neuropsychological impairment (36).

Frontal lobe epilepsy (FLE) is seen in approximately 20% of patients with partial onset seizures, and is associated with a less consistent neuropsychological profile than TLE. In contrast to TLE in which hippocampal sclerosis is the predominant morphological feature, frontal lobe epilepsy is associated with a more heterogeneous array of etiological factors. Moreover, executive functions mediated by the frontal lobe contribute to most other cognitive functions, resulting in diffuse and non-specific neuropsychological impairments. Patients suffer from attention problems, problems with working memory, mental flexibility, response inhibition, or planning. Tests of motor coordination appear particularly sensitive to frontal lobe epilepsy. At the highest level, a dysexecutive syndrome may comprise problems with response selection, initiation,

execution and inhibition. No consistent lateralized impairment has been associated with focal left vs. right FLE (37-40).

The neuropsychological characteristics of *parietal lobe epilepsy* and *occipital lobe epilepsy* have rarely been described in a series with adequate sample sizes. Acute parietal or occipital neuropsychological symptoms become evident in seizure semiology, but in chronic epilepsy, most with early lesions or malformations, the classic posterior symptoms of aphasia, alexia, agraphia, acalculia, agnosia, and neglect are very uncommon. Primary or secondary perceptive and sensory problems that may be evident at the beginning of epilepsy are often well compensated for behaviorally. Impairments are diffuse, and, as it has been described with seizure semiology and EEG, often mimic frontal or temporal lobe dysfunction (41, 42). Nevertheless, tests of stereognosis or haptic search may be sensitive to parietal lobe epilepsy (43, 44).

Etiology. Partial epilepsy is associated with a variety of etiologies. Lesions include stationary lesions such as developmental malformations, hippocampal sclerosis or atrophy, traumatic brain injury or vascular malformations, as well as potentially progressive defects such as neoplastic and paraneoplastic tumors, CNS infections, inflammatory and autoimmunological processes. Independent of seizure effects, these lesions themselves are associated with cognitive impairments that range from mild impairment in circumscribed domains to severe generalized neuropsychological impairment. However, cognitive impairments in symptomatic epilepsy are not lesion specific, but rather differ according to age at the lesion onset, differences in functionality of the affected tissues, differences in the course and dynamics of the underlying disease, and finally differences in lesion lateralization and localization (45). Although the lesions themselves and generally not associated with ongoing cognitive function, activation of heterotopic grey matter has been demonstrated using fMRI (46).

A major concern is the cumulative effects of chronic epilepsy on the brain and cognition. Seizures, and in particular severe seizures, may result in significant damage, although this is more of an individual patient concern than a concern across all patients. For example, multiple reports exist describing amnestic syndromes following either status epilepticus or a series of generalized tonic clonic seizures. The cumulative effect of less severe seizures on cognition, however, is less well clear-cut. In a review of 20 longitudinal studies in children-adults, 12/20 reported a relationship between duration of poorly controlled seizures and neuropsychological decline, 5/20 described mixed results, and 3/20 no relationship (47).   For those studies reporting an effect, lower IQ with associated increased seizure frequency, greater performance "improvement" in controls than patients, and more importantly, neuropsychological declines were associated in non-memory domains.

Cross-sectional studies of chronic uncontrolled temporal lobe epilepsy suggest a significant IQ decline after three decades (48). Comparison the age regressions of memory in healthy subjects to those from epilepsy patients puts such finding into perspective (49). In chronic uncontrolled TLE, memory decline in a longitudinal design is very slow and individually proceeding cognitive decline can be suggested. Presumably, this applies for chronic focal epilepsy, but it remains whether specific domains are affected or whether decline is diffuse and non-specific. Impairment may be seen in patients with symptomatic focal epilepsy even prior to the onset of epilepsy, and cognitive impairment may develop from the interference of lesions/epilepsy with brain maturation and cognitive development. The impact of additional lesions and the interaction of aging with pre-existing damage appear much more relevant for individual cognitive change than accumulation of seizures alone (21, 45).

