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### Allgemeines

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*Prof. Dr. Hennric Jokeit*

Auch die Neuropsychologie ist, wie die meisten Fachgebiete, von zunehmender Spezialisierung in immer enger gefassten Teildisziplinen geprägt. Diese allgemeine Entwicklung ist Ausdruck des Erfolgs, aber auch des Preises für einen Fortschritt, der sich weniger in neuen Konzepten als in verfeinerten Methoden und Techniken verwirklicht.

Die institutionalisierte klinische Neuropsychologie findet ihre Struktur entlang zweier Gegenstandsdomänen: Dies sind einerseits die spezifischen neurologischen Erkrankungen, wie zum Beispiel Multiple Sklerose, Alzheimer Demenz, Morbus Parkinson und andererseits die Funktionssysteme, wie beispielsweise Sprach-, Gedächtnis- und exekutive Funktionen. Die Schnittpunkte zwischen nosologischer und funktionsorientierter Domäne fokussieren bestimmte Fragestellungen bei spezifischen Erkrankungen. So ist das dominierende neuropsychologische Thema im Demenzbereich wie in der Epileptologie das anterograde Gedächtnis.

Die starke Präsenz des Themas Gedächtnis in der epileptologischen Klinik und Forschung hat viele Gründe. So werden Gedächtnisplagen von nahezu allen Patienten beklagt und jeder, der sie vernimmt, bringt ein eigenes, empathisches Verständnis für Gedächtnisprobleme auf. Kaum eine andere höhere Hirnfunktion ist beim Menschen wie im Tiermodell so einfach zu messen wie das Lernen, Behalten und Vergessen. Und noch wichtiger, das Zentralorgan der Gedächtnisbildung ist zugleich die epileptogenste Struktur des Gehirns.

Die Balzan-Preisträgerin 2009, Brenda Milner, entdeckte vor mehr als 50 Jahren die Bedeutung des Hippokampus für die Gedächtnisbildung, nachdem der Epilepsiepatient Henry Gustav Molaison (HM) sich einer bilateralen Temporallappenteilresektion unterzogen hatte. Mit ihrer Entdeckung begründete Brenda Milner, die sich heute, 93-jährig, mit funktioneller Bildgebung am Montreal Neurological Institute beschäftigt, eines der bedeutendsten und klinisch hochrelevanten Forschungsgebiete der kognitiven Neurowissenschaften.

Dass Neuropsychologie in der Epileptologie nicht

nur um das Thema Gedächtnis kreist, zeigt der letzte Beitrag der vorliegenden Ausgabe (Broicher/Jokeit), der eine konzeptionelle und methodische Einführung in das Thema der Defizite sozialer Kognition bei Patienten mit Epilepsie bietet.

Die grösste methodische Veränderung in der Neuropsychologie war die Einführung der funktionellen Kernspintomographie (fMRI) vor etwa nunmehr zehn Jahren, die allerdings immer noch in den Kinderschuhen steckt, wenn man das Instrumentarium an seiner Wertigkeit für die klinische Einzelfalldiagnostik bemisst. Unsere österreichischen Kollegen (Kuchukhidze/Trinka) fassen in ihrem Beitrag die Entwicklungen des Einsatzes des fMRI in der Epileptologie zusammen. Am häufigsten wird fMRI heute zur Lateralisation von Sprachfunktionen in der präoperativen Diagnostik eingesetzt. Unsere Berner Kollegen (Gutbrod et al.) berichten ihre positiven Erfahrungen mit einer Untersuchungsanordnung, die es vergleichsweise einfach erlaubt, anteriore und posteriore Sprachareale mittels fMRI zu lateralisieren.

Eine deutlich ältere Methode zur Lateralisation von Hirnfunktionen, die auf der temporären Inaktivierung einer Hirnregion basiert, ist der intrakarotidale Natrium-Amytaltest, kurz Wada-Test genannt. Früher als Goldstandard der Lateralisation von Funktionen betrachtet, wird sein Einsatz heute kontrovers diskutiert, was sich aktuell in einer weltweit deutlich gesunkenen Zahl von Testdurchführungen niederschlägt. Die heutige Wertigkeit des Tests und die Belastbarkeit der Pro- und Kontra-Argumente werden von der Zürcher Gruppe (Kurthen et al.) diskutiert.

Der erste Beitrag in diesem Heft widmet sich dem Gedächtnis. Die Autoren (Jokeit/Bosshardt/Reed) haben den Versuch gewagt, nach Invarianten und Unterschieden von Gedächtnisstörungen verbreiteter neurologischer Erkrankungen zu fragen und diese zu vergleichen. Was noch vor 50 Jahren eine verbreitete Herangehensweise war, um das Störungsverständnis zu vertiefen, nimmt sich heute wie ein „transdisziplinäres“ Projekt aus. Für uns jedenfalls war es lehrreich, über den epileptologischen Tellerrand hinaus zu schauen.

Ich danke allen Autorinnen und Autoren sowie Frau Becker und Frau Depping ganz herzlich für ihre Mitarbeit an dieser Ausgabe. Ihnen, geneigte Leserinnen und Leser, wünsche ich eine gewinnbringende Lektüre.

  
Hennric Jokeit



*Prof. Dr. Hennric Jokeit*

Neuropsychology, like the majority of specialist fields, is also characterised by increasing specialisation in ever narrower sub-disciplines. This general development is indicative of the success, although also indicative of the price of progress, which is realised less in new concepts and more in refined methods and techniques.

Institutionalised clinical neuropsychology is structured along two subject domains: these are on the one hand specific neurological diseases, such as for example multiple sclerosis, Alzheimer's dementia, Parkinson's disease and on the other hand the functional systems, such as for example speech, memory and executive functions. The point of intersection between nosological and function-oriented domains is the focus of certain questions raised with specific diseases. Thus, anterograde memory is the dominant neuropsychological subject in both the area of dementia and in epileptology.

There are many reasons for the strong presence of the subject of memory in clinical studies and research in epileptology. Thus, practically all patients complain of memory problems and each one examined raises a personal, empathic understanding of memory problems. There is almost no other higher function of the brain in man and the animal model which is as easy to measure as learning, remembering and forgetting. And even more importantly, the central organ of memory development is at the same time the most epileptogenic structure of the brain.

The 2009 Balzan prize-winner, Brenda Milner, discovered more than 50 years ago the importance of the hippocampus for memory development after the epilepsy patient Henry Gustav Molaison (HM) had undergone a bilateral partial resection of the temporal lobe. With her discovery Brenda Milner, who today, aged 93, works with functional imaging at the Montreal Neurological Institute, established one of the most important and clinically highly relevant areas of research of cogni-

tive neuroscience.

The fact that neuropsychology in epileptology does not only revolve around the subject of memory, is demonstrated by the last article in this edition (Broicher/Jokeit), which offers a conceptual and methodological introduction to the subject of the deficits of social cognition amongst patients with epilepsy.

The greatest methodological change in neuropsychology was the introduction of functional magnetic resonance imaging (fMRI) approximately ten years ago now, which, however, is still in its infancy if we measure the instrument against its significance for clinical investigations in individual cases. Our Austrian colleagues (Kuchukhidze/Trinka) summarise in their article the development of the use of fMRI in epileptology. Today fMRI is most frequently used for lateralisation of speech functions in preoperative investigations. Our Bernese colleagues (Gutbrod et al.) report positive experiences with an examination structure, which relatively simply permits anterior and posterior speech areas to be lateralised using fMRI.

A distinctly older method for lateralisation of brain functions, which is based on the temporary inactivation of one brain region, is the intracarotid sodium amytal test, called Wada test for short. Previously considered to be the gold standard of lateralisation of functions, its use is the subject of controversial discussion today, which is currently reflected in a markedly reduced number of tests being performed worldwide. The current significance of the test and the resilience of the arguments in its favour and against it are discussed by the Zurich group (Kurthen et al.).

The first article in this issue is devoted to memory. The authors (Jokeit/Bosshardt/Reed) have ventured to attempt to inquire about invariants and differences of memory disturbances common to neurological diseases and to compare them. What 50 years ago was still a common approach for deepening understanding of the disorder, today looks like a "transdisciplinary" project. At all events we found it informative to look out at the broader picture beyond epileptology.

I extend my thanks to all authors as well as Ms Becker and Ms Depping for their collaboration in this edition. I wish you, dear readers, a stimulating and productive read.

*Hennric Jokeit*



*Prof. Dr. Hennric Jokeit*

Comme la plupart des spécialités médicales, la neuropsychologie est caractérisée par une spécialisation croissante en sous-disciplines de plus en plus pointues. Si cette évolution générale est la marque du succès, elle est aussi le prix à payer pour un progrès qui se traduit actuellement davantage par une sophistication des méthodes et des techniques que par de nouveaux concepts.

La neuropsychologie clinique institutionnelle se structure en deux domaines : d'une part les affections neurologiques spécifiques, telles que la sclérose en plaques, la maladie d'Alzheimer et la maladie de Parkinson, d'autre part les systèmes fonctionnels comme les fonctions langagières, mnésiques et exécutives. Les points d'intersection entre les domaines nosologiques et fonctionnels concentrent certaines questions concernant des affections spécifiques. Ainsi, le sujet neuropsychologique prépondérant, à la fois dans le domaine des démences et en épileptologie, est-il la mémoire antérograde.

La présence marquée du thème de la mémoire dans la clinique et la recherche épileptologiques est motivée par différentes raisons. Ainsi, presque tous les patients se plaignent de problèmes de mémoire et ceux qui les entendent apportent chacun leur propre compréhension empathique vis-à-vis de ces troubles. Chez l'homme comme chez l'animal, rares sont les autres fonctions cérébrales avancées aussi faciles à mesurer que l'apprentissage, la mémorisation et l'oubli. Plus important encore, l'organe central de la formation de la mémoire est aussi la structure cérébrale la plus épileptogène.

Brenda Milner, lauréate du Prix Balzan 2009, a découvert il y a plus de 50 ans l'importance de l'hippocampe pour la formation de la mémoire, après qu'un patient épileptique, Henry Gustav Molaison (HM), a subi une ablation bilatérale du lobe temporal. La découverte de Brenda Milner, qui se consacre aujourd'hui, à l'âge de 93 ans, à la neuro-imagerie fonctionnelle à l'Institut neurologique de Montréal, a débouché sur un domaine de recherche majeur et de haute pertinence clinique dans les

neurosciences cognitives.

Le dernier article du présent numéro (Broicher/Jokeit), qui propose une initiation conceptuelle et méthodologique au thème des déficits de cognition sociale chez les patients épileptiques, montre que le champ d'exploration de la neuropsychologie dans l'épilepsie ne se résume pas à la mémoire.

Le principal changement méthodologique en neuropsychologie a été l'introduction, il y a une dizaine d'années, de l'imagerie par résonance magnétique fonctionnelle (IRMf). Toutefois, celle-ci n'en est qu'à ses premiers balbutiements si l'on mesure cet instrument à son utilité dans le diagnostic clinique individuel. Nos collègues autrichiens (Kuchukhidze/Trinka) résument dans leur article les développements de l'utilisation de l'IRMf en épileptologie. À l'heure actuelle, l'IRMf sert le plus souvent à latéraliser les fonctions langagières dans le diagnostic préopératoire. Nos collègues bernois (Gutbrod et al.) font part de leurs expériences positives avec une méthode d'examen comparativement simple, permettant de latéraliser les zones antérieure et postérieure du langage à l'aide de l'IRMf.

Une méthode nettement plus ancienne de latéralisation des fonctions cérébrales, dite test de Wada, consiste en l'injection intracarotidienne d'amytal sodique. Autrefois considérée comme le « gold standard » pour la latéralisation des fonctions, elle est aujourd'hui controversée, de sorte que son utilisation a fortement diminué partout dans le monde. La valence actuelle du test et la solidité des arguments pour ou contre sont discutées par le groupe zurichois (Kurthen et al.).

Le premier article de ce numéro est consacré à la mémoire. Les auteurs (Jokeit/Bosshardt/Reed) ont tenté de rechercher et de comparer les invariants et les différences entre les troubles de la mémoire associés à des affections neurologiques fréquentes. Ce qui, il y a 50 ans encore, était une approche très répandue pour approfondir la compréhension des troubles, fait aujourd'hui figure de projet « interdisciplinaire ». Pour nous en tout cas, il a été instructif de ne pas nous cantonner à l'épileptologie.

Je remercie chaleureusement l'ensemble des auteures et auteurs, ainsi que Mesdames Becker et Depping, pour leur collaboration à cette édition. Quant à vous, chers lectrices et lecteurs, je vous souhaite une lecture enrichissante.

*Hennric Jokeit*

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### Summary

Memory complaints are the most commonly reported cognitive problems in patients with epilepsy. Perceived forgetfulness, however, is also an issue for up to 50% of neurologically healthy elderly individuals. Moreover, some degree of memory impairment is also a prominent feature in the majority of neurological and psychiatric disorders. Therefore, when considering memory impairment in epilepsies, it is useful to take an epidemiological perspective and take into account not only the base rates of memory impairment in these conditions, but also to recognize the fact that there is a high rate of comorbidity between such disorders and epilepsy. In order to highlight common and divergent pathways of memory impairment, we have compared symptoms of memory deficits and underlying pathology in a representative selection of neurological and psychiatric disorders.

Our comparative analysis reveals that impairments in memory encoding and memory retrieval are a common feature in all selected disorders as well as in normal aging. This suggests that the majority of memory failures in those patients may arise from transient or chronic prefrontal dysfunction. Retention, in contrast, seems to be almost exclusively affected in Alzheimer's dementia and mesial temporal epilepsy (MTLE) as it depends on the functional integrity of the hippocampal formation and anterior diencephalic structures. Due to frequent additional prefrontal disturbances we assume that MTLE is characterized by memory impairment of a fronto-temporal spectrum. In idiopathic generalized epilepsy (IGE) and frontal lobe epilepsy (FLE), a more prefrontal profile characterizes the memory impairments which resemble those seen in non-epileptic disorders such as ADHD.

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**Key words:** Memory, epilepsies, aging, frontal lobe, temporal lobe, hippocampus

### Interiktuale Gedächtnisbeeinträchtigungen bei Patienten mit Epilepsie im Vergleich zu mnestischen Symptomen ausgewählter neurologischer Erkrankungen und psychiatrischer Störungen

Die von Epilepsiepatienten am häufigsten geäußerte Beeinträchtigung kognitiver Leistungen betrifft das Gedächtnis. Wendet man sich klinisch und wissenschaftlich Fragestellungen des Gedächtnisses bei Menschen mit Epilepsie zu, wird häufig ausser Acht gelassen, dass Vergesslichkeit von mehr als der Hälfte älterer neurologisch gesunder Menschen beklagt wird und zum Symptombild der meisten neurologischen und psychiatrischen Erkrankungen gehört. Die vorliegende Arbeit vergleicht Gedächtnisbeeinträchtigungen von Menschen mit Epilepsie mit denen von gesund alternden sowie einer Reihe ausgewählter neurologischer Erkrankungen und psychiatrischer Störungen. Wir zeigen auf, dass insbesondere Beeinträchtigungen der Gedächtnisenkodierung und des -abrufs ein Merkmal aller beschriebenen Erkrankungen und Störungen wie auch des normalen Alterns sind. Die häufigsten Fehlleistungen des Gedächtnisses resultieren aus transienten oder chronischen Beeinträchtigungen präfrontaler Funktionen. Behaltensleistungen sind dagegen akzentuierter betroffen bei der mesialen Temporallappenepilepsie und der Demenz vom Alzheimerstyp. Behaltensleistungen sind insbesondere von der Integrität der hippocampalen Formation und anteriorer diencephaler Strukturen abhängig. Weil bei Patienten mit hochaktiver mesialer Temporallappenepilepsie frontale Strukturen häufig funktionell beeinträchtigt sind, postulieren wir als häufiges klinisches Bild charakteristische Beeinträchtigungen von Gedächtnisleistungen im Sinne eines Spektrums fronto-temporaler Minderleistungen. Bei idiopathischen Epilepsien und Frontallappenepilepsie weisen die Beeinträchtigungen ein deutlicher frontal ausgeprägtes Muster auf, das eher mit Symptombildern vergleichbar ist, wie wir es auch bei Patienten mit Aufmerksamkeitsstörungen (ADHS) finden.

**Schlüsselwörter:** Gedächtnis, Epilepsie, Altern, Frontallappen, Temporallappen, Hippokampus

## Comparaison des affections interictuelles de la mémoire de patients atteints d'épilepsie avec les symptômes mnésiques d'affections neurologiques et de troubles psychiatriques choisis

La déperdition de la performance cognitive la plus citée par les patients épileptiques concerne la mémoire. Lorsqu'on s'intéresse dans une perspective clinique et scientifique aux questions touchant à la mémoire des personnes atteintes d'épilepsie, on a tendance à oublier que plus de la moitié des personnes âgées sans troubles neurologiques se plaignent d'une mémoire déficiente et que la distraction et l'oubli entrent aussi dans le schéma symptomatique de la plupart des affections neurologiques et psychiatriques. Le présent travail établit une comparaison entre les troubles de la mémoire de personnes atteintes d'épilepsie, de personnes saines vieillissantes, ainsi que d'une série d'affections neurologiques et de troubles psychiatriques. Nous montrons notamment que des „pannes de codage“ et de décryptage de la mémoire sont le dénominateur commun de toutes les maladies et des troubles décrits, mais aussi du vieillissement ordinaire. Les ratées les plus fréquentes de la mémoire proviennent de dysfonctionnements passagers ou chroniques des fonctionnalités préfrontales. Les facultés mnésiques sont concernées davantage en cas d'épilepsie des structures mésiales du lobe temporal et de démence du type Alzheimer. Les facultés mnésiques sont avant tout tributaires de l'intégrité de la formation hippocampique et des structures diencephaliques antérieures. Parce que l'on observe fréquemment des perturbations fonctionnelles des structures frontales chez les patients avec une épilepsie mésiale du lobe temporal hautement active, nous postulons que les affections caractéristiques des facultés mnésiques au sens d'un spectre de déficiences des performances fronto-temporales constituent une manifestation clinique caractéristique. Lors d'épilepsies idiopathiques et d'épilepsies du lobe frontal, les affections affichent un schéma nettement plus frontal avec une symptomatique plutôt comparable à celle que nous trouvons chez les patients avec une déficience d'attention (ADHS).

**Mots clés :** Mémoire, épilepsie, vieillissement, lobe frontal, lobe temporal, hippocampe

### 1. Introduction

As far back as Aristotle, ancient philosophers considered memory to be an instrumental function in contrast to traits such as temperament that were held to be more of a core feature of a person. However, the study of the effects of memory impairment and loss has shown us that memory is more than a mere instrumental function. Our personal history is essential in helping us define who we are. Once that history is

disturbed or, as in the case of amnesia or dementia, entirely vanishes, one loses an indispensable element in the perception and awareness of selfhood.

Memory impairment can be a significant added burden for patients with epilepsy who are already struggling with a debilitating and chronic disorder. One should be particularly aware of its potential impact on academic achievement in children with epilepsy. The present paper provides a phenomenological and comparative perspective on the epidemiology of memory symptoms and impairment in epilepsies.

When general practitioners question their patients about possible memory impairments, usually every second older patient complains of memory problems [1]. Why are these complaints so frequent in the general population, and why are they more frequent in patients with epilepsies?

With the exception of very rare savants everybody experiences their memory to some degree as fallible. Since long before Sigmund Freud formulated psychoanalysis, forgetting has been part of the “Psychopathology of Everyday Life”. Forgetting is probably the most frequently used excuse for things we failed to do or for things we did wrong. The excuse of forgetting is usually socially acceptable because it is much easier to say, “It is not me, it is my memory!”; and it is easier to forgive forgetting than it is to forgive a character flaw. In addition, it appears that having a bad memory is more acceptable and less stigmatising than admitting to other faults such as anhedonia (no longer finding activities pleasurable), depression, or anxiety. Thus, we feel that a thorough understanding of the almost universal memory complaints necessarily integrates the influences of social norms and conventions, folk psychology, and individual experiences of memory decline and failure.

Patients with epilepsy more frequently report memory impairments than individuals without epilepsy. One reason could be that they tend to overestimate their memory problems [2-5], possibly as a result of their commonly low mood and diminished self-esteem. Indeed, various studies have repeatedly reported a stronger correlation between subjective memory complaints and measures of depression and anxiety than between subjective complaints and actual performance in memory tests [6, 7]. **Table 1** provides a summary of common comorbidities seen in patients with epilepsy that may in part explain the increased frequency of memory complaints in this population. Depression and ADHD themselves may have a considerable impact on memory performance, as will be discussed later. The influence of psychiatric comorbidities on memory in epilepsy has been widely neglected.

The absence of a close correlation between subjective memory complaints and objective memory measures can also be explained by the fact that patients usually evaluate their own memory based on the frequency of “tip of the tongue” states and “going back to check” phenomena rather than their ability to learn

a word-list or to reproduce a prose passage [8, 9], the most common objective memory tests. In addition, patients are unable to differentiate between memory impairment and insufficient information processing due to weak or fluctuating attention.

reserve capacity – helps to explain individual differences observed in the expression of symptoms during the course of chronic or progressive disorders.

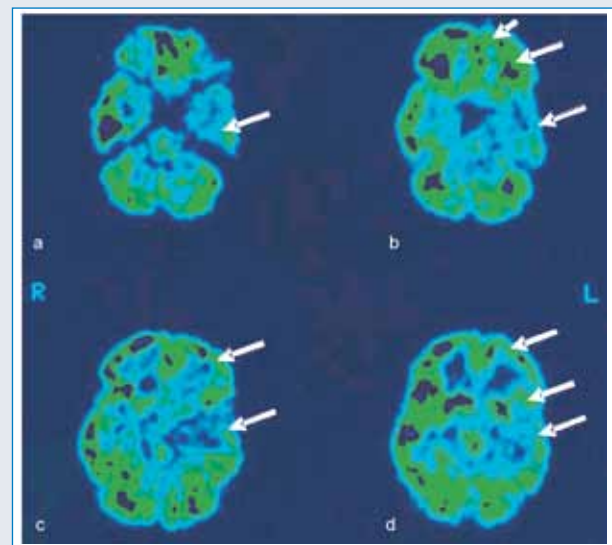
In focal epilepsies remote functional deficit zones are further sources of inter-individual variability.

**Table 1:** Estimates of the prevalence of selected psychiatric disorders in epilepsies after Kanner [10].

	Epilepsy	General Population
Depression	11-60%	2-4%
Anxiety	19-45%	2.5-6.5%
Psychosis	2-8%	0.5-0.7%
ADHD	25-30%	2-10%

There are considerable differences in the results of memory tests within samples of aged-matched healthy controls and patients sharing the same pathology. State dependent intra-individual differences as well as inter-individual differences in memory encoding, memory consolidation, and recall are the source of substantial variability in memory performance. Inherited factors such as ApoE genotype, neurochemical and brain metabolic activity, brain maturation, education, and medication are among various additional factors that can influence everyday memory as well as test performance.

