

COGNITION AND EPILEPSY: NEUROIMAGING FINDINGS

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Epileptic seizures, ranging from subjective auras to loss of consciousness and tonic-clonic seizures severely deteriorate patients' quality of life and can be - depending on the situation - life threatening. However, beyond this main aspect, which dominates public perception of the disease, epilepsy has a strong impact through sometimes less obvious presence of cognitive alterations. Whether epilepsy in the individual patient is associated with cognitive dysfunctions, is dependent on the respective epilepsy syndrome. The spectrum ranges from rare, but severe cognitive impairment in childhood epilepsies, such as the West- or Lennox-Gastaut-syndrome, to symptomatic epilepsies, which may be accompanied by location related deficits, and to idiopathic epilepsies largely without dysfunctions.

Although alteration doesn't mean impairment in every case, there is a wide spectrum of cognitive deficits and symptoms in patients with epilepsies. Affected systems range from low-level sensory functions up to the complex high-level systems of sensory processing, attention and memory. A number of reasonable models exist which explain the observed changes of cognition mainly by impact of structural lesions and alterations predating the epilepsy onset itself, as well as by direct interference of epileptic and functional activity, however in a much more subtle degree.

Diagnostics and therapies of epilepsies offer unique opportunities for the understanding of human brain function. Preoperative diagnostics enable extensive and detailed investigations regarding the relation of neuropsychological findings to neuroimaging results, structural alterations and electrophysiological findings. The rather novel methods of neuroimaging, such as electro(EEG)-/magnetoencephalography (MEG), as well as functional magnetic resonance imaging (fMRI) enable us to observe interaction of pathologic

ic and physiologic activity, as well as the impact on structural correlates, e.g. fiber connections of the individual networks by the use of diffusion tensor imaging (DTI) and morphological analysis of MRI. Such findings offer new insights into the pathophysiology of cognitive alterations and allow tailoring of epilepsy therapy.

Using neuroimaging techniques, models can be developed to contribute to the explanation of observed deficits. While the term "cognition" doesn't typically include lower level, basic functions, such as visual or auditory perception; however epilepsy-related disturbances in these may share common pathomechanisms with deterioration of higher-level systems. Furthermore, such alterations might give rise to or enhance deficits of cognitive functions.

Korostenskaja and colleagues¹ investigated impaired cortical auditory processing in pediatric focal epilepsy patients versus age- and gender-matched controls. Using auditory stimuli, they repeatedly found reduced amplitudes of the evoked responses measured by MEG in patients compared to controls, both in paradigms testing stimulus encoding and discrimination. They also report that early onset and long duration of epilepsy were significantly correlated to delay of responses. The alterations were however not restricted to the auditory system. Processing speed indices (PSI) were also assessed, reflecting the complex ability to scan and process visual information under time pressure, also involving fine-motor and visual-motor skills. Psychomotor performance was found to be reduced in patients and correlated to reduced response amplitudes.

These findings, representative for a number of similar studies, also including adults, illustrate the type of dysfunctions found in focal epilepsies: Location-

related alterations, however not strictly limited to only single components of the affected system; here both stimulus encoding and discrimination were altered. In addition, diffuse impairment was also found in other, higher level systems, resulting in slower psychomotor responses.

Impact of early epilepsy onset has been recognized as a major factor for cognitive alterations². In contrast, evidence regarding impact of long duration of epilepsy by itself seems contradictory. Kaaden and Helmstaedter could not confirm long duration of epilepsy to have an exceptionally deteriorating effect on cognitive function. Instead, they found that epilepsy causes mainly a developmental hindrance during childhood and adolescence, which introduces the statistical difference in performance between epilepsy patients and age matched controls and who then develop in parallel regarding age related decline³. Other studies report significant relationships between epilepsy duration and functional performance^{4,5}, but also with seizure frequency and polytherapy. This apparent contradiction is resolved when the point in time is considered when the insult leading to epilepsy occurred. Thus an insult early in life leads to an early onset of epilepsy and is also often present in patients with long duration of epilepsy and thus has to be considered as a confounding factor³. Duration of epilepsy by itself seems to only lead to cognitive dysfunction if frequent tonic-clonic seizure or status epilepticus occur^{9,10}. Furthermore, psychosocial context, individual compensatory capacity, comorbidities and anti-epileptic medication impact cognitive functions. Especially the latter may lead to deterioration of cognitive processing speed, memory, language and executive functions due to type and dosage of anti-epileptic drugs (AED)⁶⁻⁸.

The (limited) selectivity of deterioration of specific systems is reflected in the location of epileptic activity in the brain. Korostenskaja and colleagues¹ found, that the amplitude reduction of auditory responses was correlated to the side of the epileptic focus, however did not investigate the localization in more detail. A study by Wolff and colleagues¹¹ can illustrate this further. They investigated selective cognitive deficits in benign partial epilepsy in childhood (BPE) using EEG/MEG source analysis of interictal spikes. In spite of the interictal nature of the analyzed signals, a specific correlation of dipole localization and type of

deficit was found: Localizations in the left perisylvian region performed significantly lower in language tests however did not differ in global IQ; localizations in the right perisylvian region did not show this correlation. Furthermore, occipital spikes were associated with deteriorated simultaneous information processing in a visual transformation task. This study nicely illustrates the (at least in focal epilepsies) tight correlation of localization of epileptic activity in regard to functional areas and the respective affected system and is supported by studies of other groups^{3,12}. This parallels findings of localization of (interictal) activity and occurrence of specific semiology elements during seizures, such as different types of auras in temporal lobe epilepsy when MEG spikes are seen in different compartments of the temporal lobe¹³.