Antiepilepsy Drug Effects

Given the many potential influences on cognition for patients with epilepsy such as age of onset, disease substrate, or seizure frequency and severity, antiepilepsy drugs (AEDs) occupy a unique position since they are under the direct control of the treating physician and their patients. Although choice of specific AED is guided by seizure type and epilepsy syndrome (50), within seizure/syndrome categories, AED selection is typically based upon clinical experience rather than evidence-based practice. Most major AEDs used to treat partial epilepsy have comparable efficacy (51), although many recently introduced AEDs are associated with move favorable tolerability profiles that includes less neuropsychological impairment (52).

Because AEDs decrease membrane excitability, increase postsynaptic inhibition, or alter synchronization of neural networks, they are often associated with neuropsychological side effects including decreased motor/psychomotor speed and attention (53). Adverse AED effects are a significant component of treatment effectiveness. The landmark VA Cooperative study reported that standard AEDs including CBZ are associated with significant adverse effects that contribute to initial treatment failure in more than 40% of patients (54), and a separate European trial reported that tiredness was described by more than 50% and sleepiness by more than 35% of patients on PHT or CBZ monotherapy (55). Adverse AEDs effects are strongly associated with poor health reported by patients (56) and with decreased health-related quality of life (57). After seizure control, the most important aspect of AED treatment is the side effect profile, including problems with cognition, energy level, school performance, childbearing, coordination, and sexual function. Because of side effects, 20% of patients adjusted their AED dosing (58).

In young adults, neuropsychological AED profiles are generally comparable for the older generation AEDs carbamazepine (CBZ), phenytoin (PHT), and valproate (VPA), with each AED associated with modest psychomotor slowing accompanied by

decreased attention and memory (53). Neuropsychological side effects generally emerge according to a dose-dependent relationship (53); however, both quality of life (59) and memory may be affected, even when AED blood levels are within standard therapeutic ranges. CNS effects of AEDs are reflected by EEG slowing that not only is correlated with short-term neuropsychological decline (60, 61), but is also related to poorer neuropsychological outcome following one year of treatment (62). With the exception of topiramate (TPM) (53, 63-65) and possibly zonisamide (ZNS) (66, 67), most newer generation AEDs have more favorable tolerability and neuropsychological profiles than their predecessors (68-71).

Although direct head-to-head comparisons examining the neuropsychological profiles of newer AEDs have not typically included medications thought to have favorable neuropsychological outcomes, there are data to suggest differences in this regard. For example, in one study, OXC was associated with both neuropsychological impairment and EEG slowing in healthy volunteers (72). Thus, there are data to suggest that there may be important AED differences, even across newer AEDs considered to have favorable neuropsychological side effect profiles. Several recent Class I healthy volunteer studies suggested increased risk of cognitive impairment associated with TPM (71, 72). Because there may be individuals who are at greater risk for developing cognitive impairment, it may be possible to ultimately predict individuals at increased risk for developing treatment-emergent side effects based upon pharmacogenetic or pharmacokinetic patient characteristics.

Subjective report versus objective performance

In addition to poor performance on memory tests and other neuropsychological measures, epilepsy patients often complain of poor memory (73). Although both subjective and objective memory findings indicate decreased memory, subjective

memory ratings and objective memory performance are poorly correlated (74-78). In studies with sufficient sample sizes, statistically significant relationships between objective and subjective performances have been reported, although these correlations are generally small and account a small portion of the variance. In contrast, subjective memory correlates much more highly with mood (73, 76, 79-81). Depressed or anxious patients tend to rate their memory as poor, whereas patients less burdened by poor mood states rate their memory more favorably. Correlations generally account for approximately half of the variance (81, 82) with mood being the single best predictor of subjective memory functioning (76, 79, 83).

The association between subjective memory and mood is informative, yet, a large portion of the variance remains to be explained. Most studies show no significant relationship between subjective memory and clinical factors such as sex, gender, chronological age, seizure onset age, seizure type, seizure frequency, region of seizure onset, and number of AEDs (79, 80). However, memory "complainers" may have a later age of seizure onset (73), and a small inverse relationship between age and subjective memory reports has been described (81, 83). There is a tendency for patients on polytherapy to report greater cognitive difficulty than patients on monotherapy (83), although this relationship is well-established with formal neuropsychological measures (53). Although most studies are restricted to TLE patients, those that included both temporal and extra-temporal patients report greater reports of memory impairment in TLE (73). Although some investigators report no influence of seizure laterality (82), others have found significant associations between perceived memory and objective verbal memory in left patients, and with objective nonverbal memory in right TLE patients (84). Although there are reports of a relationship between perceived and objective language performance (84), others have not observed this relationship (82).