It is reasonable to assume that brains develop a functional reserve or have a spare capacity to cope with neuronal loss via efficiency, redundancy, plasticity, and reorganisation [11, 12]. Studies of various degenerative brain disorders (for example, Parkinson's disease, vascular dementia, and Alzheimer's dementia) suggest that a functional decline becomes apparent only if a certain amount of brain tissue is insulted. This means that individual performance differences are related to differences in available reserves and, thus, that the greater the reserve, the more severe the pathology must be in order to cause functional impairment [13]. Epidemiological evidence indeed suggests that individuals with better cognitive abilities, including memory, have a reduced risk of developing Alzheimer's disease (AD) [14]. Various animal models also suggest that enriched environments, a factor that is supposed to enhance brain reserve capacity, may prevent brain disorders. It has been shown that enriched environments provide resilience to hippocampal insults resulting from seizures and excitotoxic injury [15]. In summary, the heuristic concept of brain reserve capacity – including memory



**Figure 1.** Characteristic metabolic maps (FDG-PET) of a 24-year-old male patient with left-sided medial temporal lobe epilepsy demonstrating the most prominent hypometabolic zones in medial (a) and lateral temporal (b) regions [16]. Note the additional remote metabolic depressions in left fronto-orbital (b), prefrontal (b, c), and fronto-opercular cortex (d). R and L indicate the patient's right and left side.

**Figure 1** shows a representative FDG-PET scan of a 24-year-old male patient with left-sided medial temporal lobe epilepsy. It is noteworthy that the patient showed MRI-proven abnormalities exclusively within left-sided mesial temporal lobe structures whereas FDG-PET demonstrated widespread metabolic disturbances within left temporo-lateral structures, left pre-

frontal structures, and within the left thalamus. It is well known that these structures modulate or govern the formation and recollection of new episodic memories. However, there are very few studies that have investigated the influence of remote effects on cognition and especially on memory in patients with focal epilepsies. Functional or structural deafferentation, excitotoxic effects, antiepileptic drugs, and aging act on the functional integrity of mesiotemporal, diencephal, and prefrontal circuits that are critically involved in memory formation and recall.

Various factors like memory reserve capacity, inherited vulnerability of memory functions, localisation and age at lesion, pathological electrical brain activity, and seizures affect memory performance of patients with epilepsies. More than 50 years of neuropsychological examination of patients with epilepsy has shown that one group of patients in particular is especially prone to develop deficits of declarative memory: those with mesial temporal lobe epilepsy. This syndrome, which is usually characterized by febrile convulsions, hippocampal sclerosis, and a seizure onset rarely prior to school age, has the status of being a model disorder for the study of anterograde episodic memory. Moreover, the comprehensive pre-surgical and post-surgical evaluation of many patients with refractory MTLE has provided excellent research opportunities far beyond the diagnostic standards in other disorders. In clinical samples of patients with unilateral MTLE, however, the textbook material-specific deficits and specific deficits in certain memory processes are frequently absent at the individual level and are only represented in group sample statistics by weak to moderate effect sizes [17]. Without question, memory research is indebted to the epilepsies for its temporo-limbic model of episodic memory. However, despite an almost homogenous morphology, MTLE has tremendous intrinsic developmental and seizure-related dynamics that challenge linear and dichotomous memory models such as verbal vs. non-verbal, retrograde vs. anterograde and episodic vs. semantic.

In the following sections we comparatively describe the effects of normal aging, epilepsy as well as selected psychiatric and degenerative disorders. Such a comparative approach should help broaden our understanding of the pathological core processes and characteristics of memory impairment in epilepsies by revealing similarities and differences among disorders that primarily or only incidentally affect memory processes.

## 2. Conditions and disorders of long-term memory

### 2.1 Normal aging

We are all probably susceptible to memory loss if we live long enough. From both a neuropsychologi-

cal as well as a neurophysiological perspective, the frontal lobes are presumed to be the most vulnerable area with regard to normal aging processes. Regarding memory, it has been shown that performance of older adults is especially disrupted in tasks that involve frontal structures. Hence, memory deficits in older adults appear to originate largely from insufficient control strategies during encoding and retrieval, which explains why healthy older adults seem to be more susceptible to false memories and have more difficulties in source memory than younger adults [18]. An analysis of the normative data from the German adaptation of the Auditory Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest, VLMT [19], and of a Swiss normative sample of the CERAD (The Consortium to Establish a Registry for Alzheimer's Disease [20]), demonstrates that the impact of normal aging on memory processes is moderate (around one standard deviation over 30 years) and affects mainly encoding, retrieval, and recognition, and to a lesser extent retention. The Seattle longitudinal study revealed a comparable decline of roughly two standard deviations from the age of 25 to the age of 81 in episodic memory functions [21]. Whereas episodic memory experiences a gradual decline across the adult lifespan, semantic memory, on the other hand, is stable until late in life [22]. From a clinical point of view it should be noted that memory complaints are more frequent in healthy subjects aged forty and older. Therefore, patients with epilepsies could potentially falsely attribute age-related memory impairments to their epilepsy.

### 2.2 Epilepsies

As already noted, epilepsy as a chronic illness is associated with various factors that may influence the course of an individual's memory performance. The differences between three major types of epilepsies, idiopathic generalized epilepsies, temporal lobe epilepsy, and frontal lobe epilepsy stress the significance of disease-related pathological pathways and lesions on the nature of memory deficits.

#### 2.2.1 Idiopathic Generalized Epilepsies (IGE)

About one third of all epilepsies are idiopathic generalized epilepsies (IGE). The most prevalent major risk factor for IGE identified to date is the 15q13.3 microdeletion [23]. About 50% of patients with IGE suffer from Juvenile Myoclonic Epilepsy (JME). This syndrome with a complex inheritance is clinically characterized by myoclonic jerks upon awakening, generalized tonic clonic seizures (GTCS) and frequent typical absences [24].

An essential characteristic of IGE is normal morphological MRI-scans. Volumetric MRI-studies, however, provide evidence of smaller thalami and frontal

lobe tissue early in the course of recent-onset JME [25]. Similarly, magnetic resonance spectroscopy (MRS) has revealed reduced N-acetyl aspartate levels in prefrontal areas and reduced choline and myo-inositol levels within the thalamus [26]. Memory test performance has been found to be correlated with MRS-measures of neuronal dysfunction in the temporal lobes [27]. Because the temporal lobes were exclusively measured in this study no conclusion can be drawn as to whether IGE specifically affects memory residing within temporal lobe structures.

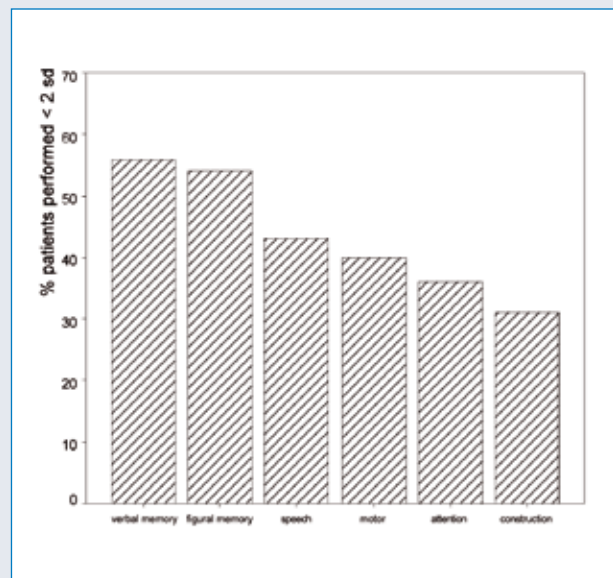
A recent positron emission tomography (PET) study suggests that dopamine signalling is impaired in the target regions for dopaminergic neurons, the striatum and frontal lobe, and is apparently related to interictal neuropsychological dysfunctions in JME [28].

Neuropsychological frontal lobe functions in JME have been examined in several studies. Working memory, set shifting, reasoning, planning, verbal fluency, and mental flexibility are frequently found to be mildly impaired in JME [29, 30]. Only a few studies, however, have investigated memory functions in patients with either IGE or JME [27]. Patients with IGE have been reported to exhibit poorer initial learning efficiency than controls, to require a greater number of trials to reach a learning criterion, and to have retrieval rather than retention difficulties [31]. Dickson et al. [27] reported that 85% (26/30) of patients with IGE complained of memory impairments. Neuropsychological testing in this sample revealed poor performance in recall, recognition, visual and verbal memory tests. Unfortunately, the influence of antiepileptic drugs and other epilepsy associated factors was not controlled. The same methodological shortcoming limits the conclusions that can be drawn from the study by Pascualichio et al. [29] that reported cognitive impairments in patients with JME in various domains including memory.

There are contradictory results as to whether verbal or non-verbal memory is more impaired in IGE [21]. Task difficulty could be partly responsible for inconclusive findings [32]. To summarize, to date we have no clear evidence whether IGE specifically and directly impairs memory or whether verbal or non-verbal memory is more affected. Learning and encoding, rather than retention and recognition, appear to be more affected in IGE. It is reasonable to assume that secondary impairments of episodic and semantic memory processing due to affected executive functions and impaired attention comprise the primary pathological mechanism of memory impairments in patients with IGE.

## 2.2.2 Focal Epilepsies

In 60-70% of all epilepsies seizures originate from an epileptogenic zone that usually can be localized by ictal EEG and MRI. Early ictal symptoms are usually determined by localisation and not aetiology. A retrospec-



**Figure 2.** Data by Hoppe et al. [33]. Frequency of patients with focal epilepsies (N = 3,193) who performed below two standard deviations on a range of cognitive tasks. Note it is a sample of consecutive patients from a Grade IV epilepsy centre and epilepsy surgery program in Bonn, Germany.

tive analysis of more than 3,000 neuropsychological patient files from the Bonn epilepsy surgery program revealed that the majority of patients with focal epilepsies demonstrated severely affected (< 2 sd) performance in various functional domains. Verbal and figural memory were the most frequently impaired functions [33]. It is noteworthy that this sample represents consecutive patients in a Grade IV epilepsy centre that is specialised for epilepsy surgery and is therefore not representative of the majority of epilepsy patients. However, it illustrates that patients with refractory focal epilepsies are prone to suffer from significant memory disturbances.

### 2.2.2.1 Mesial temporal lobe epilepsy (MTLE)

In 50% of focal epilepsies, seizures originate within the temporal lobes, mostly within the mesial temporal lobe. Not only because of its high prevalence but also because of its potential for drug resistance and its risk of memory impairment, MTLE is the most important focal epilepsy in clinical practice as well as in research.

Since the landmark publications by Brenda Milner 50 years ago on tragic memory losses following bilateral temporal lobectomy MTLE is considered to be a model disorder for anterograde episodic memory disturbances [34]. Although gradual memory impairment can be shown by neuropsychological testing in the majority of patients with MTLE, only a minority suffer from clinically relevant memory disturbances [35]. Nevertheless, memory is considered to be the main neuropsychological impairment in MTLE. Patients with

MTLE typically perform worse than controls in tests assessing the ability to retain new information over a delay of about 30 minutes. Consolidation, retention, and delayed recall are the greatest affected functions in patients with MTLE. The degree and type of impairment depends on the lateralization of TLE. Left-sided TLE is usually associated with more pronounced deficits in verbal memory whereas right-sided TLE is less consistently related to non-verbal memory deficits. The Rey Auditory Verbal Learning test is one of the most frequently used tests to evaluate memory functions in patients with MTLE. Patients with left-sided MTLE usually benefit less from the repeated learning trials, recall fewer words after presentation of an interference list and forget more words after a 30 minute retention interval compared to patients with right-sided temporal lobe epilepsy. The latter commonly perform at a level between that of healthy controls and patients with left-sided MTLE. Age at lesion, duration of epilepsy, degree of pathological abnormalities, seizure frequency and seizure type are correlated with memory performance [36-38]. In patients with MTLE lateralized to the speech dominant hemisphere semantic memory can be as impaired as episodic memory (Giovagnoli et al. 2005) [39]. Semantic memory specifically is more susceptible to structural temporal lateral lesions and an early seizure onset [39, 40].

The frequent propagation of epileptic activity from temporal to frontal structures in complex-partial seizures and secondarily generalized seizures can temporarily or chronically impair the functional integrity of remote symptomatogenic zones [16]. Therefore, it is not surprising that several studies have revealed that patients with MTLE and FLE are impaired in certain aspects of executive and attentional functions [35].

More recently remote memory and accelerated forgetting have been identified as possible additionally affected memory processes in patients with MTLE [41].

### 2.2.2.2 Frontal lobe epilepsy (FLE)

In about 2% of all epilepsies, seizures originate from a primary epileptogenic focus somewhere within the frontal lobes which cover about 40% of the cerebral cortex [24]. The frontal lobes are anatomically as well as functionally subdivided into motor cortex, premotor cortex, prefrontal cortex, and limbic and paralimbic cortex. Frontal lobe lesions in general, and more specifically frontal lobe epilepsy, do not typically produce the kind of severe memory disturbances that is seen in patients with mesial temporal lobe epilepsy (MTLE) [42]. Consequently, memory studies in patients with FLE are rare [43]. Lesional as well as functional imaging studies in subjects without epilepsy, however, provide sufficient evidence that the prefrontal cortex promotes the formation of episodic long-term memory [44]. It is reasonable to assume that deficits in executive functions

combined with attentional and working memory weaknesses may affect encoding as well as retrieval. Indeed, attention and working memory are equally affected in patients with FLE and MTLE [40]. Clinical observations and theoretical considerations favour the assumption that memory deficits in patients with prefrontal disturbances arise from deficits in control processing rather than from a primary deficit in memory retention. A review of the literature finds that patients with prefrontal lesions are impaired in the following memory related processes: free-recall, memory clustering, memory strategies, metamemory, consistency of recall, source memory, memory for temporal order, associative learning and insight into one's own memory problems [44, 45, 46]. Despite these deficits, patients with frontal lobe lesions may perform almost normally under highly structured memory encoding and retrieval conditions. Semantic memory is apparently not specifically affected, with the exception of memory retrieval processes which are vulnerable to frontal lobe pathology [39].

Although determining lateralisation of the epileptogenic zone in frontal lobe epilepsies via neuropsychological tests is rather difficult [40], McDonald et al. [45] described a complex relationship between functional lateralisation within the frontal lobes and aspects of memory processing: Left frontal epileptogenic lesions impaired encoding but not recognition. In contrast, right frontal lesions impaired recognition but not recall.

To summarize, memory symptoms in frontal lobe epilepsies are similar to those frequently reported in patients with IGE but do not resemble the pattern seen in TLE. Memory symptoms in FLE patients are predominantly related to executive and attentional dysfunctions. The lateralisation issue appears to be rather complex due to the more intricate interplay between prefrontal cortices compared to primary motor or sensory cortices. Moreover, epileptic brain electric activity and seizures propagate rapidly into contralateral structures and may cause bilateral functional impairment.

## 2.3 Psychiatric disorders

### 2.3.1 Schizophrenia

A large body of evidence has shown memory to be an area of significant cognitive deficit in schizophrenia and more severe than that seen in most other psychiatric disorders [47-50]. Far-reaching and pervasive cognitive deficits have been identified in schizophrenia in a variety of cognitive domains; however, the largest effect sizes have been identified for global verbal memory [51]. A more detailed look at memory was provided in a meta-analysis performed by Aleman et al. [48]. This explored the degree, extent and pattern of memory impairment in schizophrenia as well as studying possible moderator variables (medication, duration of illness,

positive / negative symptoms etc.). Large effect sizes were found for delayed and immediate recall measures and moderate effect sizes for recognition measures. Deficits were also found in short-term memory (digit span, digit span backwards) and in the learning curve. Impairments were independent of the type of material (visual-nonverbal / verbal), a finding replicated by other studies [51]. The impairments seen in immediate recall (and not affected by longer retention intervals) and weaker learning have been interpreted by some authors [46, 52] to be indicative of impairments in encoding, and some researchers hold the deficits in encoding to be a core deficit in schizophrenia [53]. In this light, Gold et al. [49] found their patients with schizophrenia to be less able to benefit from semantic information to aid encoding and Boyer et al. [52] have outlined evidence for impairments in contextual binding.

Patients with unrecognized mesial temporal lobe epilepsy could be misdiagnosed as having schizophrenia because of ictal or interictal psychotic symptoms and pronounced memory deficits. However, MRI- and EEG-diagnostics would disclose the etiology of memory deficits in these patients.

### 2.3.2 Depression

Deficits in cognitive functions, primarily in the domains of executive functioning and memory have been consistently reported in the literature on cognition in depression [54]. Findings as to exactly which aspects of memory are impaired and the severity of the impairments, as well as associations with disease variables, are less consistent than research findings in schizophrenia. Most often, deficits have been identified in verbal recall and recognition [50, 55] and one meta-analysis of cognitive function found the largest effect sizes for encoding and retrieval [56]. While the main focus of research on memory in major depressive disorder has focussed on verbal memory, deficits have also been found in recall and recognition of visuo-spatial information [53, 57]. The effects of duration of illness and / or number of hospitalizations and symptom severity on memory impairment are unclear. Numerous studies have indicated that first-episode patients are not as impaired as patients with recurrent episodes [58, 59] while other groups have failed to find an association between memory dysfunction and duration of illness [55, 60]. Generally, inpatients have been found to have more severe impairments [50] and two recent studies exploring outpatients with less severe symptomatology (including a majority of first-episode and non-medicated patients) have failed to find significant verbal memory impairments [57, 60]. Further, research groups have found persistent verbal memory impairments after remission of symptoms [61-63]. The persistency of memory impairment after remission as well as the inability of some studies to find a correlation be-

tween memory impairment and symptoms [54] have led several authors to argue that the observed memory dysfunctions are a trait rather than state abnormalities or are epiphenomena related solely to depressive symptoms [55, 53, 63].

The high prevalence of depression in patients with epilepsies (**Table 1**) raises the question of whether depressive symptoms are responsible for memory impairments beyond those caused by the epilepsy itself.

### 2.3.3 Attention deficit / Hyperactivity disorder (ADHD)

The majority of memory research in attention deficit / hyperactivity disorder has focussed on working memory. A meta-analysis by Martinussen et al. [64] revealed moderate to large impairments in working memory with the largest impairments found in spatial storage and spatial central executive (i.e., manipulation of information stored in short-term memory) domains and more moderate impairments in verbal working memory functions. A further study of ADHD subtypes found that poor performance in the central executive domain (regardless of modality) tended to be associated with the inattentive subtype of ADHD [65]. In more classical memory research, a meta-analysis examining overall neuropsychological functioning in adults with ADHD as compared to controls found that verbal memory (along with complex attention variables) was one of the best discriminator variables [66]. A study of verbal memory and learning (a word-list learning task) found that adults with ADHD were able to learn significantly fewer words and to use fewer semantic clusters, but they did not differ from controls in rates of forgetting. The authors interpreted the findings as evidence of deficient encoding or reduced retrieval performance.

The high levels of comorbidity between ADHD-like symptoms and epilepsies (**Table 1**) raises the prospect that ADHD symptoms are an additional factor contributing to memory impairments in a substantial number of patients.

## 2.4 Degenerative disorders

### 2.4.1 Alzheimer's disease (AD)

In Alzheimer's Disease (AD) the anterograde episodic memory deficit is profound and pervasive. Depending on the pathology starting in the medial temporal lobe, more specifically the entorhinal cortex, memory impairment is usually the first symptom in the course of the disease [67]. It is the predominant impairment in 71% of patients [68] and accounts for 68% of the measured cognitive deficit [69]. The severe hippocampal dysfunction leads to an inability to store and consolidate

new information. Therefore, all aspects of anterograde episodic memory performance – encoding, retention, retrieval and recognition – are equally disturbed. However, the most sensitive measure with regard to differential diagnosis is rapid forgetting, resulting in poor retention. Moreover, low recognition performance in AD patients generally reflects a profound storage deficit [70]. Since atrophy spreads from the medial temporal lobe to lateral temporal areas, semantic memory is often affected quite early in the disease process as well, although this finding seems to be controversial, and the degree of semantic impairment in patients with AD may be variable in the early stages [69, 71, 72].

Patients with unrecognized mesial temporal lobe epilepsy aged fifty and older could be misdiagnosed as to having AD due to severe memory deficits in their everyday life or due to poor performance in the Mini-Mental State Test [73-75]. However, MRI- and EEG-diagnostics would disclose the etiology of memory deficits in these patients.

#### **2.4.2 Fronto-temporal dementia (FTD, frontal variant)**

Compared to other neurodegenerative disorders, episodic memory seems to be relatively well preserved in fronto-temporal dementia [76]. Retention especially has been shown to be fully normal [77]. Nevertheless, on formal neuropsychological testing memory deficits may account for 41.1% of the fronto-temporal dementia (FTD, frontal variant) patients' overall cognitive impairment [69]. In accordance with the restriction of pathology to the frontal lobes at the beginning of the disease, memory is primarily impaired due to executive problems, i.e. inefficient learning strategies or deficient retrieval monitoring. Consequently, qualitative errors such as confabulations or misconstructions have often been found in the performance of FTD patients [77]. Semantic memory is generally found to be unimpaired in early stages of the frontal variant of FTD.

#### **2.4.3 Vascular dementia (VaD)**

In contrast to most neurodegenerative disorders, which show relatively intact semantic memory, semantic memory impairment in VaD appears to be common and also more profound than in patients with AD [72]. As in the case of episodic memory, the impairment is moderate with no distinction between different memory processes. However, the individual cognitive profiles of patients with VaD are quite variable: Reed et al. [68] characterized subjects by their neuropsychological profiles and found that only 45% demonstrated a predominant executive impairment, while 18% showed a profile of below-average memory functioning and 36% fit neither pattern. The reason for this variability

presumably lies in the heterogeneity of cerebrovascular pathology. Jellinger [78] distinguishes between multifocal (disseminated) lesions and focal disease and points out that episodic memory can be markedly compromised if focal vascular pathology in the hippocampus leads to neuronal damage and necrosis. Yet, Price et al. [79] found no strong relationship between white matter abnormalities (WMAs) as a marker for vascular pathology and memory performance and they suggested that functional abnormalities induced by WMAs do not produce impairments in memory.

Due to the highly variable cognitive profiles in patients with beginning VaD, the cognitive profile does not necessarily discriminate between VaD and that of certain idiopathic and focal epilepsies.

#### **2.4.4 Multiple sclerosis (MS)**

Long-term memory is impaired in 40-65% of Multiple Sclerosis (MS) patients and is one of the leading cognitive symptoms of the disorder. Earlier studies suggested that the primary cause of memory deficits was difficulty in retrieving information from long-term memory. More recent studies have shown that the primary deficit lies in the initial learning of information. Patients with MS require more repetitions to reach a learning criterion. Recall and recognition of acquired information, however, is apparently unimpaired. Autobiographical episodic memory was found to be affected in 60% of patients, whereas autobiographical semantic memory appeared to be unaffected [80]. Many factors have been considered to be responsible for the observed memory deficits including slow processing speed, susceptibility to interference, executive dysfunction, and perceptual deficits [81]. Recent findings, however, provide evidence for selective and progressive hippocampal atrophy in MS localized initially to the CA1 subregion that is associated with deficits in memory encoding and retrieval [82]. In MS patients, semantic memory is less affected than episodic memory [80, 83].