Language and memory systems in epilepsy patients are frequently in the focus of both scientific and clinical investigations, due to the high percentage of temporal lobe epilepsies and impairment in these systems. In presurgical evaluation, language and memory performance are evaluated and respective related brain areas are localized in the individual patient using neuropsychological testing, fMRI and EEG/MEG. Results then decide on viability of respective surgery and on individual surgical strategy, e.g. by using the localization results for neuronavigation¹⁴. Alterations of language networks have been investigated using different neuroimaging methods. Powell and colleagues¹² combined fMRI and MR tractography to study differences in activation and connection patterns in temporal lobe epilepsy with hippocampal sclerosis. fMRI was applied to define functional regions involved in verb generation and reading comprehension. These were then used as starting regions for identification of connection tracts in the white matter. Results were evaluated in patients with right and left temporal lobe epilepsy, as well as compared to healthy controls. Both activation and structural connection were comparable in controls and patients with right-sided epilepsy; however patients with left-sided epilepsy deviated and demonstrated more symmetrical activations, as well as lower connectivity on the left and increased connectivity on the right. They could also show that functional activation and lateralization of connectivity was tightly correlated. This study, which combines methods, which had been ap-

plied separately before in comparable patient populations¹⁵⁻¹⁷, achieves to demonstrate several interesting points: They could demonstrate that language processing seems to shift away from the focus side, as demonstrated by fMRI activations, a finding that has been reported before^{16,17}, however they were able to also show that this is tightly associated with specific alterations of structural connectivity. While less obvious, the shift of function (and structural connectivity) to the side contralateral to the focus was also seen in patients with right-sided epilepsy.

Thus, presence of an epileptogenic lesion in the temporal lobe seems to be associated with disturbance of networks spatially close to the epileptic focus. This interference may be theoretically due to direct either acute or chronic interaction of ictal/interictal epileptic and physiologic activity, but may also be due to a common underlying pathology, possibly including a genetic component, that both cause epilepsy and network alterations. Considering findings of cognitive dysfunctions already at or even before the onset of epilepsy^{Error! Reference source not found.} clearly favors the latter mechanism, if the specific form of epilepsy is not accompanied by numerous tonic-clonic seizures and status epilepticus. If the initial insult leading to epilepsy occurs early in life, the brain's neuroplastic capacity may be sufficient to adapt, thus functions may shift to other, possibly functionally homologous networks. Such changes may be based on a selection process of 'competing' networks, i.e. networks that are normally redundant (which doesn't exclude lateral dominance, like in language networks). If then one of these redundant networks deteriorates, the other takes over. The fact that Powell and colleagues saw a rather symmetrical distribution of activation in left-sided TLE shows that this process seems to be gradual. In addition, adaption rather than only functional replacement plays a role, as is suggested by the increased right-sided level of connectivity in left-sided TLE even compared to healthy controls.

Several findings of other studies demonstrate direct interference of epileptic and physiologic activity. Seri and colleagues²⁰ investigated patients suffering from the Landau-Kleffner Syndrome, which is associated with a deficit in language comprehension and production. Using spike-triggered auditory stimulation, they demonstrated that during these interictal spikes, amplitudes of the responses were reduced and latencies increased, when the spikes appeared on the left side. Responses triggered by right-sided spikes, as well as outside the discharges did not show this behavior, although a comparison to healthy controls was not done.

Cognitive alterations also play an important role for therapy. Next to tailored medication to prevent further AED induced impairment, planning of epilepsy surgery has to consider the individual patient regarding functional performance, reorganization and compensation capacity. ^{Error! Reference source not found.} Here, neuroimaging methods become of crucial importance. Viability of focus resection can be evaluated using EEG, MEG and fMRI, consisting of localization of both the epileptic network and neighboring functional cortex. ^{Error! Reference source not found.} Small distances or even an overlap may prevent respective surgery in favor of multiple pial transections or conservative therapy, such as further AED or vagal nerve stimulation. In addition, invasive diagnostics, such as invasive EEG using subdural and depth electrodes may be optimized using such findings. Neuroimaging techniques may also add or replace invasive procedures like the Wada-test in selected cases to estimate individual compensatory capacity and predict postoperative functional outcome. ^{Error! Reference source not found.}

Epilepsy is a complex disease with major impact on patients' lives, which is not limited to seizures. Indeed, cognitive impairment has to be regarded as a major effect, rivaling importance of seizures themselves. Scientifically, cognitive alterations in epilepsy offer a window into the brain as an adaptive system.