Ecological validity of objective measures

Formal neuropsychological measures are established indicators of lateralized or localized cognitive dysfunction (85). However, the modest correlation between subjective and objective results raises questions regarding ecological validity of conventional memory tests. Neuropsychological memory tests typically require learning and recall of word lists or abstract designs, whereas 'everyday memory' typically requires incidental memory for complex events in which individual is personally involved (86). In two independent studies utilizing memory tests simulating everyday memory demands (79, 86), more ecologically valid tests correlated weakly with subjective ratings, but correlated more highly with conventional test performance. Although a small but significant correlation was found between ecologically valid memory performance and subjective report in patients "without" memory impairment (86), the absence of a significant correlation in the "impaired" group may be related to the more restricted performance range.

The demands of various activities differ considerably, and cognitive deficits may be more apparent in high versus low demand situations. In one post-operative series, patients staying at home ("low demand") reported greater subjective complaints than employed subjects ("high demand") (87), and this corresponded with objective memory performance as well (i.e., weaker objective memory in the low-demand). Although patients were self-selected for group assignment, these data suggest that patients with poorer objective memory were in less demanding situations due to their genuine memory deficits, as well as feeling more impaired.

Tip-of-the-tongue phenomena (TOT) or "word finding difficulty" is one of the top three cognitive complaints among epilepsy patients (88), although the relationship between objective performance using confrontation naming tests (73) or language composite scores (76) ; (82) with patient self-report is low or nil. However, the absence

of a stronger relationship may result from language test selection using measures that poorly correlate with word finding difficulty. For example, in a study addressing the ecological validity of object naming measures, no correlation between self reported word finding difficulty and traditional visual object naming, although a small but significant correlation with auditory description naming, a task developed to better simulate word finding in the context of everyday speech (27).

Subjective memory "theories"

Several studies suggest that that lay-persons, (i.e., patients, proxies and normal controls) have a broader definition of "memory" than that of neuropsychologists and neurologists. Specifically, performances on various language tasks, such as word fluency, expressive vocabulary, and naming, correlate significantly with subjective memory ratings (77, 81, 89). Thus, when persons are asked to rate their memory, they often consider language fluency and word finding difficulty as well as declarative memory processes.

The poor relationship between subjective performance ratings and objective test results raises the question of whether impaired deficit recognition (e.g., anosognosia) exists. A problem in assessing subjective memory in a population with genuine memory deficits is that the task is retrospective, and therefore, a memory tasks itself (77, 86). The discrepancy between objective and subjective scores is greater in patients with right hemisphere seizure onset, with a greater tendency to overestimate their genuine memory abilities (90). This pattern is consistent with the specialized role of the right hemisphere in deficit awareness reported in lesions of other etiology.

It has been suggested that some patients, unaware of their real memory conditions, exaggerate their memory failures and report this inaccurate self-perception in questionnaires (80). Although epilepsy patients with and without memory complaints

obtain comparable scores across a range of neuropsychological measures, the 'complaint' group scored significantly higher in neuroticism (75). Thus, both disease-related and personality factors reduce self-awareness, thereby contributing to the discrepancy between subjective complaints and objective performance.

Subjective change in postoperative patients

Whereas pre- (or non-) surgical epilepsy patients tend to "over-report" memory deficits, the prevalence of memory complaints among patients following temporal lobe resection is quite low (91, 92). In fact, postoperative patients tend to report improved memory functioning despite evidence of memory decline on objective measures (93, 94). Accordingly, most studies report little correlation between changes in objective performance and changes in subjective ratings following surgery. Rather, subjective memory ratings in postoperative patients correlate significantly with seizure outcome (i.e., good seizure outcome associated with improved subjective ratings) (92-95), AED side effects, and, similar to that demonstrated in preoperative patients, with mood (92, 94) and neuroticism (96). Although a higher prevalence of subjective decline might be expected following left ATL rather than right ATL given the more consistent objective decline following left surgery (85), subjective complaints do not appear to predict surgical laterality (78, 92-94, 96). Because of the overall poor correspondence between performance and complaints after surgery, postoperative memory complaints might be considered a marker of depression or other mood disorder (92). Nonetheless, there is general agreement that, despite these group findings, individual cognitive complaints should be followed up with both formal mood assessment and neuropsychological evaluation.