Finally, multiple sclerosis may mimic the memory profile of epilepsy patients, especially of patients with MTLE. Epilepsy itself, with a prevalence of 3-4%, is an infrequent but not rare consequence of multiple sclerosis [84].

#### **2.4.5 Huntington's disease (HD)**

Memory impairment in patients with Huntington's Disease (HD) appears to be mainly characterized by a retrieval deficit. Their difficulties in initiating and monitoring retrieval processes reflect the predominant pathology in subcortical frontal circuits. It has been shown that HD patients and AD patients exhibit comparable deficits in immediate and delayed free recall. In contrast, retention and recognition performance

are almost normal in HD, showing that storage is only minimally affected by the disease. In general, semantic memory is preserved in HD. Nevertheless, performance in semantic memory tests may be impaired due to the general retrieval deficit if the testing procedure requires efficient and flexible retrieval of information from semantic stores, e.g. in category fluency tasks.

HD's memory profile, which is characterized by a clear benefit from recognition procedures which minimize the need for effortful, strategic retrieval, can be regarded as prototypical for subcortical neurodegenerative disorders [85].

#### 2.4.6 Dementia with Lewy bodies (DLB), Parkinson's Disease Dementia (PDD)

In concordance with their subcortical pathology and relative sparing of the medial temporal lobe, DLB and PDD show a pattern of memory impairment with a prominent retrieval deficit while retention and recognition are less affected [86]. Although there is considerable overlap between DLB and PDD [87], memory performance in these disorders seems to be rather variable and the pattern is less salient than that seen in HD [85]. In particular, there seems to be a less clear advantage of recognition procedures over free recall. A

**Table 1:** Impairment of long term memory processes in different cerebral affections.

IGE, idiopathic generalized epilepsy with absence seizure or GTCS; MTLE, medial temporal lobe epilepsy; FLE, frontal lobe epilepsy; ADHD, attention deficit hyperactivity disorder; MD, major depression; AD, Alzheimer's disease; FTD, frontotemporal dementia (frontal variant); VaD, vascular dementia; MS, multiple sclerosis; HD, Huntington's disease; PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies.

	Episodic Memory				Semantic Memory
	Encoding	Retention	Retrieval	Recognition	
Normal aging	*	=	*	*	=
Epilepsy					
IGE	*	=	*	=	?
MTLE	**	**	**	**	*§
FLE	*§	=	*	*§	*
Psychiatric					
ADHD	*	=	*		
Schizophrenia	**		**	*	
MD	*	=	*	*	
Degenerative					
AD	***	***	***	***	*/**
FTD	*	=/*	*/**	*	=
VaD	**	**	**	**	**
MS	***	*	*	=	*
HD	*	=	***	*	=
DLB, PDD	***	** §	**	**	

- = - no impairment
- \* - mild impairment
- \*\* - moderate impairment
- \*\*\* - severe impairment
- =/\* - variable
- § - verbal vs visual-nonverbal asymmetry

consistent finding, however, is that DLB patients benefit to a high degree from contextual information (such as that which is provided in story recall) which helps them compensate for their executive deficit [88]. Also, a disadvantage in encoding visual-nonverbal versus verbal material has been suggested, possibly indicating abnormal function of visual cortical areas [87].

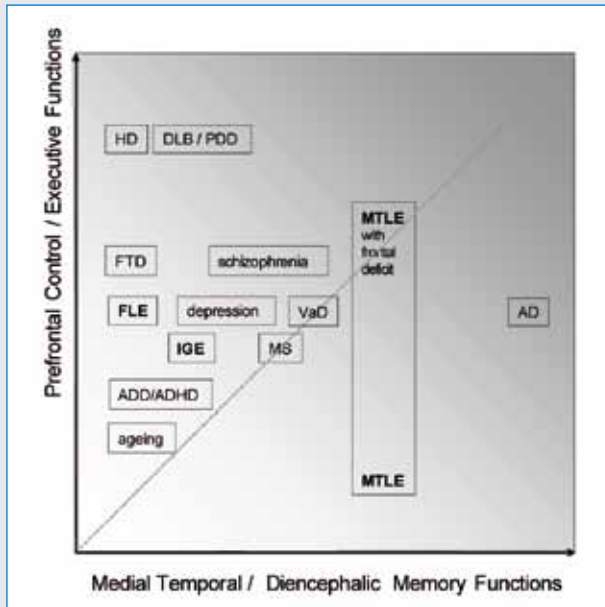


Figure 3 illustrates that the majority of disorders have a spectrum of memory impairments along prefrontal and medial temporal /diencephalic memory functions. Increased impairment is in the direction of the arrow.

### 3. Discussion

The analysis of the patterns of memory impairment in a representative selection of neurological and psychiatric disorders and normal aging suggests that episodic memory encoding and retrieval are affected in all conditions (Table 2). Encoding and retrieval processes are reliant on both the integrity of prefrontal functional systems and on functions associated with the hippocampal formation [89]. Prefrontal functions are more or less affected in all selected disorders as well as in aging, with the end result that the majority of memory failures in those patients may arise from transient or chronic prefrontal dysfunction.

Retention, in contrast, seems exclusively to be affected in some degenerative disorders, particularly in Alzheimer's dementia (AD) and to a lesser degree and less consistently in patients with vascular dementia, multiple sclerosis, and mesial temporal lobe epilepsy (MTLE). Retention is almost entirely determined by the functional integrity of the hippocampal formation and anterior diencephalic structures serving as "bottleneck" structures of memory formation [89, 90].

In the highlighted disorders the extent of prefrontal and mesial-temporal impairment is variable. Hence, we found it useful to organize disorders along dimensions of relative involvement of prefrontal and mesial-temporal functioning. In Figure 3 we aimed to assign each disorder on a prefrontal and mesial-temporal axis based on the overview we provided in Table 2.

Regarding the epilepsies, we conclude that IGE and FLE share similar aspects of memory impairment, namely weaknesses in encoding and retrieval. Although IGE and FLE usually differ in aetiology, pathology, seizure type, and course of epilepsy both demonstrate neuropsychological impairment of various prefrontal functions. Because retention is usually not impaired in FLE and IGE, their memory profile resembles those of ADHD, FTD, schizophrenia, depression, and aging. From a neuropsychological point of view, it is not possible to discriminate FLE and IGE on individual memory test performance, nor can a memory profile help to exclude the presence of comorbidities such as ADHD or depression.

In contrast, the memory profiles of MTLE, MS and VaD have more in common with regard to impaired retention than the epilepsy memory profiles within themselves. We propose that MTLE and probably also multiple sclerosis may serve as neuropsychological prototypes that can be characterized by a memory impairment of a fronto-temporal spectrum. Prefrontal metabolic disturbances have been repeatedly reported in patients with MTLE [91-93]. In accordance with these findings, impaired cognitive functions associated with the frontal lobes have been well documented in patients with MTLE [16, 35, 94]. The intra- and inter-individual differences in the degree of prefrontal impairment are probably a significant factor in the observed performance variability seen in patients with MTLE.

In addition, the cognitive side-effects of anti-epileptic drugs, particularly in polytherapy and with the use of higher dosages as administered in patients with refractory epilepsy, are prone to affect prefrontal executive functions, attention, and working memory [96]. Therefore, the memory phenotype of patients with MTLE probably results from a combination of mesial temporal structural and functional impairments, seizure related temporo-lateral and prefrontal impairments and impairment of prefrontal functions due to high dose AED polytherapy.

Consequently, seizure-free status, low dose or no AEDs could help preserve the memory capacities of patients with epilepsies. Beyond that, there are therapeutic measures to improve prefrontal functions in neurological and psychiatric patients. Behavioural therapy, consideration of the cognitive and psychiatric profiles of AEDs, the use of external memory aids, cognitive enhancers as well as future memory enhancing drugs may help preserve or improve memory performance of affected patients with epilepsy. Finally, we suggest that the comparison and integration of knowledge and ex-

perience gained from disorders other than epilepsies stimulates and widens our perspective on memory impairments in epilepsies. This in turn can only improve our consideration and treatment of our patients' memory complaints.

Regardless of disorder and independent of the individual degree of impairment, one should not forget that memory is more than an instrumental cognitive function. Its loss can have grave effects on the awareness, integrity and perception of self.

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### Summary

Numerous studies tested whether functional magnetic resonance imaging (fMRI) is capable of replacing the Wada test for determination of language dominance. We reviewed 24 studies with 486 patients. The overall mean concordance rate is only about 90%. Furthermore, atypical language dominance is not reliably detected. The objectives of the present study were to develop and validate a new linguistic based fMRI task that specifically activates all putative essential language areas and reliably detects language dominance. The main components of language were assessed with three different tasks (rhyme, synonym, and sentence). It was hypothesized, that the novel sentence task would fulfil the objectives of the present study best because it contained all the main components of language processing, that is phonology, semantic, and syntax. fMRI was performed in healthy right- (n=13) and left-handed controls (n=8), and 20 patients at 1.5 T prior to neurosurgery. In controls, activations were quantified by an individual volume of interest analysis. Four neuroimagers tested a visual rating score in the patients group. Interrater agreement and concordance between fMRI and Wada test were calculated. As expected, the sentence task showed high sensitivity and specificity to activate all putative essential language areas. In healthy right-handed controls, the frontal language area was activated by the sentence and synonym task in 100%, and in 73% by the rhyme task. The temporal language area was activated in 100% by the sentence-, in 64% by the synonym-, and 55% by the rhyme task. The sentence task also reliably detected atypical language dominance. Because of low sensitivity and specificity, the rhyme task was not used in patients. In patients, interrater agreement was 0.90 for activations

in the inferior frontal and 0.97 in the superior temporal gyrus. Correlation between the Wada test and fMRI was 0.86 for the sentence and 0.89 for the synonym task. For the sentence task, the Wada-test and fMRI were concordant in all cases in determining the hemisphere with greater language representation. Thus, our novel sentence task provides robust activations in all putative essential language areas and can be used for a simple clinical visual analysis in determination of language dominance.

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**Keywords:** Language dominance, Wada test, functional magnetic resonance imaging, review, clinical rating

### Bestimmung der Sprachdominanz durch die funktionelle MRT im Vergleich zum Wada-Test: ein Literaturüberblick und eine neue Satzaufgabe

Eine grosse Anzahl von Studien prüfte, ob die funktionelle Magnetresonanztomographie (fMRT) in der Lage ist, den Wada-Test bei der Bestimmung der Sprachdominanz abzulösen. Wir geben einen Literaturüberblick über 24 Studien mit 486 Patienten. Die durchschnittliche Konkordanzrate beträgt lediglich ca. 90%. Darüber hinaus wird eine atypische Sprachdominanz nicht zuverlässig entdeckt. Das Rationale der vorliegenden Studie bestand darin, eine neue linguistisch basierte fMRT-Aufgabe zu entwickeln und zu validieren. Diese sollte spezifisch alle potenziell essenziellen Sprachgebiete aktivieren und die Sprachdominanz zuverlässig bestimmen. Mit drei verschiedenen Sprachparadigmen (Reime, Synonyme, Sätze) wurden die Hauptkomponenten der Sprachverarbeitung erfasst. Wir gingen davon aus, dass die neue Satzaufgabe am besten die

Anforderungen der aktuellen Studie erfüllt, da sie die wichtigsten Komponenten der Sprachverarbeitung beinhaltet, das heisst Phonologie, Semantik und Syntax. Bei gesunden rechts- (n=13) und links-händigen (n=8) Kontrollprobanden sowie bei 20 prächirurgischen Patienten wurde ein fMRT (1.5T) durchgeführt. Bei Kontrollprobanden wurden die Aktivierungen durch eine individuelle „Volume of interest“-Analyse quantifiziert. Bei den Patienten testeten vier Neuroradiologen ein visuelles Ratingverfahren. Wie erwartet, zeigte die Satzaufgabe eine hohe Sensitivität und Spezifität in der Aktivierung potenziell essenzieller Sprachgebiete. Frontale Sprachareale wurden bei 100% der rechtshändigen Kontrollprobanden durch die Satz- und Synonymaufgabe, und bei 73% durch die Reimaufgabe aktiviert. Temporale Sprachareale wurden bei 100% der Kontrollprobanden durch die Satz-, bei 64% durch die Synonym- und bei 55% durch die Reimaufgabe aktiviert. Die Satzaufgabe entdeckte auch zuverlässig eine atypische Sprachdominanz. Aufgrund einer zu geringen Sensitivität und Spezifität wurde die Reimaufgabe bei den Patienten nicht mehr durchgeführt. Bei den Patienten lag bei inferior frontalen Aktivierungen die Interrater-Übereinstimmung bei 0,90, bei Aktivierungen im Gyrus temporalis superior bei 0,97. Die Korrelation zwischen Wada-Test und fMRT betrug 0,86 für die Satz- und 0,89 für die Synonymaufgabe. Bei der Satzaufgabe stimmte die Bestimmung der Sprachdominanz mit dem Wada-Test und fMRT bei allen Patienten überein. Insgesamt zeigt also unsere neue Satzaufgabe stabile Aktivierungen in allen potenziell essenziellen Sprachgebieten und ist geeignet für eine einfache klinische visuelle Analyse zur Bestimmung der Sprachdominanz.

**Schlüsselwörter:** Sprachdominanz, Wada-Test, funktionelle Magnetresonanztomographie, Literaturüberblick, klinisches Rating

### **Détermination de la dominance pour le langage par IRM fonctionnelle en comparaison avec le test de Wada : une revue de la littérature et une nouvelle tâche syntaxique**

De nombreuses études ont été menées afin de vérifier si l'imagerie fonctionnelle par résonance magnétique (IRMf) pouvait remplacer le test de Wada pour déterminer la dominance pour le langage. Nous faisons revue de la littérature portant sur 24 études et 486 sujets. Le taux de concordance moyen n'est que d'env. 90%. En plus, une dominance pour le langage atypique ne peut être repérée avec fiabilité. La motivation de la présente étude avait été de développer et de valider une nouvelle tâche syntactique pour l'imagerie IRMf. Son but spécifique consistait à activer toutes les aires de la parole potentiellement essentielles et de déterminer la dominance pour le langage de manière fiable. À l'aide de trois paradigmes linguistiques (rimes,

synonymes, phrases), les composantes essentielles du traitement sémantique ont été testées. Notre hypothèse de travail était que la nouvelle tâche syntaxique « phrase » répondait le mieux aux besoins de l'étude actuelle, étant donné qu'elle contenait les composantes essentielles du traitement de la parole, à savoir : la phonologie, la sémantique et la syntaxe. Chez des sujets témoins sains droitiers (n=13) et gauchers (n=8), ainsi que chez 20 patients en attente d'une intervention chirurgicale, une fMRI (1.5T) a été effectuée. Chez les sujets témoins, les activations étaient quantifiées par une analyse individuelle du « volume d'intérêt ». Chez les patients, quatre neuroradiologues ont testé un procédé de classement visuel. Comme anticipé, la tâche syntaxique « phrase » affichait une grande sensibilité et spécificité dans l'activation des aires de la parole potentiellement essentielles. Les aires frontales de la parole étaient activées chez 100% des sujets témoins droitiers par la tâche de construction de phrases et de recherche de synonymes, et chez 73% pour la tâche de création de rimes. Les aires temporales de la parole étaient activées chez 100% des sujets témoins pour la tâche de création de phrases, chez 64% pour les synonymes et chez 55% pour les rimes. La tâche syntaxique « phrases » repérait aussi de manière fiable une dominance pour le langage atypique. En raison de la trop faible sensibilité et spécificité, la tâche « rime » n'a plus été proposée aux patients. Chez les patients, la concordance d'interclassement était de 0,90 en cas d'activations des aires frontales inférieures et de 0,97 en cas d'activations du gyrus temporal supérieur. La concordance entre le test de Wada et l'IRMf était de 0,86 pour la tâche « phrase » et de 0,89 pour la tâche « synonyme ». Pour la tâche « phrase », la détermination de la dominance pour le langage par le test de Wada et par TEPf concordait pour tous les patients. Globalement, notre nouvelle tâche « phrase » montre donc des activations stables dans toutes les aires de la parole potentiellement essentielles et elle convient à une analyse visuelle clinique simple visant à déterminer la dominance pour le langage.

**Mots clés :** Dominance linguistique, test de Wada, tomographie par résonance magnétique fonctionnelle, revue de la littérature, classement clinique

### **Introduction**

We recently reported a Wada test validated fMRI study on language dominance using a novel sentence task [1]. Here we describe this study and the results more comprehensively. We additionally provide a comprehensive review of studies, which compared the concordance of the Wada test and fMRI in determination of language dominance.

Determination of language dominance is crucial prior to epilepsy surgery and any other neurosurgery

close to language cortex in order to avoid postoperative deficits. Historically, the Wada test has been the standard for determination of language dominance [2]. Although still considered as a „gold standard“ the Wada test has several important limitations because of its invasiveness [3, 4], difficulties related to its application and interpretation (e.g. in the case of arterial cross flow, excessive or too low sedation, emotional reactions of the patients) [5-8] or absence of spatial resolution. Methodological drawbacks of the Wada test include the limited time window to explore language functions during the procedure, the lack of normal control data and rather weak test-retest reliability [5, 9, 10]. Compared to alternative non-invasive approaches such as fMRI the Wada test is time consuming, requires more staff and is less cost effective (up to three times) [11, 12].

Considering all these drawbacks, the role of the Wada test as the clinical standard for determination of language dominance seems to be rather weak and has been increasingly challenged in recent years [13-15]. Therefore, the need to replace this procedure with less invasive and more reliable techniques has long been recognized. Due to its high availability, one of the most promising methods is fMRI.

The major difference between the Wada-Test and fMRI lies in the fact that the Wada-Test is an inactivation method blocking the function of one hemisphere, thus allowing to test the function of the non-anesthetized hemisphere. It therefore designates the hemisphere that is essential or nonessential for language. By contrast, fMRI is an activation method by providing information about which hemisphere (or set of brain regions) is activated more for a certain language task relative to a control task or rest. It may be that some of these hemispheric activations (or activated brain regions) are superfluous, that is not essential for language processing [16]. For instance, if fMRI shows bilateral activation this does not necessarily mean a bilateral distribution of language-essential cortex. It is possible, that it results from the co-activation of language or other cognitive-associated but not language-essential cortex contralateral to the dominant hemisphere [6, 12, 17].

Mistaking language-associated cortex or artificially highlighted regions for language-essential cortex may have relevant impact on the surgical strategies and thus on postoperative outcome [12, 17-19].

Therefore, the optimal fMRI design should not only be highly sensitive but also specific in activating the language dominant hemisphere, i.e. should reliably activate all putative essential language areas. Additionally, it should be able to detect atypical cerebral language organization, that is right and bilateral language dominance, which is a well-described phenomenon in epilepsy patients [20-22].

Brain regions are considered language-essential, if their lesion or dysfunction causes a characteristic

aphasic syndrome. These language areas do not only comprise the ‚classical‘ Broca’s (opercular part of the inferior frontal gyrus) and Wernicke’s area (posterior superior temporal gyrus). In vascular aphasia, they also involve most of the inferior frontal (opercular and triangular part) and middle frontal gyrus, the anterior insula and subcortical regions in the case of Broca’s aphasia [23-26]. In Wernicke’s aphasia, the characteristic lesion involves the posterior superior and middle temporal gyrus as well as the inferior parietal lobe (posterior supramarginal and angular gyrus) including subjacent white matter [25-28]. The investigation of language localization with electrical stimulation mapping during neurosurgical operations [29-32] and in patients with primary progressive aphasia [33-35] additionally disclosed the anterior and inferior temporal cortex as essential language regions. In the following, we refer to the mentioned regions as language essential areas, and all other regions as language non-essential areas.

To evaluate studies comparing the Wada test with fMRI of language, we have listed them in a table in the appendix with a description of subject sample size, number of patients with left-, right- or bilateral language dominance, fMRI activation/control tasks employed, behavioural monitoring, region of interest, activation patterns, quantification scores, concordance, correlation and discordance between Wada-test and fMRI.

We found 24 studies with valid Wada tests and fMRI in 486 patients. In the Wada test 78% of the patients showed left and 22% atypical (right or bilateral) language dominance. This prevalence is similar to the pioneering work of Rasmussen and Milner [36], Loring and co-workers [21], and others [19, 37].

To determine hemispheric language dominance of the fMRI tasks, usually a language laterality index (LLI) is calculated as the difference between left and right activation divided by the sum of the two activations multiplied by 100, thus yielding scores from +100 (strong left hemisphere dominance) to -100 (strong right hemisphere dominance). In some studies somehow arbitrarily, fMRI-LLI cut-off scores between  $\pm 10$  and  $\pm 26.5$  (mean  $\pm 20$ ) are used [38-47] to discriminate typical from atypical language dominant patients (for alternative methods see [17]). To facilitate clinical interpretations, a few studies have used an easier to perform clinical rating procedure based on visual interpretation of fMRI activation patterns. Four studies [44, 48-50] have investigated interrater agreements ranging from 0.36 – 1.0 with a fairly well mean of 0.85.

Taking the best concordance score between the Wada test and fMRI in each study, the overall mean concordance rate is 88.9% with a range of 55-100% (see summary at the end of the **Table in the appendix**). In five studies also correlation scores were calculated [7, 46, 51-53] with a mean correlation score of 0.93 (range 0.89 – 0.96) between Wada- and fMRI language laterality indices. If a single study with an extremely low con-

cordance rate of only 55% is excluded [54] there seems to be no difference in concordance rates in studies using LLI (mean: 91%; range 79-100%) compared to studies using clinical ratings (mean: 88%; range 78-100%).

Note that the percentage of the overall discordance rates do not fully add to 100% to the percentage of the concordance rates, because in some studies discordance data are not given. The overall discordance score between Wada test and fMRI is higher in patients with atypical language dominance (5.7%) compared to patients with left-typical language dominance (2.5%; see the end of the **Table in the appendix**).

Most frequently, the fMRI probes consisted of different alternatives of a verbal fluency task. In these tasks, patients had to produce words from predefined letters or semantic categories, or have to produce verbs or rhymes from predefined nouns [38-41, 48, 51-57]. Neuropsychologically, verbal fluency tasks are considered relatively pure measures of lexical-semantic retrieval [58]. None of these studies incorporated an adequate control task. In no study, direct behavioural monitoring of task performance during fMRI acquisition was performed. Verbal fluency tasks seem only to be sensitive to activate putative anterior language areas. In all studies, more or less strong activations were found in the inferior frontal gyrus spreading to putative non-essential language regions of the dorsolateral prefrontal cortex and variably activating other regions like the supplementary motor area, posterior language areas, or subcortical regions. Concordance rates are in the usual range (mean 94%; range 83-100%) with discordance scores over-represented in patients with atypical (primarily bilateral) language dominance (mean 5%; range 0-17%) compared to left language dominance (mean 1%, range 0-6%). Overall, sensitivity of verbal fluency tasks to activate all putative essential language areas is low. Thus, these tasks seem not to be capable to reliably determine language laterality or activate all putative essential language areas.

Others administered different versions of a semantic decision task as fMRI probe. In some, patients had to decide if a given noun represents either a living or a nonliving object [42], is either of concrete or abstract nature [12], is a synonym to one of four other nouns [43] or if a given noun-pair is synonymous [59]. Using a decision task in which not only verbal-semantic decisions but also world-knowledge was assessed, Binder et al., 1996 [7] and Benke et al., 2006 [49] presented their participants nouns designating animal names or common objects. Patients had to decide if the animals are native to the United States and commonly used by humans, or if the objects are available in a supermarket and costs less than seven Euros, respectively. Gaillard et al., 2002 [44] used a semantic-lexical retrieval task in which object descriptions had to be named. With one exception [42], all of these studies incorporated a control task and direct behavioural monitoring of task performance during fMRI acquisition. Although, these

tasks activate both putative anterior and posterior essential language areas, the sensitivity rate to activate both putative language areas on an individual basis is unknown. Additionally, they also activate putative non-essential language areas like the fronto-orbital cortex, the superior frontal gyrus, the cingulum, the temporal fusiform gyrus, the inferior temporal gyrus, the superior parietal lobule or the precuneus. These activations seem to be more frequent in studies in which broader semantic decisions are required [7, 49] compared to narrower semantic-verbal decisions [12, 42-44, 59]. Concordance rates are in the usual range (mean 87%; range 60-100%) with discordant scores similar in patients with left (4%; range 0-10%; not considering the study of Baciú et al., [42]) and atypical (4%; range 0-12%) language dominance.

One study used a phonological decision task [60] in which patients had to decide whether word-pairs rhymed. It activated primarily putative essential anterior, variably also putative posterior essential language regions, as well as putative non-essential language areas in the occipital and superior parietal lobe.

Several authors have tried to reduce the discordance rate between Wada test and fMRI by using a panel of tasks [45-47, 50, 61]. Although this holds true for certain single studies [e.g. 47, 50], the mean concordance rate (85%; range 79 – 90%) of these studies is in the usual range misclassifying patients with atypical language dominance (mean 10%; range 0-18%) more often than with typical language dominance (mean 5%; range 0-12%). Since most of these studies used the described fMRI tasks like verbal fluency tasks, semantic decision tasks, or naming, sensitivity to activate both putative language areas is similar as in the studies using only one task. It is noteworthy, that in two studies by Arora et al. [45] and Carpentier et al. [61] a semantic and syntactic decision task was used in which patients had to decide whether auditory presented sentences were semantically or syntactically correct. The authors report, that this study activated Broca's and Wernicke's area. Unfortunately, separate data for the semantic and the syntactic task are not given.

Taken together, numerous studies tested whether fMRI is capable of replacing the Wada test for determination of hemispheric language dominance. However, the overall concordance rate of the reviewed studies is only about 90%. Additionally, atypical hemispheric language dominance, which is relatively high in epilepsy patients, is not reliably detected.

Methodological concerns have been expressed regarding sample size, underlying lesion, functional reorganization, determination of language lateralization, input mode, task difficulty, fMRI threshold, and in particular behavioural monitoring and task design [6, 46, 49, 61-69]. A major problem in more than half of the studies is the fMRI design used.

As stressed by Swanson et al., 2007 [62], methodologically the usefulness of fMRI language maps

depends on how well the probe and control tasks are designed to identify putative essential language areas with high specificity. Most of the fMRI language tasks are not based on linguistic considerations. Investigators tend to retain task paradigms known to them (e.g. verbal fluency tasks). A common methodological limitation is the failure to incorporate an adequate control task in the activation protocol to minimize unwanted mental activity. Since all reviewed studies used a subtraction technique, the control task should incorporate all mental or other processes involved in the activation task, without that of the interesting language component.

Thus, there is still no recommendation for a validated fMRI protocol that can be reliably used in surgery. The objectives of the present study were to develop and validate a new linguistic based fMRI-task that reliably lateralizes language and is sensitive to activate all putative essential language areas.

Recent advances in the study of language show that

the language system seems to be conceived as a set of integrated but distinct subcomponents: phonology (the combination of individual speech sounds), semantics (the meaning of words), and syntax (the grammatical structure of sentences) [70, 71]. All studies comparing the validity of fMRI of language with the Wada tests used lexical-semantic retrieval processing in the form of fluency tasks and object naming, phonological, or semantic decision tasks as fMRI probe (see the **Table in the appendix**). Thus, syntactical processing as one main component of language was not evaluated yet.

To assess all the main components of language processing we designed a baseline (letter control task) and a novel sentence decision task. For reasons of comparison with other studies, we also incorporated a phonological and semantic decision task. It was hypothesized that the sentence task, which contained all the main components of language, should be able to reliably detect typical and atypical language organization and activates all putative (i.e. based on a priori

**Table 1:** Clinical data.

Patient	Age(y)/sex	Pathology (MRI)	Seizure focus/site	HLI <sup>a</sup>	LLI <sup>b</sup>
1	43/F	Mesiotemporal sclerosis	Right temporal	+100	+76
2	30/M	Subependymal heterotopia	Bilateral temporal	+100	0
3	34/M	Mesiotemporal sclerosis	Left temporal	+100	+100
4	39/F	Mesiotemporal sclerosis	Left temporal	+100	+100
5	33/M	Arteriovenous malformation	Left temporal	+100	+75
6	32/M	Cortical dysplasia	Left temporal	+29	+100
7	38/F	Astrocytoma	Right frontal	-53	+67
8	41/M	Glioma	Right frontal	-70	-36
9	38/F	Arteriovenous malformation	Left temporal	+100	+100
10	17/M	Mesiotemporal sclerosis	Left temporal	+100	+67
11	30/F	Mesiotemporal sclerosis	Right temporal	+100	+100
12	35/F	Dysembryoplastic neuroepithelioma	Right temporal	0	+100
13	37/F	Mesiotemporal sclerosis	Left temporal	-100	+80
14	30/F	Left frontal, left temporal and hippocampal lesions	Left frontal, left temporal, left hippocampal	+86	-80
15	29/M	Astrocytoma	Left temporal	+86	+68
16	22/M	Mesiotemporal sclerosis	Left temporal	+100	+87
17	39/F	Cavernoma	Left temporal	+100	+80
18	38/F	Cortical dysplasia	Left temporal	+30	+94
19	36/M	Arteriovenous malformation	Right temporal	+100	+100
20	52/M	Cavernoma	Right temporal	+45	+100

<sup>a</sup> Handedness laterality index; <sup>b</sup> Language laterality index based on the Wada testing (see text)

anatomical knowledge) essential language areas in the individual. Furthermore, we assumed that presurgical determination of language lateralization could be performed alternatively by a clinical rating procedure based on neuroanatomical representation of putative essential language areas.

## Methods

### Participants

To evaluate and validate the activation patterns in putative essential language areas, thirteen right-handed (6 females, 7 males; mean age 30.8 years) and eight left-handed (4 females, 4 males; mean age 33.0 years) healthy participants without neurological impairment and normal structural MRI were studied. Afterwards, twenty consecutive patients (10 females, 10 males; mean age 34.7 years), who were assessed for surgical treatment of medically intractable seizures (12 patients) or brain tumours giving rise to symptomatic seizures (8 patients) were studied with both fMRI and Wada testing (see **Table 1**). Handedness was assessed using a modification of the Edinburgh Handedness Inventory [72]. All participants were native German speakers and provided written informed consent according to a protocol approved by the local ethics committee.

### Wada Test

We have performed the WADA test procedure according to Loring et al. [21]. The standard dose was 125 mg sodium amytal injected by hand over a 4- to 5-second interval. Language testing consisted of object naming, reading – and repetition of nouns. The number of total errors was calculated for each side of injection. Only trials conducted before return of motor functioning and EEG normalization were included in the calculation. A language lateralization index (LLI) was calculated as  $(L-R) / (L+R) \times 100$ , with L and R are the percentage of correct responses (of the total possible) after injection of sodium amytal in the left and right hemisphere. This approach yields Wada-LLIs ranging between +100 (complete left language dominance) and -100 (complete right dominance), and indices in between reflecting varying degrees of language laterality. The Wada-LLIs are given in **Table 1** ranging in our patients from +100 to -80.

## fMRI tasks

### Material

To assess the main components of language we employed a baseline and three different language decision tasks on visually displayed stimuli: letter, rhyme, synonym, and sentence. All four tasks had an identical design: They consisted of pairs of items. Half of the trials required a same-response and half required a different-response. An overview of the fMRI language tasks is given in **Table 2**.

In the letter-decision task (baseline condition) engaging visual processing, participants determined whether pairs of consonant strings were identical. In the rhyme-decision task engaging visual and phonological processing, participants determined whether pairs of non-word strings rhymed. In the synonym-decision task engaging visual, phonological, and semantic information processing, participants determined whether pairs of words were synonymous. In the sentence-decision task, engaging visual, phonological, semantic, and syntactic information processing participants determined whether pairs of grammatically different sentences contained the same meaning.

The pairs of items were projected in a black bold-face font on a white background, one item above the other. To keep general luminance constant across tasks, x-flankers were added to the left and right of each item. Since the sentence tasks made more eye-movement necessary, the horizontal position of each item of the pairs was presented randomly in an attempt to approximately hold this effect constant across the tasks. Note, that the rhyme task was not used in patients, since in healthy right-handed controls this task was not sensitive enough to activate putative essential tasks. The constructions of the tasks were as follows:

For the letter task pairs of consonant-strings, each string consisting of 6 different consonants randomly chosen from the alphabet were constructed, which were either identical (e.g. ‚Tqblms‘ and ‚Tqblms‘) or different with respect to only one consonant (10 pairs differing in the first consonants [e.g. ‚Pktgrs‘ and ‚Dktgrs‘], 10 pairs differing in the second consonants [e.g. ‚Lfvjmp‘ and ‚Lbvjmp‘], and so forth).

For the rhyme task pairs of pronounceable non-word strings, each string from 4 to 15 characters in length were constructed, which were (according to German orthographic pronunciation rules) either phonologically similar (e.g. ‚Xahre‘ and ‚Phare‘) or phonologically different (e.g. ‚Xahre‘ and ‚Tille‘). Care was taken that orthography of the pairs were dissimilar. According to ratings by 10 normal subjects, the non-words had a low degree of association value to real words.

For the synonym task pairs of nouns, each from 4 to 15 characters in length were constructed, which were either semantically similar (synonyms, e.g. ‚idea‘ and

**Table 2:** fMRI design.

Task	Example	Correct Response	Putative processes engaged
Letter	xxxxxxx Cspwnh xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Cspwnk xxxxxxxx	≠	• visual
Rhyme	xxxxxxxxxxxxxxxxxxxxxxxxxxxx Xahre xxxxxxxxxxxxxx xx Pfaare xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	=	• visual • phonological
Synonym	xxxxxxxxxxxxxxxxxxx Decision xxxxxxxxxxxxxxxxxxxxxx xxxxxx Condition xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	≠	• visual • phonological • semantic
Sentence	x The woman with the bag loves the man xxxxxxxxx xx The woman with the bag is loved by the man xxxx	≠	• visual • phonological • semantic • syntactic

,thought') or semantically different (non-synonyms; e.g. ,decision' and ,condition'). All nouns had a high degree of abstractness [73, 74].

For the sentence task pairs of syntactically varied sentences with the same content words were constructed, which denoted either the same (e.g. ,The man with the bag kisses the woman' and ,The man, who kisses the woman, has a bag') or a different (e.g. ,The man with the bag kisses the woman' and ,The man with the bag is kissed by the woman') meaning. All sentences had as their underlying form the simple subject - action (verb) - object structure. There were 10 different sentences denoting an interaction between two persons or objects (e.g. ,The truck from Denmark passes the Mercedes'). All sentences were reversible, i.e. the object could also be the subject with the same plausibility. Syntactic variations referred to active / passive voice and center-embedded relative clause. Sentence pairs were constructed so that the meaning of at least one of the two sentences could not be denoted simply by semantically based heuristics (e.g. word order), but by an algorithmic analysis of the syntactic structure of the sentence (e.g. pair of items with active and passive voice).

### Procedure

Participants were instructed to respond by pressing one of two pneumatic squeeze balls. Half of the participants indicated same-responses with the right hand, and different responses with the left hand. For the other half of subjects, this order was reversed. The subjects determined speed of presentation. After a response,

the next trial was immediately presented. Error scores were recorded for each task. The trials in each task were arranged in a pseudorandom order with the constraint that no more than four same- or different-responses appeared consecutively.

Thus, in all tasks visual parameters (letter size, luminance, eye movements), decisions (same, different) and motor responses (left, right hand) were comparable, the sole difference between the tasks being the type of linguistic information engaged by each.

### fMRI acquisition

All examinations were performed with a 1.5-T MRI (Siemens Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) with a standard 4-channel head coil.

Functional data were acquired with a multi-slice single-shot T<sub>2</sub>\*-weighted echo planar imaging sequence (TR 6000 ms; TE 82 ms) including 30 slices and a voxel size of 1.56 x 1.56 x 4 mm; FOV = 192mmx192mm, matrix size = 128x128.

The fMRI-BOLD was performed including 68 runs with cycles of 24 s (language decision) and 24 s OFF (letter decision), repeated 8 times resulting in a total presentation time of 384 sec. All tasks alternations were trained beforehand in a practice session.

### fMRI analysis

Analysis of the fMRI data was performed using a standard procedure provided by the BrainVoyager QX

1.2 (Brain Innovation, Maastricht, Netherlands, www.BrainVoyager.com). The first four images of the time-series were excluded from analysis to exclude a T1 saturation effect. Preprocessing of the images included the removal of low-frequency drifts, 3-D motion detection and correction and spatial smoothing with 6 mm FWHM. Voxelwise correlations between the BOLD signal and the predictor were computed using a General Linear Model (GLM). The six motion parameters derived from the fMRI preprocessing (translation and rotation in the X, Y and Z direction respectively) were used as covariates in the GLM. Correlation estimation was done with a threshold  $p < 0.05$  corrected for multiple comparisons (family-wise errors) with  $t > 3.1$  and minimum cluster threshold of 40 mm. For illustration, the images were additionally coregistered to an anatomical dataset.

### **Volume of interest analysis**

In the developmental phase with healthy controls, we used a more fine-grained method of individual volume of interest (VOI) analysis to test the power of our language tasks to activate all putative language areas of the dominant hemisphere. *A priori* VOIs (see also the centre of **Figure 1**) were defined using the individual anatomical parcellation method described by Rademacher and co-workers [75]. The frontal lobe VOIs comprised the frontal pole (FP), the superior and middle frontal gyri (F1, F2), the opercular and triangular part of inferior frontal gyrus (F3o, F3t), the precentral (PRG), and the supplementary motor cortex (SMC). The temporal VOIs included the anterior and posterior superior (T1a, T1p) and middle (T2a, T2p) temporal gyrus as well as the most posterior temporo-occipital (TO) part of the middle temporal gyrus. Parietal VOIs included the postcentral gyrus (POG), the superior parietal lobule (SPL), the anterior and posterior supramarginal gyrus (SGa, SGp), the angular gyrus (AG), and the precuneus (PCN). In the occipital lobe, the occipital lateral gyri (OL) and the cuneus (CN) formed additional VOIs. Finally, the medial paralimbic VOIs comprised the paracingulate cortex (PAC) and cingulate gyrus (CG). We analyzed the percentage signal change relative to the control task average subjected to the typical statistical procedure in every VOI from all subjects, i.e. testing the null hypothesis of no change by calculation of z scores.

Although, from a scientific point of view the individual VOI approach has several advantages [76-78] it is very time-consuming. In today's clinical routine, neuroimagers perform fMRI studies almost daily, and with an increasing number of patients undergoing fMRI, it is important to provide simple and reproducible interpretations that are less time consuming and that can be easily carried out during clinical routine. Therefore, we further analyzed, if a simple clinical rating procedure produces reliable results, when interpreted by different

raters. Thus, we tested the interrater reliability of four different neuroimagers blinded to the kind of fMRI language tasks in the interpretation of the fMRI images. Additionally we were interested how good this clinical rating corresponded to the LLI of the Wada test. Four independent neuroimagers were asked to determine the extent (independent of intensity) of BOLD correlates (statistical maps) in predetermined regions of interest (ROIs). The ROIs comprised the superior and middle frontal gyrus, the inferior frontal gyrus including the opercular and triangular part (Broca's area), the posterior superior and middle temporal gyrus (Wernicke's area), the inferior parietal lobule, and the precuneus/cuneus. If the ROI showed no signal increase, the rating was defined as 1. If approximately one or two thirds of the BOLD signal increase was found at the ROI, rating was 2 or 3, respectively. If the whole ROI was activated, rating was 4. Ratings were performed separately for each hemisphere and each task comparison. Based on these ratings, LLI for every ROI and every rater were calculated with the formula  $(L-R)/3 \times 100$ , where L and R are the rating scores for the left and right hemisphere. This approach yields LLIs ranging between +100 (complete left language dominance) and -100 (complete right dominance), and indices in between reflecting varying degrees of language laterality.

The graded rating of BOLD correlates in predefined ROIs allowed us to calculate intra-class correlations [79] based on the LLI for each ROI and task for general interrater agreement instead of Kappa coefficients or Cramers V for pairs of raters.

## **Results**

### **Right-handed controls**

Initial inspection of the fMRI images revealed, that one male right-handed participant showed right language dominance in all tasks. In another female right-handed participant, there were indications of partial crossed language dominance. These two participants were excluded from further analysis and will be described in the next section. For the remaining 11 participants, percentages of participants with significant activity in the selected VOIs, percentage signal change relative to the control task and corresponding z-scores separated for the three tasks are given in **Table 3**. **Figure 1** depicts the amount of activation in the VOIs considered as potential essential language areas as a function of language task. A representative example of a typical left-hemisphere language dominant participant is given in **Figure 2 A**.

The opercular part of the inferior frontal gyrus was activated in all participants by the sentence and synonym task (100%), while the rhyme task activated this area in 73% of the participants. The triangular part of

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<sup>1</sup> BAG, SL, 1.7.2011

<sup>2</sup> Crepeau AZ et al. Levetiracetam: a comprehensive review, *Expert Rev Neurother*, 2010 Feb, 10(2), 159–171

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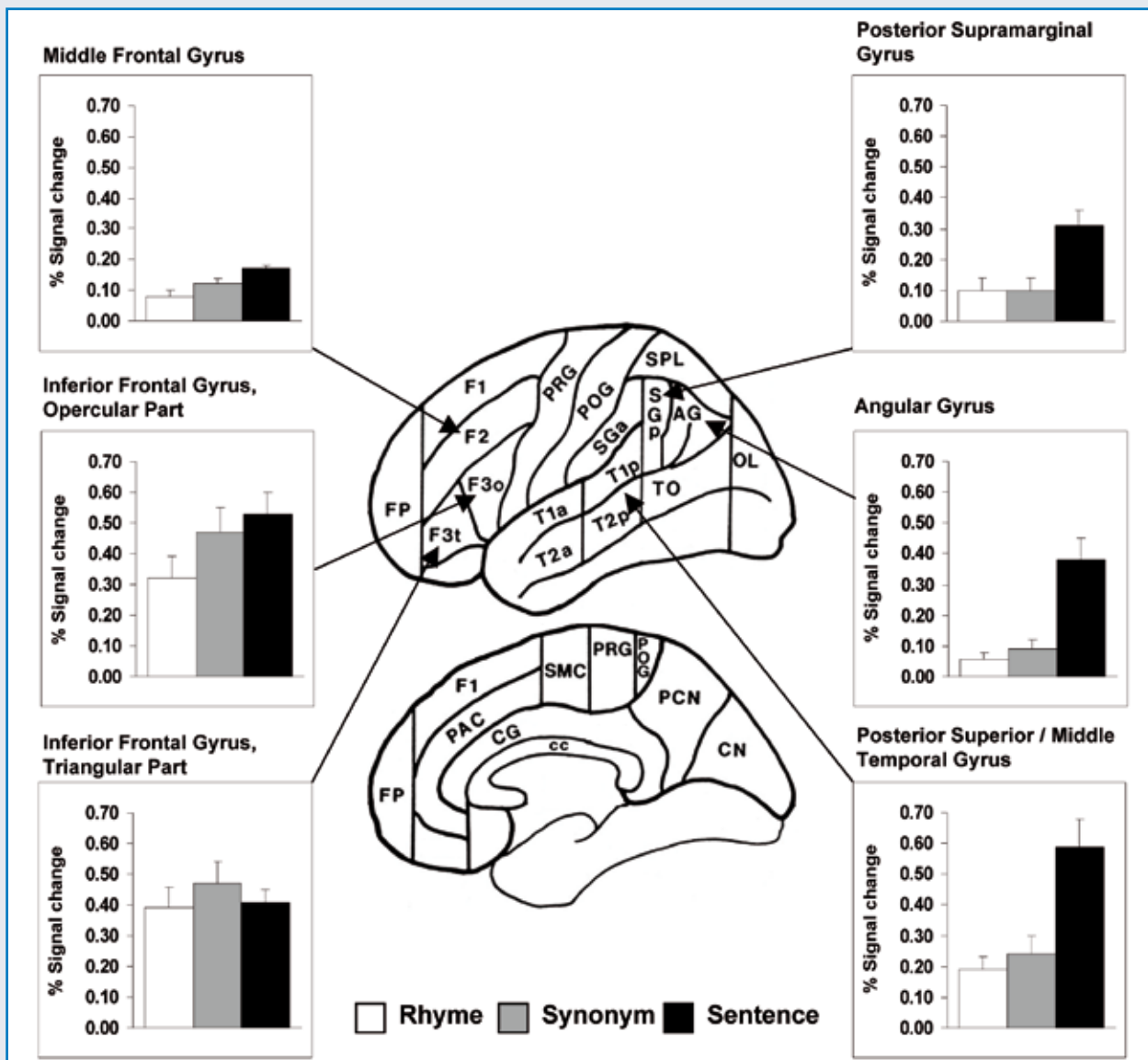


Figure 1: The schematic drawing in the centre shows the anatomically defined volumes of interest (VOI), adapted from the parcellation scheme described and depicted in Rademacher et al. ([75], abbreviations see text and Table 3). The associated graphs depict the amount of activation the VOIs considered as potentially essential language areas as a function of language task (rhyme, synonym, sentence, with the letter task as control). The amount of activation is defined as group average of percentage BOLD signal change. The error bars represent the standard error of the mean. Note: The posterior superior and middle temporal gyrus (T1p, T2p) were combined to one VOI due to nearly identical activation in both VOIs.

the inferior frontal gyrus was activated to the same degree by all tasks (82%), while the middle frontal gyrus was significantly activated in 73% of the participants by the sentence task. The posterior superior and middle temporal language area were activated in all participants by the sentence task (100%), in 64% by the synonym, and in 55% by the rhyme task.