Practical implications

The poor correspondence between subjective report and objective performance suggests caution when drawing conclusions from subjective complaints. This is obviously a concern to the treating physician since, in most cases, the presence or absence of memory complaint is based upon questioning the patient rather than formal memory assessment. Factors to consider include emotional and psychosocial factors, the potentially broader definition of "memory" held by patients and their relatives, the patient's level of daily cognitive demands, and seizure onset laterality. For postoperative patients, one should additionally consider seizure outcome and AED burden. Each of these factors carries a potential influence on cognitive self-appraisal; distinguishing among them on an individual basis is critical, as each would implicate a different treatment approach.

Wada testing and functional imaging

One of the primary goals in the preoperative evaluation is to identify patients who may be at increased risk for developing significant post-operative neuropsychological impairment. Patients undergoing TL resection in the language dominant hemisphere are at higher risk for experiencing postoperative memory decline than those undergoing non-dominant ATL, and knowledge about language dominance and memory representation is important to establish the relative risks to memory associated with temporal lobectomy.

The Wada test is one of the major procedures to establish relative memory risk following anterior temporal lobectomy, although not all epilepsy surgery centers perform this procedure routinely on all ATL candidates (97). Wada testing to assess both language and memory function emerged in the 1950s when structural and functional imaging was almost non-existent. Although variability in specific protocols exist, the

technique generally involves the introduction of amobarbital (or other anesthetic agent) through a transfemeral catheter into the internal carotid artery, which temporarily anesthetizes the distribution of the anterior and middle cerebral arteries. During the period of hemispheric anesthesia, the patient is presented with language and memory acquisition tasks, with memory tested after the drug effects have worn off. Although the memory component of this task was developed to avoid developing a significant post-operative amnesia, this role has largely been supplanted by current functional neuroimaging using MRI, PET, and SPECT. Wada memory results, however, are often now often used to indicate risk of significant memory decline that may interfere with a patient's overall quality of life (98).

The Wada test differs from all other approaches to functional assessment, including neuropsychological testing, in that it tests each hemisphere in isolation. By doing so, it helps to therefore disentangle the effects of large scale distributed brain networks and can assess the specific contributions of the anesthetized region and their functional connections to language and memory function. When the hemisphere ipsilateral to a medial temporal lobe focus is anesthetized, the reserve capacity of the contralateral temporal lobe to sustain memory function in isolation is assessed (99). There are multiple reports that demonstrate the contribution of Wada memory results to memory outcome prediction (100-106). There is an aphasia confound when testing memory following dominant hemisphere injection, and because of this confound, a selective procedure anesthetizing the distribution of the posterior cerebral artery may be used (107), although this approach is associated with a greater risk of stroke and consequently in generally not employed routinely (108). Selective procedures involving other vascular distributions may be performed based upon clinical indications (109, 110).

Because the Wada procedure is invasive, functional MRI of MEG are advanced as a non-invasive alternatives. There are many language fMRI paradigms that reliably identify language representation, and the use of fMRI has decreased the frequency of Wada use in some epilepsy centers (111). Magnetoencephalography is an alternative measure of functional imaging that, unlike fMRI which relies on indirect measures of neural activity based upon blood flow changes, is a direct measure of neuronal function. MEG is also a reliable non-invasive measure of language lateralization (112, 113).

Imagining the medial temporal lobes has proven to be more difficult. However, there are several reports demonstrating the effectiveness of fMRI related to seizure onset laterality (114-116) as well as memory outcome following surgery (117, 118). As the components needed for successful hippocampal activation continue to be undersood (119), it is likely the fMRI will increasingly be used in pre-operative epilepsy evaluation with a corresponding decrease in Wada use.