None of the putative non-essential language VOIs were activated by the sentence task with the exception of visual areas in some of the participants (lateral occipital gyri: 55%, cuneus: 64%). BOLD correlates in the supplementary motor cortex were found in 55% of the participants during the synonym and rhyme task.

According to a repeated measures ANOVA accuracy

scores were statistically not different between the activation tasks ( $p > 0.05$ ; mean  $\pm$  Std: rhyme:  $84.3 \pm 7.1$ ; synonym:  $91.4 \pm 3.2$ ; sentence:  $84.6 \pm 9.7$ ). The mean accuracy score of the letter control-task was  $94.2 \pm 2.7$ . Accuracy scores of the activation tasks did not correlate ( $p < 0.05$ ; Bonferroni corrected) significantly to fMRI activations in none of the VOIs.

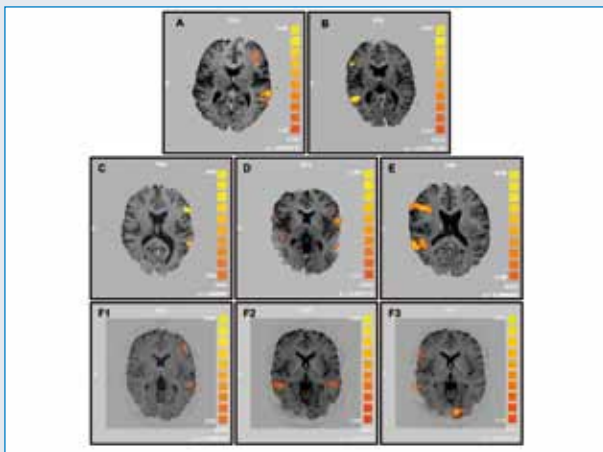
### Left-handed controls and atypical language dominance

Two of the eight left-handed participants showed right-hemispheric language dominance, one bilateral

**Table 3:** Analysis of volumes of interest in healthy right-handers (n=11) with left hemisphere language dominance (shaded VOIs are considered as putative essential language areas). Note: The anterior/posterior superior and middle temporal gyrus as well as the paracingulate and cingulate cortex were combined to single VOIs because nearly identical activation in these VOIs.

Volume of interest (VOI)	Percentage of participants with significant activity in the VOI*			Percentage signal change relative to the control task (mean±std)			z-score (mean±std)		
	Rhyme	Synonym	Sentence	Rhyme	Synonym	Sentence	Rhyme	Synonym	Sentence
Frontal lobe									
FP, frontal pole	-	-	-	0.10±0.15	0.22±0.21	0.10±0.10	0.99±1.50	2.59±2.49	1.06±1.19
F1, superior frontal gyrus	-	-	-	0.03±0.06	0.02±0.03	0.06±0.12	0.22±0.45	0.24±0.44	0.47±0.80
F2, middle frontal gyrus	-	-	73	0.08±0.07	0.12±0.07	0.17±0.04	1.06±0.91	1.39±0.99	2.10±0.61
F3o, inferior frontal gyrus, opercular part	73	100	100	0.32±0.23	0.47±0.26	0.53±0.22	3.30±2.30	5.52±3.35	5.35±2.39
F3t, inferior frontal gyrus, triangular part	82	82	82	0.39±0.24	0.47±0.21	0.41±0.22	4.10±2.57	4.66±2.28	3.77±1.96
PRG, precentral gyrus	64	-	-	0.14±0.09	0.09±0.09	0.11±0.11	2.34±1.64	1.26±1.41	1.49±1.60
SMC, supplementary motor cortex	55	55	-	0.16±0.14	0.27±0.16	0.15±0.15	1.61±1.39	2.29±1.41	1.25±0.94
Temporal lobe									
T1a/T2a; anterior superior/middle temporal gyrus	-	-	-	0.04±0.05	0.12±0.11	0.23±0.24	0.47±0.64	1.51±1.44	2.95±3.28
T1p/T2p; posterior superior/middle temporal gyrus	55	64	100	0.19±0.12	0.24±0.20	0.59±0.32	2.60±1.90	3.05±2.70	4.18±2.14
TO, temporo-occipital cortex	-	-	-	0.03±0.05	0.00±0.00	0.02±0.03	0.47±0.79	0.01±0.01	0.23±0.39
Parietal lobe									
POG, postcentral gyrus	-	-	-	0.09±0.08	0.03±0.03	0.03±0.02	1.25±1.41	0.39±0.30	0.46±0.34
SPL, superior parietal lobule	-	-	-	0.04±0.09	0.01±0.02	0.10±0.07	0.43±0.94	0.09±0.22	0.66±0.52
SGa, anterior supramarginal gyrus	-	-	-	0.02±0.04	0.02±0.04	0.02±0.03	0.36±0.85	0.25±0.58	0.24±0.48
SGp, posterior supramarginal gyrus	-	55	73	0.10±0.12	0.10±0.12	0.31±0.18	1.63±1.92	1.68±1.92	3.70±1.88
AG, angular gyrus	-	-	82	0.06±0.05	0.09±0.11	0.38±0.22	0.77±0.73	1.47±2.11	4.49±2.70
PCN, precuneus	-	-	-	0.01±0.03	0.03±0.04	0.12±0.12	0.21±0.48	0.41±0.62	1.33±1.19
Occipital lobe									
OL, occipital lateral gyri	-	-	55	0.05±0.08	0.10±0.04	0.18±0.11	0.52±0.71	1.35±0.55	2.08±1.29
CN, cuneus	-	-	64	0.06±0.11	0.12±0.09	0.25±0.20	0.51±1.02	1.19±0.89	2.28±1.51
Medial paralimbic cortices									
PAC/CG, paracingulate/cingulate cortex	-	-	-	0.10±0.13	0.15±0.21	0.02±0.06	1.23±1.27	1.86±2.97	0.19±0.58

\*Only percentages > 50% are given



**Figure 2:** Representative examples of activation maps in healthy participants. (A,B) right-handers with left-hemispheric (A) and right-hemispheric (B) language dominance in the sentence task; (C,D,E) left-hander with left-hemispheric (C), bilateral (D), and right-hemispheric language dominance (E) in the sentence task; (F1-3) partial crossed language dominance in a right-hander with left-hemispheric language dominance in phonological processing (rhyme vs. letter task), F1), bilateral activation in semantic processing (synonym vs. rhyme task, F2) and right-hemispheric dominance in syntactic processing (sentence vs. synonym task, F3)

As mentioned before, two of the 13 right-handers showed atypical language dominance, one with right-hemispheric language dominance (see **Figure 2 B**). Another right-handed participant seemed to have a partially crossed language dominance: phonological and semantic aspects of language seemed to be processed with the left hemisphere, while syntactical aspects of language seemed to be processed with the right hemisphere (see also [80]). Therefore, we contrasted higher with lower order tasks (see **Table 2**), i.e. the rhyme to the letter (isolating phonology), the synonym to the rhyme (isolating semantic), and the sentence to the synonym task (isolating syntax). These contrasts showed left-hemispheric activations in phonological processing (**Figure 2 F1**), bilateral activation in semantic processing (**Figure 2 F2**) and right-hemispheric dominance in syntactic processing (**Figure 2 F3**).

### Patients

Since the activations of the rhyme task revealed less constant BOLD signal increases in healthy right handed controls compared with the other tasks, in the clinical fMRI study this task was not used to shorten patients scanning time.

**Table 4:** Intra-class correlations for interrater agreement

Region of interest	Synonym		Sentence	
	Correlation	F(19,57)	Correlation	F(19,57)
Superior frontal gyrus	.57	2.4	.55	2.2
Middle frontal gyrus	.67*	3.0	.78*	4.6
Broca's area	.96*	23.1	.90*	10.1
Wernicke's area	.97*	30.3	.93*	15.3
Inferior parietal lobe	.70*	3.7	.61*	2.8
Precuneus / cuneus	.71*	3.4	.75*	3.8

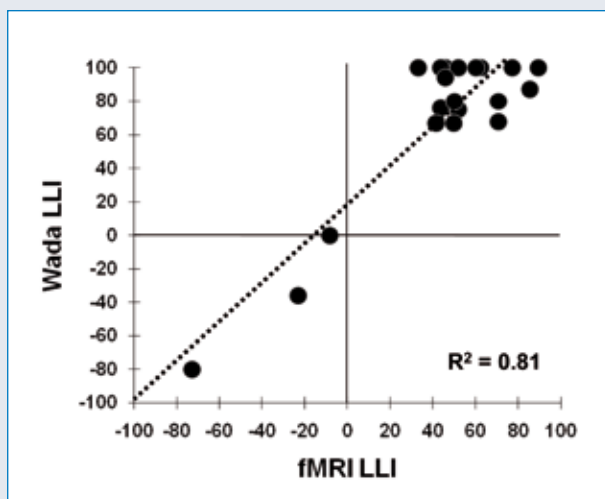
\*p < 0.05 (Bonferroni corrected, corresponding to p < 0.004)

language dominance and the others (5/8) typical left-hemispheric dominance (see **Figures 2 C-E** for representative examples).

According to a repeated measures ANOVA mean accuracy scores in left-handers were statistically not different between the activation tasks ( $p > 0.05$ ; rhyme:  $85.1 \pm 4.9$ ; synonym:  $89.1 \pm 1.6$ ; sentence:  $83.1 \pm 8.3$ ) and were comparable to right-handers. The accuracy score of the letter control task was  $93.8 \pm 3.7$ .

### Visual rating

To evaluate interrater agreement of the four raters we calculated intra-class correlation coefficients [79] based on the LLI for each ROI and each task. Intra-class correlation coefficients and F-statistics (testing the null hypothesis of no agreement) are given in **Table 4**. With one exception for the superior frontal gyrus, all correlation coefficients were significant with excellent interrater agreement of  $r \geq .90$  for the



**Figure 3:** Wada LLI plotted against fMRI LLI for the best predictor, i.e. the combined ROIs of Broca's and Wernicke's area and both tasks (synonym, sentence). The regression function,  $y = 1.162x + 18.3$ , is shown as dashed line. The correlation coefficient is 0.90.

classical Broca's and Wernicke's language area. Interrater agreement was lower for the other putative essential language areas ranging from .61 to .78 in the inferior parietal lobule and middle frontal gyrus.

### Concordance of Wada-test and fMRI

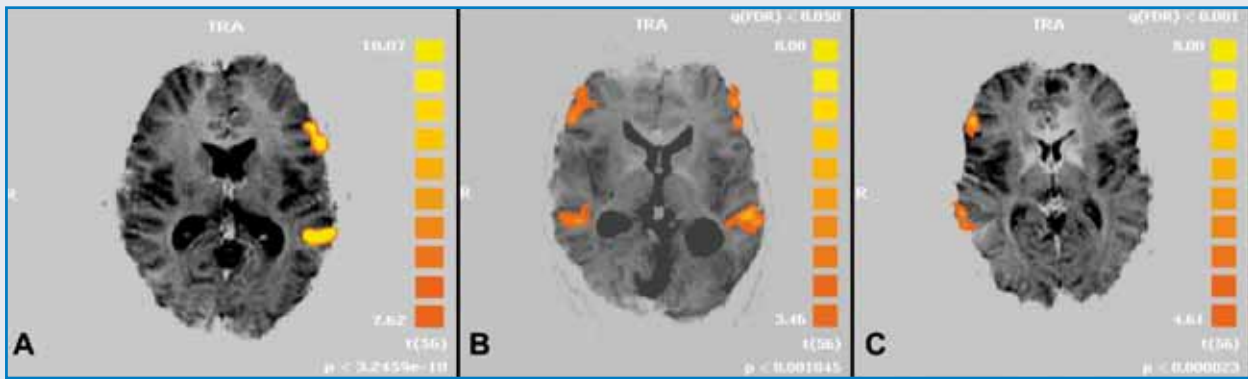
Since interrater agreement was very high, the LLIs of the four raters were averaged to calculate correlations between the Wada-test LLI and fMRI LLI separate for all the ROIs and each task-comparison. To evaluate whether combined scores across ROIs or tasks yielded better concordance between the Wada-LLI and fMRI-LLI compared to single ROI analysis, the following scores were calculated: (1) average of the classical Broca's and Wernicke's area separate for and averaged over both tasks; (2) average of all putative essential language areas, i.e. the middle frontal gyrus, Broca's and Wernicke's area and the inferior parietal lobe separate for and averaged over both tasks.

Correlation coefficients are given in **Table 5**. Highly significant correlations between the Wada- and fMRI-LLIs were observed for Broca's and Wernicke's area for both tasks, and both tasks combined ranging from .82 - .88. Although partially still in a high range (.52 - .71) correlations between the Wada LLI and activations in the inferior parietal lobe were not significant. None of the correlations for the middle frontal gyrus (.46 - .50) or

**Table 5:** Correlation coefficients between the language laterality indices of the Wada-test and fMRI activations.

Region of interest (ROI)	Synonym	Sentence	Both tasks
Single ROIs			
• Superior frontal gyrus	.84*	.56	.82*
• Middle frontal gyrus	.47	.46	.50
• Broca's area	.88*	.84*	.88*
• Wernicke's area	.83*	.82*	.84*
• Inferior parietal lobe	.71	.52	.64
• Precuneus / cuneus	.11	.02	.09
Combined ROIs			
• Broca's and Wernicke's area	.89*	.86*	.90*
• Middle frontal gyrus, Broca's area, Wernicke's area, inferior parietal lobule	.81*	.75*	.85*

\* $p < 0.05$  (Bonferroni corrected, corresponding to  $p < 0.002$ )



**Figure 4: Representative examples of activation maps of three patients in the sentence task. (A) left-hemispheric language dominance (#16); (B) bilateral language dominance (#2); (C) right-hemispheric language dominance (#14).**

the precuneus (.02 - .09) reached the critical level of significance. Finally, there were also significant correlations between the Wada LLI and activations in the superior frontal gyrus for the semantic task (.84), and both tasks combined (.82).

The best predictor of the Wada-LLI were activations in Broca's and Wernicke's areas averaged over both tasks (.90; see **Figure 3**), yet concordance rates separate for Broca's (.84 - .88) and Wernicke's area (.82 - .84) and separate for the synonym and sentence task were comparable. For all these variables fMRI and the Wada test was concordant in all cases in determining the hemisphere with greater language representation with no exception.

Seventeen patients had strong left hemispheric dominance for language as judged by the Wada test, with LLIs ranging from +67 to +100 (see **Table 1** and **Figure 3**) and fMRI, with LLIs ranging from +33 to +90. Three patients showed an atypical language distribution by the Wada test and fMRI. Wada LLIs in these patients ranged from -80 to 0, and corresponding fMRI LLIs ranged from -73 to -8.

Representative examples of activation maps of three patients with left, bilateral, and right hemispheric language dominance in the sentence task are given in **Figure 4**.

### **Sensitivity of the tasks to activate putative essential language areas**

To evaluate sensitivity of the tasks to activate putative language areas we calculated percentages of patients with significant activations in the predefined ROIs. Data are summarized in **Table 6**. The sentence task showed the best sensitivity to activate putative essential language areas. Broca's (100%) and Wernicke's (100%) area were significantly activated by this task in all patients.

### **Accuracy scores**

The data of three patients got lost because of a software problem. According to a t-test (dependent samples) accuracy scores of the synonym task ( $85.6 \pm 5.1$ ) were significantly higher compared to the sentence task ( $78.3 \pm 7.1$ ;  $t(16) = 5.9$ ;  $p < 0.001$ ). The mean accuracy score of the letter control-task was  $92.0 \pm 4.9$ . Compared to right- and left-handed healthy controls (t-test, independent samples) accuracy scores were lower in patients both in the synonym ( $t(34) = -3.5$ ;  $p < 0.01$ ) and the sentence task ( $t(34) = -2.09$ ;  $p < 0.05$ ), while no such difference was found for the letter task ( $p > 0.05$ ).

In patients, accuracy scores of the activation tasks did not correlate ( $p < 0.05$ ; Bonferroni corrected) significantly to fMRI activations in none of the ROIs.

### **Discussion**

Clinical fMRI studies are increasingly used as an additional tool in the assessment of patients who are candidates for resective surgery in eloquent areas of the brain. To warrant reliable results, fMRI studies have to ensure easy and reliable interpretation by the neuroimager and neurosurgeon in charge to plan resection. In addition, the time of scanning should be as short as possible to ensure patients' comfort and compliance. Finally, the selected paradigm must unambiguously provide an activation of putative essential language areas to provide comprehensive data about the lateralization and anatomical topology of the brain areas under investigation.

The study at hand demonstrated that the sentence task showed robust BOLD responses in putative essential language areas in right-handed healthy controls and patients. Activations were found in Broca's and Wernicke's area in all participants (100%). Additionally, the inferior parietal lobe and the middle frontal gyrus were activated in almost all right-handed controls and patients. Furthermore, none of putative non-essential

**Table 6:** Percentage of patients (> 50%) with significant activity in the region of interests

Region of interest (ROI)	Synonym	Sentence
• Superior frontal gyrus	70	75
• Middle frontal gyrus	80	90
• Broca's area	100	100
• Wernicke's area	95	100
• Inferior parietal lobe	75	85
• Precuneus / cuneus	–	–

language areas were activated by this task with the exception of visual associated cortical areas in about half of the healthy right-handers and the superior frontal gyrus including the SMA in 75% of the patients. This indicates on the one hand that the visual demands of the sentence task are experimentally not fully balanced compared to the letter control task, and on the other hand that the sentence tasks need more intensive articulatory planning and articulatory execution (e.g. [81]) compared to the letter control task.

One limitation of this study is the relative small sample size. However, our results re-confirm an observation derived from a variety of different language paradigms (see **Table in the appendix**) that inferior frontal activation occurs reliably and constitutes a good marker of language lateralization. What appears to be new in this study (and in the validation literature in general) is the universal activation of the frontal opercular region in particular, probably reflecting the syntactic components of the sentence task (for a review and critical discussion of this aspect see [82]). Additionally, the posterior temporal language region was also universally activated in controls and patients by the sentence task. However, the activations in this study did not go substantially beyond previously reported anterior and posterior markers of language lateralization and did not activate other putative essential language areas like the anterior temporal language areas. It seems that activations of these regions need other task designs (e.g. semantic audio-visual processing; (see Figure 3 of Vigneau et al. 2006 [82])).

The sentence task lateralized 11/12 (8%) right-handed, 3/8 (37%) left handed healthy participants, and 3/20 (15%) of the patients to the right hemisphere or showed bilateral activations. These rates in healthy right and left-handers are consistent with other studies [22, 36]. More importantly, our task allowed a correct classification of patients with atypical language dominance, which has to be considered in the presurgical

evaluation of patients with epilepsy, particularly after early brain injury and left sided medial lobe epilepsy and reaches about 25% [19, 21, 37, 45, 49, 83]. The slightly lower incidence rate of 15% atypical language dominance in our patients may be due to the fact, that we incorporated eight patients with brain tumours. Also important, there was full concordance between the Wada Test and the fMRI tasks in determination of the language dominant hemisphere. Our task allowed a correct classification of all patients, even those with atypical language dominance.

One right-handed (handedness laterality +100) healthy participant showed partial crossed language dominance with left-hemispheric language dominance in phonological processing, bilateral activation in semantic processing, and right-hemispheric dominance language in syntactic processing (**Figure 2 F1-3**). She is a well functioning person with a high academic level and known familial sinistrality and ambidexterity (her father, a surgeon was famous to operate with equal dexterity with the left or right hand). She has no history of difficulties while delivery, development or any neurological or psychiatric problems. Detailed anatomical MR analysis gave no hints of cerebral pathology. Thus, partial crossed language dominance, i.e. interhemispheric dissociation of language functions not only seems to be a phenomenon in chronic epilepsy [84-88] but also a genetic variability in healthy individuals. While the Wada Test only gives an index of language laterality, it does not localize specific language abilities; fMRI paradigms have this ability and the ability to indicate partially crossed language dominance as demonstrated with our right-handed healthy participant.

A practical goal of this study was to test whether the sentence task can be used in clinical routine. A simple clinical rating procedure of language lateralization was performed by different neuroimagers. Additionally, we were interested how good this clinical rating corresponded to the LLI of the Wada test. Since fMRI activation heavily depends on the capability of an individual to perform a task (cf. [78]), no constant activations were used for the visual ratings. In contrast to previous studies that investigated visual ratings of language lateralization [44, 48-50] we used a graded rating (1=no, 2=slight, 3=moderate, 4=strong) of BOLD correlates in predefined eloquent cortical areas allowing us to calculate intra-class correlations for general interrater agreement. Interrater reliability between the four raters was very good for classical Broca's and Wernicke's area with highly significant intra-class correlations ranging from .90 to .97. Intra-class correlations were also significant for the other essential or non-essential language areas, i.e. the inferior parietal lobe, the middle frontal gyrus and the precuneus/cuneus ranging from .61 to .78.

Interrater concordance in this study was higher compared to other studies that used a clinical rating system [44, 48-50] except from the study of Gaillard and co-workers [50]. In that study, however, a panel of

## Appendix. Studies comparing the Wada test with fMRI of language

Tasks	Year	n <sup>a</sup>	Wada			fMRI						Concordance		Discordance <sup>b</sup>
Study			L	R	B	Probe: Stimulus-Response	Control	Behavioral monitoring	ROI	Regions activated <sup>c</sup>	Quantification	%	r	
<b>Verbal fluency</b>														
Adcock [38]	2003	19	15	1	3	Letter-Words	Rest	No	Whole brain excluding occipital cortex and CER	Different regions activated for left and right TLE patients	LLI(±26.5)	89%	-	B: 11%
Bahn [55]	1997	7	5	2	0	Letter-Words Noun-Rhyme	Rest Rest	No No	Br (F3o), We (post T1), post F2, Caudate, SMA	Br, post F2, SMA, We, Caudate	CR	43-86% <sup>d</sup>	-	B: 14%
Bazin [51]	2000	7	6	1	0	Semantic category-Exemplifiers	Rest	No	F3, F2, F1, SMA, T1, T2/T3, PAR, PCN	F3, F2, SMA, PAR, F1, T1, PCN, T2/T3	LLI(±100)	100%	0.85-0.94 <sup>e</sup>	-
Benson [56]	1999	12	9	2	1	Noun-Verbs	Rest	No	Whole brain	ng	LLI(±100)	100%	-	-
Chlebus [52]	2007	15	12	3	0	Letter-Words	Rest	No	Whole brain, anterior two-thirds of the hemispheres (ATT), lateral ATT, lateral PFC, Br, SMA, CER	F3, F2, F1, CER, SMA, T2, T3, HIPPI, SPL	LLI(±100)	33-100% <sup>f</sup>	0.64-0.94 <sup>e</sup>	-
Deblaere [39]	2004	17	15	0	2	Word-Wordchain	Motor	No	Whole brain, FRON (F1,F2), TP (post T1, T2, SG, AG)	F3, F2, F1, T2, SG, AG, THAL	LLI(±20)	88-100% <sup>g</sup>	-	-
Hertz-Pannier [57]	1997	6	5	0	1	Letter-Words Semantic category-Exemplifiers	Rest Rest	No No	F3, F2, F1, CING, TEMP	F3, F2, F1	LLI(ng)	66-83% <sup>h</sup>	-	B: 17%
Liegeois [40]	2002	4	1	2	1	Noun-Verbs	Rest	No	F1	ng	LLI(±20)	100%	-	-
Sabbah [41]	2003	20	12	8	0	Letter-Words Semantic category-Exemplifiers	Rest	No	Whole brain	F3, F2, F3, PRG, POG, SMA, T1, T2, T3	LLI(±20)	95%	-	R: 5%
Woerman [48]	2003	94	71	ng <sup>i</sup>	ng <sup>i</sup>	Letter-Words	Rest	No	Whole brain	FRON lateral (100 %) Temporo-posterior (74 %), PAR (80%), FRON mesial (51 %)	CR (0.86)	91%	-	A: 3% L: 6%
Worthington [54]	1997	9	ng	ng	ng	Letter-Words	Rest	No	ng	ng	CR	55%	-	ng <sup>i</sup>
Yetkin [53]	1998	13	12	1	0	Letter-Words	Rest	No	F3, PRG	F3, PRG, SMA, CING	LLI(±100)	92%	0.93	R: 8%
<b>Semantic decision / lexical retrieval</b>														
Baciu <sup>a</sup> [42]	2005	10	8	0	2	Nouns – living?	Rest	No	FRON (BA44-47), TP (BA21,22,37,40)	ng	LLI(±15, ±20, ±25)	50-60% <sup>h</sup>	-	L: 40%
Benke [49]	2006	68	54	6	8	Nouns-Supermarket and less than 7 €? Animal names – USA? Commonly used by humans?	Perceptual	Yes	FRON (F3,F2,F1), TP (T1,T2,T3,AG,SG)	FRON, TP, SPL, PCN	CR (0.36-0.72)	68-78% <sup>i</sup>	-	L: 9% B: 12% R: 1%
Binder [7]	1996	22	18	1	3	Nouns-concrete/abstract?	Perceptual	Yes	Whole brain	F3, F2, PRG, F1, AG, post T3, TF, T2	LLI(±100)	100%	0.96	-
Desmond [12]	1995	7	4	3	0	Noun pairs-synonym?	Perceptual	Yes	F3	F3T, FOC, ant F2, F3, CING	LLI(±100)	100%	-	-
Fernandez [59]	2001	6	5	ng	ng	Noun pairs-synonym?	Perceptual	Yes	Br, PFC outside Br, TP	post T1, SG, AG, F3, F2, F1, T2, CING	LLI(±100), CR	100%	-	-
Spreeer [43]	2002	21	16	4	1	5 Nouns-synonym pair? Object description	Visual	Yes	Whole brain, FRON, TP	FRON, TP, and others, not further specified As ROI, other not given	LLI(±20)	76-86% <sup>m</sup>	-	L: 10% R: 4% B: 6%
Gaillard [44]	2002	18	14	2	2	-naming	Perceptual	No	F3, F2, WE defined as T1, T2, IPL	F3, F2, WE defined as T1, T2, IPL	LLI(±20) CR (0.77-0.82)	72-83% <sup>n</sup>	-	L: 6% B: 11%
<b>Phonological decision</b>														
Baciu [60]	2001	8	7	0	1	Word pairs-rhyming?	Perceptual	No	F1, post T1, IPL, PFC, PMC	F3, T1, IPL, F2, T3, PMC, CING, Insula, middle occipital gyrus, SPL	CR	100% <sup>a</sup>	-	-
<b>Panel of tasks</b>														
Arora [45]	2009	40	29	4	7	Verbal fluency: Letter-Words Semantic category-Exemplifiers Semantic-syntactic decision: Reading/hearing sentences- Semantically-syntactically correct?	Perceptual Perceptual	? ?	Whole brain, and whole brain excluding midline activations	ng	LLI(±10)	65-79% <sup>p</sup>	-	R: 3% B: 18%
Carpentier [61]	2001	10	8	2	0	Semantic-syntactic decision: Reading / hearing sentences- Semantically / syntactically correct?	Perceptual	?	Whole brain, Br (BA44,45), We (BA22)	Reading: SG, We, TF, Br, PRG, SMA Hearing: We, Br	LLI(±100)	40-90% <sup>q</sup>	-	L: 10%
Gaillard [50]	2004	25	22	2	1	Verbal fluency: Letter-Words Semantic category-Exemplifiers Naming: Reading / hearing object description -naming Reading / listening: Reading / listening to stories- no response	Rest Rest Perceptual Perceptual	No No No No	Whole brain	ng	CR (single tasks: 0.60-0.86; all tasks 0.91-1.0)	84% <sup>r</sup>	-	L: 12% B: 4%
Lehericy [46]	2000	10 <sup>s</sup>	9	0	1	Verbal fluency: Semantic category-Exemplifiers Repetition Sentence-repetition Listening: Listening to stories- no response	Rest Rest Perceptual	No No No	FRON, F3, F2, F1, SMA, CING, INS, TEMP, TP, T2/T3, SPL, PCN	Verbal fluency: FRON, F3, ant INS, F2, SMA, CING, TP Repetition: No lateralized activation Listening: TP, F2, SMA, CING, F1, F3	LLI(±25)	80-90% <sup>t</sup>	0.62-0.89 <sup>v</sup>	B: 10%

Tasks	Year	n <sup>a</sup>	Wada			fMRI	Control	Behavioral monitoring	ROI	Regions activated <sup>c</sup>	Quantification	Concordance	Discordance <sup>b</sup>
			L	R	B	Probe: Stimulus-Response					%	r	
<i>Panel of tasks (continued)</i>													
Rutten [47]	2002	18	11	3	4	Verbal fluency: Letter-Words Noun-Verbs Naming: Object drawings-naming Listening: Listening to sentences-no response	Rest Perceptual Perceptual Perceptual	No <sup>d</sup> No <sup>d</sup> No	F2, F3, T1, T2/T3, AG, SG	Not given for separate tasks; for all tasks combined F3, F2, AG, SG	LLI(±25)	50-82% <sup>e</sup>	L: 6% R: 6% B: 6%
Summary	All studies; For complete data:	486 377	368 292 (76%) (78%)	47 47 (10%) (12%)	38 (8%) 38 (10%)						Mean: Std.: Range:	88.9% 11.9 55-100%	Mean <sup>n</sup> : L: 2.5% R: 1.2% B: 4.5%

- <sup>a</sup> The n includes only those with valid Wada tests and fMRI.
- <sup>b</sup> Percentages of discordance between Wada test and fMRI are given for the best concordance score separately for left-, right or bilateral language dominant patients according to Wada test.
- <sup>c</sup> In descending order – when possible – from putative language-essential to putative language-non-essential regions (for a description of putative language-essential regions see introduction).
- <sup>d</sup> There was no difference between tasks. Concordance between Wada test and fMRI varied by ROI: Br 86%, F2 71%, SMA 71%, We 43%, Caudate 43%.
- <sup>e</sup> Correlations between Wada test and fMRI varied by ROI and were significant for all ROIs together ( $r=0.85$ ), all frontal lobe ROIs ( $r = 0.94$ ) and F2 ( $r=0.88$ ).
- <sup>f</sup> Concordance and correlations between Wada test and fMRI varied by ROI. Highest concordance (100%) and correlations ( $r=0.94$ ) were found for Br.
- <sup>g</sup> Concordance between Wada test and fMRI varied by ROI. Highest concordance was found for whole brain (100%), the FRON- (88%) and the TP-ROI (88%).
- <sup>h</sup> Concordance between Wada test and fMRI varied by ROI: F2 83%, F3 66%, F1 66%, F1-F3 together 83%.
- <sup>i</sup> Twenty-nine patients had atypical language dominance, but it was not specified if dominance was right or bilateral; also, 100 patients had valid Wada test, but six had invalid fMRI.
- <sup>j</sup> Exact data are not given. It is reported, that in 3/9 cases there was a disagreement between Wada test and fMRI, and in one case the Wada test showed bilateral language functions, while fMRI was lateralized.
- <sup>k</sup> In this study 35 patients were tested. Four tasks were used, however not performed in all patients. Wada test was also not performed in all patients. Thus, we only report the results of a semantic decision task where most of the Wada tests were available. Concordance between Wada test and fMRI varied by ROI.
- <sup>l</sup> Concordance between Wada test and fMRI varied by ROI: FRON 78%, TP 69%, FRON and TP combined; 68%.
- <sup>m</sup> Concordance between Wada test and fMRI varied by ROI: Whole brain 76%, FRON 86%, and TP 81%.
- <sup>n</sup> Concordance between Wada test and fMRI varied by ROI and rater (n=3): ROI 83%, Rater1 83%, Rater2 72%, Rater3 83%.
- <sup>o</sup> Concordance between Wada test and fMRI is based on clinical rating of all ROIs (whole brain).
- <sup>p</sup> Data were analyzed separately for left or right lateralized and for bilateral lateralized patients. With respect to lateralized patients concordance between Wada test and fMRI were 77% for word fluency, 84% for the reading task, 83% for the hearing task, and 91% for all tasks. Bilateral patients showed great discrepancies between the Wada test and fMRI. For reasons of comparison with the other studies data are given for the whole group. LLI were also calculated for whole brain with excluding midline activations with higher concordance between Wada test and fMRI. Concordance between Wada test and fMRI varied by task and determination of LLI. Whole brain: reading sentences: 68%, hearing sentences: 70%, word fluency: 65%; all tasks: 71%. Whole brain excluding midline structures: reading sentences: 74%, hearing sentences: 73%, word fluency: 74%; all tasks: 79%.
- <sup>q</sup> Concordance between Wada test and fMRI varied by task and ROI. Whole brain: reading sentences: 80%, hearing sentences: 40%, both tasks: 80%. Br and We: reading sentences: 90%, hearing sentences: 80%, both tasks: 90%.
- <sup>r</sup> Concordance between Wada test and fMRI are only given for all tasks combined.
- <sup>s</sup> Wada LLIs were calculated separately for language production, language comprehension and all tasks together. For reasons of comparison with the other studies data are given for global Wada LLIs. Concordance between Wada test and fMRI are only given for the frontal LLI of the verbal fluency task (80% concordance) and the temporal LLI for the story listening task (90% concordance). Correlations between Wada test and fMRI varied by ROI and task (17 correlations are reported). Also linear regression coefficients for verbal fluency and frontal activations ( $R^2=0.772$ ) and for the listening task with temporal activations

( $R^2=0.09$ ) are given.

- u Behavioral monitoring was performed before the actual scan session. Concordance between Wada test and fMRI varied by task and ROI. Combined tasks, all ROIs: 83%; verbal fluency, all ROIs: 72%; combined tasks, frontal ROIs: 67%; combined tasks, temporo-parietal ROIs: 50%.
- v Note that in 3 studies (Fernandez et al., 2001; Woerman et al., 2003; Worthington et al., 1997) data with respect to language dominance were either not given or in the cases of right- or bilateral dominance summarized as atypical language dominant. Comparing only typical (left) and atypical hemispheric language dominance 76% of the 486 patients showed typical and 23% atypical hemispheric language dominance.
- w Note that the percentage of the discordance rates do not fully add to 100% to the percentage of the concordance rates, because in some studies discordance data are not given.
- x We excluded the study by Baciú et al., 2005, because the high discordance score of left language dominant patients is biased by an extreme score of 40% of only 8 patients in this study.

*Abbreviations (anatomical abbreviations according to [75]).* A Atypical language dominance (i.e. right- or bilateral language dominance); AG angular gyrus, ant anterior, B Bilateral-hemispheric language dominance, BA Brodman's area, Br Broca's area, CER Cerebellum, CING Cingulate, CR Clinical rating (in brackets interrater agreement, when given), fMRI functional magnetic resonance imaging, F1 superior frontal gyrus, F2 middle frontal gyrus, F3 inferior frontal gyrus, F3o inferior frontal gyrus, opercular part, F3t inferior frontal gyrus, triangular part, FOC frontoorbital cortex, FRON Frontal lobe HIPPO Hippocampus, INS insula, IPL inferior parietal lobule L Left-hemispheric language dominance, LLI Language laterality index (usually computed as  $(L-R)/(L+R)*100$ , with L and R are activations for the left and right hemisphere; this yields LLIs ranging between +100 (strong left hemisphere dominance) to -100 (strong right hemisphere dominance; in brackets:  $\pm 100$  means, that no cut off score was used, instead language laterality is considered as a continuum;  $\pm n$  means, that LLIs were classified as left hemisphere dominant (defined as  $LLI > +n$ ), bilateral ( $-n \leq LLI \leq +n$ ) or right hemisphere dominant (defined as  $LLI < -n$ ), ng not given, PAR Parietal lobe, PCN Precuneus, PFC prefrontal cortex, PMC premotor cortex, POG postcentral gyrus, PRG precentral gyrus, post posterior, r correlation (between quantitative laterality indexes of Wada-Test and fMRI), R Right-hemispheric language dominance, ROI Region of interest, SG supramarginal gyrus, SMA supplementary motor area, SPL superior parietal lobule, T1 superior temporal gyrus, T2 middle temporal gyrus, T3 inferior temporal gyrus, TEMP Temporal lobe, TF temporal fusiform gyrus, THAL Thalamus TLE temporal lobe epilepsy, TP temporo-parietal region (usually including the posterior temporal and inferior parietal lobe), We Wernicke's area

tasks targeting different aspects of language processing was used with similar results compared to our single sentence task approach. Our study showed that one fMRI task that integrates phonology, semantic and syntax, that is the main components of language processing, depicts typical and atypical language dominance and BOLD correlates of all essential language areas.

Taken together, clinical visual analysis of fMRI activations with a single sentence task offers an alternative to assess language dominance and localization of language areas in the individual. In our cohort, the visual determination of language dominance was comparable to other studies using quantitative procedures (see [44]). The graded clinical ratings scale of predefined brain areas offers an additional value since activated regions known not to be of interest of language mapping can simply be ignored [45].

The added clinical value of fMRI today seems to be increasingly important for accurate language localization in lesional surgery and resective surgery close to eloquent brain areas. In this context, the Wada Test is no longer necessary since it provides an index of language laterality, but ignores specific language localization. The data presented in this study may provide additional insights that fMRI of language is also capable as

a complementary tool to intraoperatively direct cortical stimulation in brain lesions located in language areas (for a review see [89]).

In summary, we have demonstrated that a single sentence task as proposed in this study reliably lateralizes language and activates putative essential language areas. Moreover, a visual interpretation of the fMRI activation maps by clinical neuroimagers has shown to be comparable to quantitative procedures for the determination of language dominance. This is of special relevance under clinical conditions, when patients with brain tumours or candidates for epilepsy surgery are under evaluation for surgery. Performing visual ratings of the sentence task as proposed in this study instead of a whole language test battery may help to make clinical fMRI more economic, optimize patients comfort by reducing the time of the examination, and maintain reliable data interpretation for clinical neuroimagers and neurosurgeons.

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### Zusammenfassung

Der intrakarotidale Amobarbital-Test (IAT) wird in der prächirurgischen Epilepsiediagnostik vor allem zur Bestimmung der Lateralisation von Sprach- und Gedächtnisfunktionen und somit zur Prädiktion postoperativer Einbussen in diesen kognitiven Funktionen eingesetzt. Der Stellenwert dieses Tests wird zunehmend kontrovers diskutiert. Für die Sprachdominanzbestimmung ist die Wertigkeit des Tests zwar unbestritten, bei vielen Patienten kann aber heute ersatzweise die nichtinvasive funktionelle Magnetresonanztomographie (fMRI) eingesetzt werden. fMRI-Befunde können allerdings bei bestimmten Läsionen (zum Beispiel Gliome, zerebrovaskuläre Fehlbildungen) und bei Vorliegen atypischer Sprachdominanz irreführend sein, so dass der IAT in Fällen mit solchen Läsionen oder für Patienten, bei denen der Verdacht auf das Vorliegen einer atypischen Sprachdominanz besteht, vorläufig weiterhin indiziert bleibt. Zur Prädiktion postoperativer Gedächtnisdefizite ist die Aussagekraft des IAT seit jeher umstritten, allerdings sind zur Gedächtnisprädiktion auch die alternativen nichtinvasiven Verfahren (noch) nicht ausreichend etabliert. So bleibt ein „Gedächtnis-IAT“ vorläufig noch indiziert bei Patienten mit „Hochrisiko-Konstellationen“ für postoperative Gedächtnisdefizite, bei denen ein diagnostischer Bedarf nach einem inaktivierenden Untersuchungsverfahren gesehen wird. Insbesondere kann die Indikation zum Gedächtnis-IAT weiterhin gesehen werden bei Patienten mit generell nicht stimmiger prächirurgischer Befundkonstellation in Bezug auf die Konkordanz von präoperativem neuropsychologischen Befund, Seite und Lokalisation der epileptogenen Läsion, Seite und Lokalisation des Anfallsursprungs gemäss EEG, und Anfallssemiologie („kontextuelle Indikationsstellung“).

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**Schlüsselwörter:** Intrakarotidaler Amobarbital-Test, prächirurgische Epilepsiediagnostik, Gedächtnis, Sprache

### Le positionnement actuel du test à l'amobarbital intracarotidien (test de Wada)

Le test à l'amobarbital intracarotidien (TAI) est surtout utilisé dans la chirurgie épileptique pour la détermination préopératoire de la latéralisation des fonctions de la parole et de la mémoire et partant, pour la prédiction des pertes post-opératoires de ces fonctions cognitives. L'importance de ce test fait l'objet de controverses grandissantes. Pour la détermination de la dominance langagière ce test a certes une valeur contestée, mais chez de nombreux patients, il est aujourd'hui possible de le remplacer par l'imagerie par résonance magnétique fonctionnelle (IRMf) qui est non-invasive. Cependant, les résultats de l'IRMf peuvent donner de fausses pistes pour certaines lésions (par exemple gliomes, malformations cérébro-vasculaires) ou si la dominance langagière est atypique, de sorte que le TAI reste indiqué en présence de telles lésions ou pour les patients chez lesquels on soupçonne une dominance langagière atypique. Pour la prédiction de déficits post-opératoires de la mémoire, la valeur du TAI reste contestée, mais en même temps, il faut dire que les procédés alternatifs non-invasifs ne sont pas (encore) suffisamment établis dans ce domaine. Un « TAI de la mémoire » reste donc le premier choix pour les patients avec une « constellation à haut risque » de déficits post-opératoires de la mémoire où l'on éprouve le besoin d'une procédure d'investigation inactivante pour le diagnostic. L'indication d'un TAI de la mémoire peut notamment être présente pour les patients avec une incohérence générale des résultats d'examen préopératoires au niveau de l'examen neuropsychologique préopératoire, de la latéralité et de la localisation de la lésion épileptogène, de la latéralité et de la localisation du foyer des crises d'après l'EEG et de la sémiologie des crises (« indications contextuelles »).

**Mots clés :** Test à l'amobarbital intracarotidien, diagnostic préopératoire en chirurgie épileptique, mémoire, langue

## The Current Status of the Intracarotid Amobarbital Test (Wada Test)

The intracarotid amobarbital procedure (IAP) is mainly used for the prediction of postoperative memory and language deficits after epilepsy surgery. Due to the advent of noninvasive alternatives (particularly functional magnetic resonance imaging, fMRI), the significance of the IAP seems to have declined considerably. For the prediction of memory deficits, however, the issue of the usefulness of the IAP has always been highly controversial, mainly due to methodical problems of the procedure. In the present article, the remaining indications for IAP's in presurgical evaluation are discussed. For language assessment, the IAP will still be relevant in patients with suspected atypical language dominance, or in patients with lesions known to be associated with misleading fMRI results (e.g., gliomas). For memory prediction, the IAP can still selectively be applied in patients with a high risk of postoperative memory deficits, particularly in the absence of an overall concordance of the results of presurgical evaluation („contextual indication“).

**Key words:** Intracarotid amobarbital test, presurgical evaluation, epilepsy, memory, language, outcome

### 1. Einführung: diagnostische Dinosaurier

Der intrakarotidale Amobarbital-Test (IAT) gehört zu den „Dinosaurier-Methoden“ der prächirurgischen Epilepsiediagnostik, gemeinsam mit anderen traditionellen Verfahren wie der elektrischen Hirnkartierung oder auch der intraoperativen Elektrokortikographie. Welche Eigenschaften sind diesen Dinosaurier-Methoden überwiegend gemeinsam? Erstens: sie sind alt – der IAT als jüngstes dieser Verfahren wurde in den 60er Jahren des vergangenen Jahrhunderts klinisch etabliert. Zweitens: sie sind in ihrem methodischen Ansatz simpel, wenn nicht gar archaisch – beim IAT wird zur „Simulation“ eines fokalen Eingriffs gleich (fast) eine komplette Grosshirnhemisphäre kurzzeitig inaktiviert. Drittens: sie sind invasiv und somit komplikationsträchtig [1]. Viertens: sie sind nicht standardisiert. Für die Durchführung und Auswertung des IAT zum Beispiel gibt es viele lokale oder nationale „Kulturen“, eine Vergleichbarkeit ist kaum gegeben. Fünftens: es ist schwierig, die tatsächliche Relevanz der Untersuchungen wissenschaftlich sauber zu bestimmen. Dementsprechend ist diese Relevanz notorisch umstritten. Beim IAT rührt dies nicht nur von der fehlenden Standardisierung her, sondern auch von internen methodischen Problemen des Tests selbst (siehe unten). Sechstens: sie sind „vom Aussterben bedroht“ – so sinkt die Anwendungsfrequenz des IAT weltweit beträchtlich [2], und es werden in manchen epilepsiechirurgischen Zentren keine ausreichenden Untersu-

chungszahlen mehr generiert, um eine fundierte Untersuchungsroutine sicherzustellen. Siebtens: auch die Experten für diese Untersuchungen sterben aus. Mit der stark sinkenden Anwendungsfrequenz des IAT (und der Zersplitterung der prächirurgischen Epilepsiediagnostik durch Entstehung von immer mehr „Zentren“) wachsen kaum Kliniker nach, die noch eine adäquate Routine und Vertrautheit für diese Untersuchungstechnik erwerben könnten. Achtens: als Konsequenz aus den vorangegangenen Punkten driften die Untersuchungen in einen Zustand der Enigmatisierung: man kennt den IAT nur noch vom Hörensagen, hat nie einem Test direkt beigewohnt, man übersieht die unübersichtliche Datenlage nicht, man kennt keinen Experten persönlich, man weiss somit aus eigener Anschauung oder Meinungsbildung nicht recht etwas dazu zu sagen ... – Damit entsteht eine zusätzliche Verunsicherung bezüglich der tatsächlich noch gegebenen Relevanz dieser Untersuchungen in der aktuellen Praxis der prächirurgischen Diagnostik. Der vorliegende Übersichtsartikel soll ein wenig dabei helfen, hier mehr Transparenz zu schaffen.