Postoperative Outcome

Up to 80% of those patients undergoing anterior temporal lobe resection will become seizure free following surgery (120), although some patients will experience specific declines in memory, language, or some other aspect of cognitive functioning. A literature has now developed demonstrating how results from presurgical neuropsychological testing, combined with demographic variables and other neurodiagnostic findings, can predict patients who are at greatest risk for developing postoperative decline.

One of the earliest findings from neuropsychological studies is that epilepsy surgery results in very little change in IQ (111). The view that patients with lower IQ levels, which can suggested greater generalized brain impairment, do not benefit from surgery has been dispelled by research findings comparable seizure outcomes in both

low and high IQ groups (111, 121). Patients with higher IQ levels and memory performance tend to experience a greater cognitive declines following surgery, although they also continue to exhibit a higher level of postoperative functioning than patients with lower presurgical cognitive performance (122). These results support the model of cognitive reserve that has gained acceptance in the fields of dementia and traumatic brain injury (123, 124).

The majority of epilepsy surgeries are anterior temporal lobectomies (ATL) that involve resection of areas considered important for normal memory processing, and consequently predicting memory outcome has been emphasized. Different rates of memory decline ranging from 10 to 60% following ATL have been reported. The prediction of memory decline has been guided by two basic theoretical approaches. The first model is based upon Milner's (125) original observation that material-specific memory deficits in verbal and nonverbal memory are associated with ATL of the left (dominant) and right (non-dominant) temporal lobes respectively. The second approach is based on more recent model, predicting that the degree of postoperative memory deficit, as well as seizure outcome itself, will be determined by the "functional adequacy" of the tissue to be resected (99, 106). The type of surgical procedure (e.g., "standard" ATL vs. selective amygdalohippocampectomy) and post-operative seizure status also contribute to postoperative cognitive outcome (111).

Laterality Effects

Analyses of material-specific memory findings are included in nearly every neuropsychological study of post-operative outcome. The conclusion drawn from recent literature reviews is that there is strong empirical support for the link between surgery on the left temporal lobe and postoperative deficits in verbal memory (126). There is, however, substantially less support for the proposed relationship between nonverbal memory impairment and surgery on the right temporal lobe (126, 127).

There has been a recent trend moving from group methods of analysis towards predicting the risk of postoperative change in individual patient prediction. To optimize the prediction of individual risk, investigators have been using statistical methods, such as the reliable change index (RCI) and standardized regression-based (SRB) methods to control for the reliability of the instruments, practice effects, and regression to the mean. Studies using this methodology have reported that the risk for postoperative decline in verbal memory ranges from 40 to 60% in patients undergoing left ATL while the risk for decline patients undergoing right ATL ranges from 10 to 30% (128, 129). Significant declines following right ATL are not are clearly not explained by any simple version of the material-specific memory model. Much less is known about the risk of experiencing a decline in nonverbal memory as a result of methodological factors and small effect sizes.

Language dominant ATL has been associated with postoperative naming deficits, although details regarding these deficits are less well known than those associated with memory. Postoperative naming impairment is generally thought to occur in only a minority of patients (130), although at least one study has found naming declines in 40% of their left ATL sample versus none of those patients undergoing right ATL (129). The ability to predict postoperative naming deficits through presurgical language mapping using intraoperative or extraoperative methods have been inconsistent. One multicenter study found that the rate of postoperative naming decline was not influenced by the availability of mapping data (131). Others have found that identification of mapping sites critical for auditory descriptive naming is important for predicting both auditory and visual naming outcome (25).

There are no consistent findings demonstrating deficits in visual perceptual or spatial functions associated with right ATL. Surgical procedures conducted on patients with frontal lobe epilepsy and other forms of extratemporal epilepsy have been

associated with only mild declines in memory, language, or other cognitive functions unless areas of eloquent cortex are involved specifically (132, 133). Laterality effects on cognitive functioning are considered to be less of an issue with pediatric patients than with adults (45).