Hier ein „Schnappschuss“ der aktuellen Situation: Der Stellenwert des IAT in der prächirurgischen Epilepsiediagnostik hat in den letzten Jahrzehnten deutlich abgenommen [2]. Gründe hierfür sind vor dem Hintergrund einer allgemeinen Tendenz zur Nichtinvasivität in der Medizin vor allem in der zunehmenden Verfügbarkeit nichtinvasiver Alternativen und den fortbestehenden Zweifeln an der prädiktiven Wertigkeit des Tests in Bezug auf die postoperativen Gedächtnisfunktionen zu sehen. Für die Sprachdominanzbestimmung, mit Verzögerung nun auch für die Gedächtnisprädiktion, drängt als wichtigste nichtinvasive Alternative die funktionelle Kernspintomographie (fMRI) in den Vordergrund. Grundsätzliche methodische Kritik an einzelnen Aspekten des IAT hat den Test hingegen seit seiner Einführung begleitet und seine anfängliche weite Verbreitung nicht verhindert. Diese methodischen Probleme seien, da wohlbekannt, hier nur stichwortartig rekapituliert:

- die fehlende Standardisierung für Durchführung, Auswertung und prädiktive Interpretation in Bezug auf die Sprach- und Gedächtnistestung stellt ein gravierendes Problem dar. Dies beginnt schon mit unterschiedlichen Dosierungen (von ca. 75 bis ca. 250 mg Amobarbital pro Hemisphäre), unterschiedlicher Reihenfolge der Untersuchungen (linke/rechte; ipsi-/kontralaterale Hemisphäre) und unterschiedlichen Zeitfenstern zwischen den Untersuchungen (von ca. 20 min. bis 24 h). Auch die Testparadigmen (Art, Anzahl, Reihenfolge der verwendeten Testitems [Bilder, Objekte, sprachliche Information], Zeitpunkte der Abfragen, Zielgrößen [Enkodieren, Abrufen, Rekognition]) sind extrem heterogen, desgleichen Auswertung und Interpretation (Summen-Scores, Differenz-Scores, semiquan-

titative oder qualitative Auswertung, unterschiedliche „Cut-off“-Scores...). Eine Vergleichbarkeit der Ergebnisse über verschiedene Zentren hinweg wird schon damit fast unmöglich.

- Die zur Verfügung stehende Testdauer von wenigen Minuten ist für eine neuropsychologische Testung eigentlich nicht ausreichend. Zudem ist die Wirkungsdauer des Amobarbital interindividuell sehr variabel, und zu allem Überfluss ist es schwierig, den jeweils aktuellen Inaktivierungsgrad bezüglich kognitiver Funktionen zuverlässig zu überwachen (das laufende EEG und das Monitoring motorischer Funktionen können herangezogen werden, um diese Überwachung zumindest zu versuchen).
- Auch das intrahemisphärische Inaktivierungsmuster ist interindividuell variabel, in erster Linie aufgrund von Differenzen in den Versorgungsgebieten der relevanten Äste der A. carotis interna, dies betrifft insbesondere die Versorgung des Hippokampus in der Längsachse mit einem variablen Anteil der Perfusion durch Äste der A. cerebri media und A. cerebri posterior. Komplizierend kommt hinzu, dass die fehlende Perfusion eines mesiotemporalen Teilareals durch das Barbiturat nicht eine fehlende Inaktivierung impliziert [3]. Gefäßvarianten können zudem zu irreführenden Perfusionsmustern führen, die auch die kontralaterale Hemisphäre mitbetreffen, etwa bei Füllung beider Aa. cerebri anteriores bei einseitiger Injektion (mit der Folge einer beidseitigen Inaktivierung der SSMA und entsprechenden Einbußen im Testverhalten).
- Stets besteht die Gefahr einer unerwünschten Interferenz mehrerer barbituratinduzierter Defizite und damit einer verminderten Validität der Ergebnisse. Gedächtnisstörungen können mit gleichzeitigen Sprachstörungen interferieren, beide zusammen mit Aufmerksamkeits-, Bewusstseins- und Wahrnehmungsstörungen (Hemianopsie, Neglect etc.).
- Es liegt kaum Information zur Reliabilität des IAT vor. Aus den wenigen Studien, die über Wiederholungsuntersuchungen berichten, gewinnt man den Eindruck, dass die Reliabilität für die Gedächtnisuntersuchung sehr viel schlechter ist als für die Sprachuntersuchung [4].
- Dem IAT fehlt weitgehend eine externe Validierung, da der Test vielmehr selbst als Goldstandard für die Überprüfung alternativer Verfahren benutzt wird. Eine gewisse nachträgliche Validierung ist anhand der postoperativen neuropsychologischen Untersuchungen der IAT-Patienten möglich.

Angeht diese Probleme kann man sich fragen, wie ein solcher Test sich überhaupt etablieren und halten konnte. Der IAT ist jedoch in seiner Einfachheit gleichzeitig so robust, dass zumindest für die Sprachdominanzbestimmung trotz aller Vorbehalte unverändert eine sehr hohe diagnostische Treffsicherheit bezüglich der Sprachlateralisation anzunehmen ist. Die immer

noch bestehende Attraktivität des Tests in heutigen prächirurgischen Entscheidungssituationen geht auch nicht zuletzt auf die *inaktivierende* Natur des Verfahrens zurück. Die Plausibilität der Vorstellung, dass ein inaktivierendes Verfahren die möglichen postresektiven Ausfälle authentischer antizipiert als ein aktivierendes Verfahren wie das fMRI, ist nicht von der Hand zu weisen. Der IAT simuliert die Resektion gewissermassen direkt, während bei aktivierenden Verfahren die Frage, ob ein in eine kognitive Aktivierung involviertes Areal für die postresektive Intaktheit der jeweils getesteten kognitiven Funktion tatsächlich notwendig ist, stets offenbleiben muss. Dennoch stellt sich heute die Frage, für welche prächirurgischen Patienten der IAT weiterhin indiziert sein könnte. Es empfiehlt sich, diese Frage separat für die Sprachdominanzbestimmung und die Gedächtnisprädiktion abzuhandeln, also für die beiden Problemfelder, in welchen ein Beitrag des Wada-Tests immer noch relevant sein könnte. Zuvor seien noch weitere, seltenere Anwendungsfelder und methodische Varianten des IAT, die im vorliegenden Text nicht umfassend beurteilt werden sollen, zumindest kurz gestreift.

## 2. Nebenschauplätze

### IAT-Varianten, und Einsatz des IAT ausserhalb der Sprach- und Gedächtnisprädiktion

#### *Intrakarotidaler Test mit anderen Wirkstoffen?*

Verschiedentlich wurde versucht, den intrakarotidalen Test mit anderen Wirkstoffen als Amobarbital durchzuführen. Diese Versuche waren motiviert durch Lieferungs- und/oder Herstellungseingpässe des Amobarbital, aber auch durch den Wunsch, die Testdurchführung zu verbessern, zum Beispiel durch eine bessere Steuerbarkeit des inaktivierenden Wirkstoffs. Zum Einsatz kamen vor allem Etomidate, Propofol, Methohexital und Pentobarbital. Die jeweiligen Arbeitsgruppen haben ihre Erfahrungen mit diesen Wirkstoffen berichtet (zusammenfassend: [5, 6]). Die Präparate weisen unterschiedliche Vor- und Nachteile auf. Der Aspekt des Wirkstoffwechsels ist jedoch für die prinzipielle Frage nach den in der prächirurgischen Diagnostik verbleibenden Indikationen für intrakarotidale Tests nicht relevant.

#### *Selektiver statt „globaler“ IAT?*

Zur selektiveren Ausschaltung von Zielarealen wurden Varianten des IAT entwickelt, bei denen Injektionen in die A. cerebri posterior [7], die A. choroidea anterior [8, 9] oder in Äste der A. cerebri media [10, 11]

erfolgten. Ziele der selektiven Tests waren meist die umschriebenerer Ausschaltung gedächtnisrelevanter Strukturen und das Vermeiden des Auftretens störender Begleitdefizite wie zum Beispiel Aphasie [7, 8]. Bei anderen Patienten versuchte man, mit diesen selektiven Tests die Folgen extratemporaler Resektionen in mutmasslich eloquenten Arealen zu „simulieren“ [10, 11], teils auch ausserhalb der Epilepsiechirurgie. Solche Varianten bleiben Zentren mit hohem Durchsatz an selektiven Sondierungen vorbehalten, da bei mangelnder Routine ansonsten erhöhte Komplikationsraten drohen können. Angesichts der aktuellen Tendenz zur Verbesserung nichtinvasiver Alternativen zum IAT (siehe unten) ist nicht zu erwarten, dass die selektiven AT's sich in Zukunft flächendeckend durchsetzen können.

### ***IAT bei Kindern und bei behinderten Personen?***

Bei kleineren Kindern, bei Patienten mit Intelligenzminderung und bei Patienten mit Verhaltensstörungen kann die Kooperabilität im IAT eingeschränkt sein. Dann gilt es, das Testverfahren unter Umständen durch weitere Vereinfachung der Aufgaben den Fähigkeiten der Patienten individuell anzupassen. Dies geschieht am besten durch vorgängige Simulation des Tests ohne Amobarbitalinjektion. Bei erstaunlich vielen Patienten mit vermeintlich schweren Einbussen gelingt dann die Durchführung eines IAT ohne Probleme [12 - 14]. Bei unkooperativen Patienten kann die Angiographie und Sondierung der A. carotis interna auch im Rahmen einer kurzen Sedierung oder gar Kurznarkose erfolgen. Oft gelingt auf diesem Wege eine Sprachdominanzbestimmung auch bei Patienten, die für ein fMRI nicht geeignet sind. Nach unseren Erfahrungen ist bei Kindern ab Schulalter ein Wada-Test möglich, wenn eine normgerechte Intelligenz und eine gute Kooperabilität gegeben sind.

### ***Untersuchung von kognitiven Funktionen ausserhalb des Bereichs von Sprache und Gedächtnis?***

In IAT's wurden nicht nur Sprache und Gedächtnis untersucht, sondern auch andere Funktionen, für die man Hemisphärendifferenzen annehmen konnte: Prosodie, Musikkognition, Emotionalität, Neglect, Nosognosie, Zeitkognition, Aufmerksamkeit, Bewusstsein... Direkte klinische Relevanz besitzen diese Untersuchungen in der prächirurgischen Entscheidungsfindung in aller Regel nicht. Manche Forschungen (zum Beispiel zur Prosodie oder zur Zeitkognition) sind eher von wissenschaftlichem Interesse, andere (Aufmerksamkeit, Bewusstsein, Wahrnehmung) mögen ergänzende Hinweise zu den mit den Sprach- und Gedächtnisprüfungen interferierenden Begleitdefiziten geben.

### ***IAT ausserhalb der Epilepsiechirurgie?***

Der Wunsch, postresektive kognitive Defizite zu antizipieren, besteht in der Neurochirurgie selbstverständlich auch ausserhalb der eigentlichen Epilepsiechirurgie, und zwar immer dann, wenn bei zerebralen Resektionen eloquente Hirnareale erfasst werden könnten, und wenn gleichzeitig die klinisch-neurochirurgische Indikationsstellung zur Resektion einen gewissen Spielraum bezüglich des Resektionsausmasses lässt. Diese Voraussetzungen sind vor allem bei manchen Tumorsektionen gegeben, aber auch bei Therapien von Gefässmalformationen wie Kavernomen und arteriovenösen Missbildungen. Bei solchen Patienten kann der IAT (global oder selektiv) insbesondere bei einem Verdacht auf das Vorliegen einer atypischen Sprachdominanz diagnostisch hilfreich sein, zumal bei solchen Läsionen eine erhöhte Fehlerquote in der nichtinvasiven Sprachdominanzbestimmung durch das fMRI gegeben ist [15]. Häufiger als der IAT wird bei nicht epilepsiechirurgischen Tumoroperationen aber eine elektrische Hirnkartierung zu erwägen sein, deren Aufweise zur intrahemisphärischen Lokalisation eloquenter Areale zur Operationsplanung genutzt werden können [16].

### ***„EEG-IAT“?***

Aus den sechziger Jahren des vergangenen Jahrhunderts stammt die Tradition, den IAT zum Nachweis einer monohemisphärischen Epileptogenizität einzusetzen bei Patienten, deren EEG einen hohen Anteil epilepsietypischer Aktivität kontralateral zu einer geplanten Resektion (und meist damit auch kontralateral zur mutmasslichen epileptogenen Läsion) aufweist. Im Hintergrund dieser Tradition steht vor allem das Konzept der „sekundär bilateralen Synchronie“, demzufolge ein monohemisphärisches epileptogenes Areal kontralateral synchron erscheinende epilepsietypische Aktivität triggern kann, welche dann aber kein kontralaterales epileptogenes Areal anzeigen soll [17]. In einem solchen Falle würde man also erwarten, dass die ipsilaterale Amobarbitalinjektion die interiktalen Spikes in beiden Hemisphären unterbricht, während eine kontralaterale Injektion diesen EEG-Effekt nicht aufwiese. In früheren Studien zum globalen [18] oder auch zum selektiven IAT [19] wurde gezeigt, dass dieser EEG-IAT bei manchen Patienten zur präoperativen Entscheidungsfindung beitragen kann. Für Einzelfälle mit speziellen Befundkonstellationen mag dies auch heute noch gelten.

## **Prädiktion der Anfallskontrolle und Bestimmung der Lateralisation des epileptogenen Areals?**

Asymmetrische IAT-Gedächtnisleistungsmuster können bei Temporallappenepilepsien die Lateralisation des epileptogenen Areals anzeigen (Zusammenfassung in [20]), und ein vor dem Hintergrund der prächirurgischen Arbeitshypothese unerwarteter IAT-Gedächtnisbefund kann Hinweis auf eine möglicherweise reduzierte Chance auf postoperative Anfallsfreiheit geben [21]. Da bei den meisten prächirurgischen Patienten jedoch ausreichend Informationen zur Lateralisation der Epilepsie und zur Chance auf postoperative Anfallsfreiheit aus den anderen – und überwiegend nichtinvasiven – diagnostischen Verfahren vorliegen, erscheint der Aufwand, mittels einer invasiven Untersuchung zusätzliche und zudem individuell wenig verbindliche prädiktive Information zu gewinnen, in den allermeisten Fällen nicht gerechtfertigt. Es bleibt offen, ob in speziellen Subgruppen mit ansonsten nichtkonklusiven Untersuchungsergebnissen ein Nutzen des Wada-Tests gegeben sein könnte. Hierzu liegen keine verbindlichen Daten vor.

### **3. Sprachdominanzbestimmung**

**Vorbemerkung:** Im vorliegenden Text wird kein Vergleich des IAT mit der elektrischen Hirnkartierung („electrical stimulation mapping“) zur Sprachdominanzbestimmung vorgenommen. Die beiden Verfahren werden eher als komplementär denn als konkurrierend aufgefasst, da der IAT zur *interhemisphärischen* Verteilung von Sprachfunktionen Auskunft gibt, während die Hirnkartierung die *intrahemisphärische* Anordnung von Sprachzentren darstellen soll. – Auch wird die Diskussion um nichtinvasive Alternativen zum IAT auf das derzeit wichtigste konkurrierende Verfahren, das fMRI, eingeschränkt. Es ist nicht zu erwarten, dass eine der bekannten weiteren nichtinvasiven Methoden, also Dopplersonographie, TMS, NIRS, Tachistoskopie, dichotisches Hören etc., sich als Alternative zum IAT flächendeckend durchsetzen wird.

#### **IAT contra fMRI**

Zur Sprachdominanzbestimmung gilt der Wada-Test immer noch als Goldstandard, gegen den andere Verfahren zu validieren sind. Zweifel an der noch fortbestehenden Indikation zum IAT sind für den Bereich der Sprachdominanzbestimmung also nicht auf eine Kontroverse bezüglich der Aussagekraft des IAT zurückzuführen. Damit unterscheidet sich diese Fragestellung wesentlich von derjenigen bei der Gedächtnisprädiktion (siehe unten). Es ist aber zu bedenken, dass selbstverständlich auch beim Wada-Test Fehldiagnosen zur Sprachdominanz möglich sind, insbesondere bei

atypischen Gefäßversorgungsmustern und/oder eingeschränkter Testbarkeit des Patienten aufgrund von Verhaltensstörungen im Wada-Test. Unter den nichtinvasiven Verfahren zur Sprachdominanzbestimmung meldet derzeit vor allem das fMRI den Anspruch an, den IAT ersetzen zu können. Mittlerweile werden Übereinstimmungen zwischen den beiden Methoden im Bereich von 90 % oder mehr erzielt [22]. Eine besonders weitreichende Konkordanz lässt sich offenbar erzielen, wenn mehrere unterschiedliche Sprachaufgaben im fMRI eingesetzt werden [23]. Wir finden also für die Sprachdominanzbestimmung die eigentlich erfreuliche Situation vor, dass zwei Verfahren mit guter Aussagekraft, aber unterschiedlichen Vor- und Nachteilen zur Verfügung stehen. Wenn man zeigen könnte, dass das fMRI in jedem Fall dem IAT mindestens gleichwertig ist, wäre aufgrund der Nichtinvasivität des MRI diesem aktivierenden Verfahren grundsätzlich der Vorzug zu geben, der IAT wäre dann überflüssig geworden. Selbstverständlich ist auch die individuelle Konstellation denkbar, dass unabhängig von der Frage der Invasivität dem fMRI der Vorzug gegenüber dem IAT zu geben ist – etwa bei Patienten mit Kontraindikationen bezüglich des IAT, Patienten mit unklarem IAT-Ergebnis, oder auch bei Patienten, für welche nicht nur die Lateralisation, sondern auch die intrahemisphärische Lokalisation der Sprachzentren zu ermitteln ist (hierfür wäre das fMRI dann allerdings nicht mit dem IAT, sondern mit dem „Dinosaurier-Goldstandard“ der elektrischen Hirnkartierung zu vergleichen [24]). Die Indikation zum IAT wäre dann vor allem noch für diejenige Minderheit von Patienten gegeben, bei welcher die fMRI-Sprachdominanzbestimmung noch fehleranfällig ist. Bisherige Studien zeigen, dass ein „mismatch“ zwischen IAT und fMRI vor allem bei Patienten mit bestimmten, fMRI-verfälschenden Läsionen (Raumforderungen, Gefäßmissbildungen) entstehen kann. Auch kommen fMRI und IAT vergleichsweise häufig bei Patienten mit atypischer Sprachdominanz (bilaterale Sprachrepräsentation oder rechtshemisphärische Sprachdominanz) zu unterschiedlichen Ergebnissen, während bei Patienten mit klar linkshemisphärischer Sprachdominanz ein „mismatch“ ausgesprochen selten ist [25, 26]. Zum Einfluss verschiedener Läsionen auf das fMRI-Sprachergebnis konnte in einer grösseren Gruppenstudie [27] gezeigt werden, dass Patienten mit Kavernomen, Gliomen bzw. Läsionen in der Nähe sprachsensitiver „voxels of interest“ niedrigere fMRI-Lateralisationsindizes und häufigere Nichtübereinstimmungen mit IAT-Sprachdominanzbefunden aufwiesen als andere Patienten. In einer anderen Studie [28] fanden sich in einer Gruppe von 50 Patienten zwei Personen mit links frontalen Gliomen, bei denen das fMRI fälschlich (gemäss IAT-Kriterien) eine rechtshemisphärische Sprachdominanz nahelegte. Auch gemäss einer aktuellen Übersichtsarbeit, in der aus neurochirurgischer Sicht das Sprach-fMRI mit der elektrischen Hirnkartierung verglichen wird [24], erscheinen Gliompatienten besonders problematisch

in Bezug auf potenzielle fMRI-Fehllateralisationen. Generell beklagen die Autoren dieser Übersicht die inhaltliche und methodische Heterogenität der bislang vorliegenden Vergleichsstudien – dies führe dazu, dass das Sprach-fMRI derzeit nicht als verbindliche Richtschnur für den Neurochirurgen empfohlen werden könne, somit die Hirnkartierung derzeit noch nicht zu ersetzen vermöge. – All dies legt das Vorgehen nahe, bei Patienten mit gemäss fMRI atypischer Sprachdominanz den Befund mittels eines IAT zu überprüfen, desgleichen bei Patienten mit potenziell fMRI-verfälschenden Läsionen. Bei Patienten mit gemäss fMRI typischer linkshemisphärischer Sprachdominanz erscheint eine solche Kontrolle hingegen nur dann erforderlich, wenn die prächirurgische Befundkonstellation gerade nicht eine linkshemisphärische Sprachdominanz hätte erwarten lassen – und wenn durch eine Neueinschätzung der Sprachdominanz eben diese gewünschte Konkordanz hergestellt und dadurch eine Operationsempfehlung plausibel gemacht werden würde. Eine Überprüfung des fMRI-Ergebnisses wäre zum Beispiel indiziert bei einer Patientin mit links temporolateralem Kavernom und periläsionellem Anfallsursprung gemäss EEG, fokalen Anfällen ohne (post)iktale Aphasie, aber fMRI-Zeichen einer linkshemisphärischen Sprachdominanz. Ein anderes konstruiertes Beispiel wäre ein linkshändiger Patient mit neokortikaler temporaler Epilepsie, im nichtinvasiven EEG rechtshemisphärischem Anfallsursprung und -verlauf, linksseitiger Sprachdominanz gemäss fMRI, aber klinisch eindeutiger postiktaler Aphasie.

#### 4. Prädiktion der postoperativen Gedächtnisleistungen

Die Grundkonstellation bezüglich der zur Verfügung stehenden Untersuchungen zur Gedächtnisprädiktion ist wesentlich verschieden von derjenigen der Sprachdominanzbestimmung (siehe oben): Für die Gedächtnisprädiktion ist die Wertigkeit des IAT seit jeher umstritten, während zugleich die Aussagekraft des fMRI ebenfalls (noch) nicht ausreichend belegt ist. Anders als bei der Sprachdominanzbestimmung treten hier also nicht zwei hochwertige und etablierte, sondern zwei kontroverse und problematische Verfahren gegeneinander an. Ursprünglich, also in den sechziger Jahren des letzten Jahrhunderts, sollte die IAT-Gedächtnisuntersuchung verwendet werden, um Patienten mit erhöhtem Risiko für schwere postoperative Amnesien zu identifizieren. Da solche Fälle – erst recht unter den aktuellen, vor allem bezüglich der Bildgebung stark verbesserten diagnostischen Bedingungen – extrem selten sind, liegen keine ausreichenden Daten vor, um die Wertigkeit des Tests für diese Fragestellung verbindlich zu beurteilen. Solche Daten sind auch nicht aus zukünftigen Studien zu erwarten. Daher trat in den letzten Jahrzehnten die Frage in den Vordergrund, ob der IAT

nicht auch lediglich graduelle, aber gleichwohl alltagsrelevante postoperative materialspezifische Einbussen in Leistungen des episodischen Gedächtnisses vorherzusagen könne. Ermöglicht der IAT für solche Einbussen eine individuelle Prädiktion? – Obgleich dies eine hochkontrovers diskutierte Frage ist, zu deren Beantwortung in einem ersten Schritt ein sehr uneinheitlicher Korpus von Literatur zu bewerten wäre, hängt die Indikation zum IAT heute eher von der Beantwortung der anderen Frage ab: ob das Gedächtnis-fMRI eine individuelle Prädiktion solcher Einbussen leisten könne? Wenn ja, würde man – analog der Situation bei der Sprachdominanzbestimmung – ohnehin das fMRI wegen dessen Nichtinvasivität gegenüber dem IAT favorisieren. Ist das fMRI dem IAT vielleicht gar überlegen? – Schauen wir zunächst ganz kurz auf die sehr heterogene IAT-Literatur.