Functional Adequacy Model

The functional adequacy model predicts less postoperative memory decline, as well as a greater likelihood for seizure reduction, will be observed in patients exhibiting lower levels of presurgical functioning in the mesial temporal lobe ipsilateral to seizure onset (99, 106). Functional adequacy is established using both neuropsychological methods as well as measure of structural pathology using preoperative neuroimaging. Most research findings have supported this model, as opposed to a competing "functional reserve" model predicting that postoperative memory is best predicted by the functional and structural integrity of the contralateral temporal lobe.

Presurgical Neuropsychological Performance. Evidence supportinig the functional adequacy model was initailly provided by the findings that patients with higher memory performance on presurgical testing were more likely to demonstrated significant memory decline following ATL those (134, 135). These results are not simply the result of statistical "regression to the mean," but rather reflect the tendency for the most functional patients at baseline to be more vulnerable to experiencing postoperative memory loss (136). This is a robust pattern of change following ATL, and has been observed in many independent series (105, 137, 138).

Findings from MRI and Other Studies. Neuropathological studies have consistently demonstrated that memory outcome varies according to the presence of hippocampal sclerosis (HS) ipsilateral to seizure onset (85, 139, 140). Not only do individuals with severe unilateral HS exhibit lower levels of preoperative memory, but

they are also less likely to exhibit memory decline following surgery (141). Similar findings have been observed using MRI measures of hippocampal pathology (142, 143). Resection of a relatively nonatrophic left hippocampus generally results in greater memory decline, although memory loss may also occur some patients with severe presurgical HS (144). Surgery in patients with bilateral hippocampal pathology, however, does not necessarily cause global amnesia, although greater rates of memory decline are seen in patients with bilateral hippocampal atrophy who undergo dominant hemisphere ATL (144). Normal verbal memory in the presence of hippocampal atrophy may also be associated with significant post-operative memory decline (98). Thus, functional integrity of the left temporal lobe plays a critical role in predicting memory outcome independent of the presence of structural pathology (98, 145).

Studies using multiple regression methods have demonstrated that prediction of postoperative outcome is best accomplished by a combination of both functional and structural indices (105, 137). The importance of functional adequacy to post-operative change has been demonstrated using both magnetic resonance spectroscopy (MRS) and Wada testing (see below) (100, 106). Functional MRI (fMRI) has been shown to be useful for predicting postoperative naming (146). Recent presurgical fMRI studies have demonstrated the ability to predict postoperative memory functions (117, 118).

Demographic Predictors. Developmental factors, including age at the time of surgery and the stage of cognitive development at the time of seizure onset, are important factors for predicting postoperative cognitive decline. The risk of cognitive decline following surgery appears to be lower in children younger than age 16 years than in adults (147). In contrast, older patients may experience greater memory loss, consistent with a profile of accelerated aging (122). Continuing decline in memory performance may be seen in some individuals ten years or more following surgery (148). The postoperative deficit in verbal memory in patients who are seizure free is similar to

what is observed over time in nonsurgical patients that are continuing to experience seizures, suggesting normal age-related memory decline (122).

Age of seizure onset interacts with both functional and structural indices in a manner consistent with the functional adequacy model (99, 149). Those with a younger age of onset will have experienced pathology at an earlier stage of development and will have experienced seizures for a longer period of time. This leads to greater neurological compromise which is accompanied by more severe and widespread cognitive impairment. However, earlier seizure onset also permits a redistribution of function to other brain areas, which would lead to less deficit following surgery. In contrast, patients developing epilepsy later in life are not as compromised neurologically since it does not interfere with cognitive development and maturation, and consequently do not exhibit the same degree of cognitive dysfunction preoperatively. However, surgery involves resection of more functional brain tissue, which increases the likelihood of developing greater cognitive decline postoperatively. Support for these findings with age was present in some early studies, but at least one recent study has failed to find a link between severe hippocampal pathology, memory decline, and early onset of seizures (149).

In general, cognitive deficits become more specific and less reversible with surgery with increasing age. The pattern of findings involving age of onset are generally more consistent for cognitive functions associated with neocortical zones than for those associated with the mesial temporal lobe (111). For example, more severe naming deficits are observed in older patients. Other studies examining demographic factors have suggested that women, in general, exhibit less severe cognitive decline following surgery than men (150).

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