Zweifel an der Wertigkeit des IAT werden unter anderem durch diverse Berichte über falsch-positive Tests geschürt, also Patienten, die im IAT-Gedächtnis-Test „durchfallen“, dennoch zur Operation gelangen und postoperativ nicht amnestisch werden [29]. Auch ist die Reliabilität des Tests fraglich, da „durchgefallene“ Patienten bei einer Testwiederholung „bestehen“ können – und dann postoperativ ebenfalls nicht amnestisch werden (Publikation allerdings nur als Abstract: [30]; zur Übersicht siehe [31]). Da nur graduelle Gedächtniseinbussen nach Temporallappeneingriffen im Gegensatz zu schweren Amnesien sehr häufig sind, ist trotz solcher entmutigender Befunde immer wieder untersucht worden, ob der Wada-Test nicht dennoch postoperative Gedächtnisdefizite vorhersagen kann. Zumindest ist der Gedanke naheliegend, dass die Gedächtnisleistung nach Injektion auf der mutmasslich erkrankten Seite Aufschluss über die „funktionale Reserve“ des kontralateralen Hippokampus gibt, während umgekehrt die Gedächtnisleistung nach Injektion auf der gesunden Seite eine Restkapazität des erkrankten Temporallappens (sog. „functional adequacy“) anzeigen könnte [32, 33]. Eine schlechte kontralaterale und eine gute ipsilaterale Leistung wären dann Prädiktoren eines ungünstigen Gedächtnis-Outcome. Zwar wurden immer wieder Studien publiziert, die im Sinne dieser Hypothesen statistisch relevante Korrelationen auf der Ebene von Gruppenanalysen zeigten; eine *individuelle* Prädiktion erwies sich jedoch als schwierig [34]. Nicht wenige Studien kommen auch zu einem gänzlich negativen Ergebnis, indem eine signifikante Korrelation zwischen IAT-Gedächtnisleistungen und postoperativer Änderung der Gedächtnisfunktion nicht nachgewiesen werden konnte [34, 35]. Die Beurteilung der „evidence“ ist erschwert durch sehr heterogene Testparadigmen und Auswertungskriterien. Es mehren sich zudem die Anzeichen dafür, dass isolierte IAT-Gedächtnis-Daten für eine individuelle Prädiktion zu schwach sind, während die Berücksichtigung weiterer, in der Prächirurgie ohnehin anfallender Informationen mit prädiktivem Wert (präoperative Gedächtnisleistung in der neuro-

psychologischen Untersuchung, Art und Lokalisation der zerebralen Läsion, Alter bei Erstmanifestation der Epilepsie, etc.) im Rahmen multivariater Analysen die Aussagekraft deutlich aufwerten. Klinische und neuropsychologische Daten sind prädiktiv so wertvoll, dass von manchen Autoren schon gefragt wurde, ob der IAT darüber hinaus überhaupt noch einen zusätzlichen prädiktiven Wert besitzt [32, 34 - 36]. Dieser ketzerischen Interpretation stehen aber Studien entgegen [36, 37], die eine von den klinischen Variablen unabhängige prädiktive Relevanz der IAT-Gedächtnisdaten nachwiesen. So konnte in einer schon älteren Studie nicht nur gezeigt werden, dass eine multivariate Analyse eine recht gute individuelle Prädiktion des verbalen Gedächtnisverlusts nach links temporaler Resektion erlaubt, sondern auch, dass die IAT-Daten gemäss dem Modell der funktionalen Reserve (siehe oben: schlechte Gedächtnisleistung der gesunden Hemisphäre disponiert zu postoperativen Defiziten) sehr wohl zur Prädiktion spezifisch beitragen konnten [37]. Eine weitere Studie [36] kam zu einem ähnlich positiven Ergebnis, allerdings wurden dort die IAT-Daten nach dem Modell der funktionalen Adäquatheit interpretiert (siehe oben: gute Gedächtnisleistung des betroffenen Hippokampus disponiert zu postoperativen Verlusten).

Vor dem Hintergrund dieser unübersichtlichen Literaturlage zum IAT gälte es nun, die nichtinvasive Alternative des fMRI zu beurteilen. Auch hinsichtlich der Gedächtnisprädiktion wurde wiederholt versucht, das fMRI bezüglich seiner Potenz als Ersatz für den Wada-Test zu evaluieren. Das präoperative Gedächtnis-fMRI ist trotz inhärenter methodischer Probleme mittlerweile immerhin so weit entwickelt, dass die generelle Tauglichkeit der Methode als nachgewiesen gelten kann ([38] zur Übersicht). Eine definitive Bewertung der klinischen Relevanz dieses Verfahrens steht aber noch aus. Zuletzt erschienen einzelne Studien, in denen auch die Ebene der individuellen Prädiktion erreicht wurde. In einem Kollektiv (n = 72) operierter Temporalappenepilepsie-Patienten wurde der prädiktive Wert eines aufwändigen Gedächtnis-fMRI nach dem sog. „subsequent-recognition“-Paradigma untersucht [39]. Während die alleinige Berücksichtigung der fMRI-Daten noch zu viele „false positives“ (irrtümliche Prädiktion eines postoperativen Gedächtnisverlusts) erzeugte, konnte durch Hinzunahme der Daten zur präoperativen neuropsychologischen Leistung und zur Sprachlateralisation eine sehr zuverlässige Identifikation derjenigen Patienten erreicht werden, die nach links temporaler Resektion einen klinisch signifikanten Verbalgedächtnisverlust aufwiesen. Mit einem anderen Paradigma (Kombination dreier verschiedener Gedächtnisaufgaben im fMRI) wurde von einer französischen Gruppe [40] eine kleinere Gruppe (n = 25) solcher Temporalappenepilepsie-Patienten untersucht, bei denen aufgrund ungewöhnlicher präoperativer neuropsychologischer Befunde auch ein Gedächtnis-IAT durchgeführt worden war. Mit einem Auswertungsmodell, das zur

Prädiktion die fMRI-Gedächtnisdaten zur verzögerten Rekognition, aber auch die Seite des epileptogenen Areals und den präoperativen neuropsychologischen Befund berücksichtigte, konnte bei 9 von 10 Patienten mit relevantem postoperativem Verlust das Defizit vorhergesagt werden, und es konnte gezeigt werden, dass die fMRI-Daten zu dieser Prädiktion in relevantem Masse beitrugen. Die IAT-Gedächtnisdaten zeigten hingegen eine geringere Wertigkeit. – So beobachten wir in der Literatur derzeit zumindest einen beginnenden Trend zu einer „Stärkung“ der Position des Gedächtnis-fMRI zuungunsten des Gedächtnis-IAT in bezug auf die Prädiktion postoperativer Gedächtnisdefizite nach Temporallappenresektionen.

Ähnlich wie bei der Sprachdominanzbestimmung wird man zukünftig zu überprüfen haben, ob bestimmte Untergruppen prächirurgischer Patienten (zum Beispiel solche mit nichtläsioneller linksseitiger Temporallappenepilepsie, oder mit linksseitiger mesialer Temporallappenepilepsie, aber ohne Gedächtnisstörung) doch noch einer die Operation unmittelbar simulierenden, also mit einem inaktivierenden statt aktivierenden Paradigma arbeitenden, Diagnostik bedürfen. Im folgenden Abschnitt wird versucht, den aktuellen Forschungsstand in eine schnappschussartige Empfehlung zu noch verbleibenden IAT-Indikationen umzumünzen.

## 5. Welche Indikationen verbleiben?

Solange keine definitive Evidenz zum Stellenwert des IAT im heutigen Methodenwettstreit vorliegt, wird die Schwelle der verbleibenden Indikationsstellung für den IAT in den verschiedenen Epilepsiezentren vermutlich unterschiedlich hoch sein. In einem Zentrum mit einer hochaktiven eigenen fMRI-Forschung und -Anwendung wird man die Resultate der funktionellen Bildgebung wohl höher gewichten als in einem Zentrum, in dem dieses Verfahren nur eine notdürftig gepflegte klinische Routine darstellt. Umgekehrt wird in einem Zentrum, in dem traditionell eine hochstehende „IAT-Kultur“ mit ebenfalls aktiver klinischer IAT-Forschung etabliert ist, der IAT noch häufiger eingesetzt werden. In Bezug auf diesen Hintergrund sind Empfehlungen zu IAT-Indikationen stets zu relativieren.

### Sprachdominanzbestimmung

Voraussetzung für jede Indikationsstellung zur Sprachdominanzbestimmung bleibt selbstverständlich die individuelle klinische Relevanz der Sprachdominanz überhaupt. Man wird den IAT also nur für Patienten erwägen, bei denen entweder eine Resektion in einem möglicherweise sprachrelevanten Areal oder ein diskonnektiver Eingriff mit möglichen ungünstigen Folgen für die Sprachfunktionen geplant ist (zum Beispiel He-

misphärotomie, Kallosotomie, Resektion inklusive des Broca- oder Wernicke-Areals im Falle einer Sprachdominanz der zu operierenden Hemisphäre).

Nach dem im Abschnitt „Sprachdominanzbestimmung“ Gesagten wird vorgeschlagen, dass bei folgenden Befundkonstellationen bzw. in folgenden Situationen eine Indikation zum IAT weiterhin besteht:

1. Ein fMRI konnte nicht durchgeführt werden. – Hier ist an Patienten mit kognitiven Einbussen, Verhaltensproblemen und generell eingeschränkter Kooperabilität (auch Klaustrophobie) zu denken, bei denen ein fMRI nicht in geregelter Weise durchführbar ist, wohl aber ein (unter Umständen der eingeschränkten Kooperabilität angepasster) IAT. Auch fallen in diese Gruppe Patienten, bei denen ein fMRI aus medizinischer Sicht kontraindiziert ist (bestimmte Herzschrittmacher, magnetisierbare Implantate etc.).
2. Ein fMRI wurde durchgeführt, ergab aber kein eindeutiges Ergebnis im Sinne einer klaren Aussage zur Sprachdominanz.
3. Ein fMRI wurde durchgeführt, ergab einen klaren Befund zur Sprachdominanz, das Resultat ist aber vor dem Hintergrund der Befundkonstellation in der prächirurgischen Diagnostik unplausibel (kontextuelle Indikationsstellung).
4. Ein fMRI wurde durchgeführt, es ergab sich das Resultat einer atypischen Sprachdominanz.
5. Es liegt eine zerebrale Läsion vor, die bekanntermassen die fMRI-Sprachdominanzbestimmung verfälschen kann (zum Beispiel raumfordernder Tumor, zerebrale Gefässmissbildung).

## Gedächtnisprädiktion

Auch der „Gedächtnis-IAT“ kommt selbstverständlich nur noch für Patienten in Frage, bei denen die Gedächtnisprädiktion überhaupt bedeutsam und problematisch ist. Man wird den IAT also fast ausschliesslich bei Patienten mit (mesialer) Temporallappenepilepsie erwägen. Eine Indikation ist gemäss dem im Abschnitt „Gedächtnisprädiktion“ Gesagten noch bei folgenden Patientengruppen zu sehen:

1. Patienten mit „Hochrisiko-Konstellationen“ für postoperative Gedächtnisdefizite, bei denen diagnostischer Bedarf nach einem inaktivierenden Untersuchungsverfahren gesehen wird. Dazu würden zum Beispiel Patienten mit auch bei optimaler MR-Diagnostik nichtläsioneller linksseitiger Temporallappenepilepsie und geplanter linksseitiger 2/3-Temporallappenresektion zählen, oder Patienten mit dem Syndrom einer linksseitigen mesialen Temporallappenepilepsie, jedoch ohne Gedächtnisstörung in der prächirurgischen neuropsychologischen Untersuchung.

2. Patienten mit generell unplausibler bzw. nicht stimmiger prächirurgischer Befundkonstellation in Bezug auf die Konkordanz von präoperativer Neuropsychologie, Seite und Lokalisation der epileptogenen Läsion, Seite und Lokalisation des Anfallsursprungs gemäss EEG und Semiologie, und gegebenenfalls auch in Bezug auf das Ergebnis eines Gedächtnis-fMRI (kontextuelle Indikationsstellung). Beispiel wäre ein Patient mit MTLE rechts (gemäss Anfallsaufzeichnung und MRI), linksseitiger Sprachdominanz, jedoch verbaler Gedächtnisstörung in der neuropsychologischen Untersuchung. Oder (in einem Epilepsiezentrum mit gut etabliertem und für die Entscheidungsfindung routinemässig herangezogenem Gedächtnis-fMRI-Paradigma) eine Patientin mit MTLE links, neuropsychologisch verbalem Gedächtnisdefizit, aber fMRI-Zeichen einer links hippocampal lokalisierten verbalen Gedächtnisstörung.

## 6. Fazit

Die Indikation zur Durchführung eines IAT zur Sprachdominanzbestimmung bleibt vorläufig erhalten, zumindest für Patienten mit unklarem oder „unpassendem“ fMRI-Ergebnis, oder bei Hinweisen auf das Vorliegen einer atypischen Sprachdominanz. Bezüglich der Gedächtnisprädiktion bleibt der IAT umstritten, kann aber in Einzelfällen mit Hochrisiko-Konstellationen oder nicht stimmigen Befundkonstellationen in der prächirurgischen Diagnostik weiterhin indiziert sein. Die oben genannten Empfehlungen zu verbleibenden Indikationen müssen fortlaufend in Abhängigkeit von der Evidenzentwicklung bei den alternativen, nichtinvasiven Verfahren überdacht und aktualisiert werden.

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### Summary

Functional MRI (fMRI) is increasingly utilized as a non-invasive alternative to cortical mapping and Wada test during the last two decades in patients with medically refractory epilepsy who are candidates for epilepsy surgery. fMRI acquired a crucial role in everyday clinical routine in determining important brain functions such as motor, language or memory. Mapping motor function by fMRI is particularly useful when anatomic structures are distorted by mass effects or dysplastic lesions making it difficult to ascertain the location of the central sulcus with certainty. fMRI studies comparing language lateralization in right-handed normal adults with epilepsy patients, observed that patients with epilepsy had a higher incidence of atypical language dominance, which was particularly true for patients with left sided seizure foci. Preoperative language fMRI could be used to stratify patients in terms of risk for language decline after epilepsy surgery. In memory fMRI, hippocampus has been notoriously difficult to activate reliably. This may be at least partly attributable to difficulties in disengaging memory function for a control condition. The hippocampus is also in a region of comparatively high static susceptibility, resulting in decreased sensitivity for fMRI signal. Nevertheless, memory fMRI in presurgical assessment provides valuable information.

Although fMRI results increasingly influence diagnostic and therapeutic decision making in epilepsy surgery, there are still numerous problems yet to be solved.

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**Key words:** fMRI, imaging, epilepsy surgery, language, memory, motor function

### Zur klinischen Bedeutung der funktionellen Kernspintomographie (fMRI) in der Epileptologie

fMRI-Untersuchungen werden in den letzten zwei Jahrzehnten zunehmend als eine Alternative zu invasiven Verfahren, wie Wada-Test und kortikale Stimulation, in der präoperativen Diagnostik von epilepsiechi-

urgischen Kandidaten eingesetzt. Die Bedeutung des fMRIs für die Klinik liegt in der Identifizierung wichtiger Hirnfunktionen wie der Motorik, der Sprache und des Gedächtnisses. Dabei zeigt sich die Lokalisation mittels fMRI besonders hilfreich bei der Bestimmung des Sulcus centralis, wenn Massenläsionen oder ausgedehnte Missbildungen eine anatomische Bestimmung erschweren. Die Bestimmung der hemisphärischen Sprachdominanz mittels fMRI erlaubt es heute, diejenigen Patienten vor einem epilepsiechirurgischen Eingriff zu identifizieren, die ein erhöhtes Risiko möglicher sprachlicher Einbußen infolge einer Resektion im Bereich der sprachdominanten Hemisphäre eingehen. Das fMRI des Hippokampus und seiner Gedächtnisfunktionen ist ein schwieriges Unterfangen, da Gedächtnisbildungsprozesse nur in engen Grenzen experimentell kontrollier- und steuerbar sind. Zudem bestehen methodische Herausforderungen, da die hippokampale Formation aufgrund vermehrter Suszeptibilitätsartefakte geringe Signalausbeuten liefert. Einerseits beeinflussen Ergebnisse aus fMRI-Untersuchungen heute bereits vermehrt therapeutische Entscheidungen in der Epilepsiechirurgie andererseits bestehen nach wie vor wichtige ungelöste methodische Probleme, die eine grosse Herausforderung für die Methodenforschung darstellen.

**Schlüsselwörter:** fMRI, Bildgebung, Epilepsiechirurgie, Sprache, Gedächtnis, Motorik

### De l'importance clinique de la tomographie à spin nucléaire (IRMf) dans l'épileptologie

Depuis deux décennies, l'option IRMf remplace de plus en plus les procédés invasifs d'investigation tels que le test de Wada et la stimulation corticale dans le diagnostic préopératoire de candidats à la chirurgie épileptique. L'intérêt clinique de l'IRMf consiste dans le fait qu'elle permet d'identifier des fonctions cérébrales importantes telles que la motricité, la langue et la mémoire. La localisation au moyen de l'IRMf est particulièrement utile pour la détermination du sillon central lorsque des lésions massives ou des malformations étendues compliquent une détermination anatomique. La détermination du siège hémisphérique de la

dominance linguistique permet aujourd'hui d'identifier avant une intervention chirurgicale ceux parmi les patients épileptiques qui encourent un plus grand risque de pertes linguistiques en raison d'une résection dans le domaine de l'hémisphère où siège la dominance linguistique. L'IRMf de l'hippocampe et de ses fonctions mnésiques est une procédure difficile car les possibilités de contrôle et de commande expérimentale des facultés mnésiques restent très limitées. Les défis sont aussi d'ordre méthodologique, car la formation hippocampique fournit une faible moisson signalétique en raison de multiples susceptibilités artificielles. D'un côté, les résultats d'examen IRMf influencent déjà de plus en plus les décisions thérapeutiques dans la chirurgie épileptique, de l'autre côté, il reste des problèmes méthodologiques importants à appréhender qui posent de grands défis à la recherche méthodologique.

**Mots-clés :** IRMf, imagerie, chirurgie de l'épilepsie, langage, mémoire, motricité

## Functional magnetic resonance imaging

Functional neuroimaging maps the activity of the living brain in space and time. Magnetoencephalography and electroencephalography offer direct measurements of neural activity with high temporal resolution but are limited by difficulties in defining the spatial location and extent of activation. Neuroimaging methods based on metabolic and vascular parameters, while offering limited temporal resolution, provide excellent spatial resolution and localization of brain function. Functional magnetic resonance imaging (fMRI), enables completely noninvasive imaging of changes in blood oxygenation and perfusion. Unlike positron emission tomography (PET), fMRI does not require exposure to ionizing radiation. Compared to PET, fMRI provides superior temporal and spatial resolution and increased sensitivity for detecting task activation in individual subjects through signal averaging. On the other hand, PET provides a greater repertoire of image contrast sources. Whereas fMRI is primarily sensitive to hemodynamic changes, PET images can reflect blood flow, glucose utilization, oxygen consumption, and receptor binding. PET also provides a silent environment that is not affected by electromagnetic interference or the presence of ferrous objects. However, PET scanning is less widely available and significantly more costly than fMRI because of the need for on-line tracer synthesis.

The primary contrast phenomena for fMRI is blood-oxygenation-level-dependent (BOLD) contrast. BOLD reflects a complex interaction between blood flow, blood volume, and hemoglobin oxygenation [1 - 3]. Functional contrast is obtained because the iron present in hemoglobin becomes paramagnetic only when it is deoxygenated producing a local susceptibility increase manifested as a change in T2\* images [4]. This change

in hemoglobin oxygenation can be observed using a variety of pulse sequences, including routine gradient-echo sequences and gradient-echo echoplanar sequences, which particularly emphasize T2\* effects [4].

Task-specific BOLD signal changes are not directly quantifiable in physiologic units and instead are expressed as a percentage signal change or as a statistical significance level based on a particular statistical model. Absolute or resting function cannot be easily assessed, and for clinical studies it may be difficult to know whether any observed abnormalities are due to baseline or task-specific effects. A typical BOLD response consists of a 0.5-5% change in regional image intensity that develops over 2-8 seconds following task initiation, typically with an initial peak or overshoot, a somewhat lower plateau for sustained tasks, and often an undershoot of the baseline following task completion. The peak latency of several seconds represents a major limiting factor in the temporal resolution of functional imaging methods.

## Preoperative mapping of sensorimotor cortex

A large number of fMRI studies have demonstrated primary sensorimotor cortex activation along the central sulcus during movement, including demonstration of the somatotopic organization of this region [5 - 7]. Movement not only engages motor cortex but also provides tactile and proprioceptive sensory input, so activation is not confined to the motor cortex (anterior bank of the central sulcus) but rather involves primary motor and sensory areas [8]. Finger movements are used most commonly, since face or proximal limb movements increase the likelihood of unacceptable movement artifacts. The magnitude of activation in primary motor cortex is directly dependent on the rate of finger movement [9]. Complex, sequential movements of individual digits produce additional activation in associated regions such as premotor cortex, supplementary motor area, and postcentral sulcus bilaterally [10].

The clinical utility of such maps is in functional localization prior to surgery in this region for tumor or seizure focus resection. When the lesion is in close proximity to primary sensorimotor cortex along the central sulcus, precise localization of the activated region relative to the lesion could potentially help predict whether a sensorimotor deficit is likely to occur from lesion resection. It might also be possible to minimize any resulting deficit by purposefully sparing activated and immediately surrounding regions, although no quantitative studies have verified the effectiveness of such an approach. fMRI information is perhaps particularly useful when anatomic structures are distorted by mass effects or dysplastic lesions making it difficult to ascertain the location of the central sulcus with certainty (**Figure 1**). Motor cortex localization with fMRI has generally been highly concordant with intraopera-

tive electrocortical stimulation mapping [11, 12].

widely used language paradigms compared to listening, repeating, reading. Subjects are given a beginning letter, a semantic category, or a word, and must retrieve a phonologically or semantically associated word. This

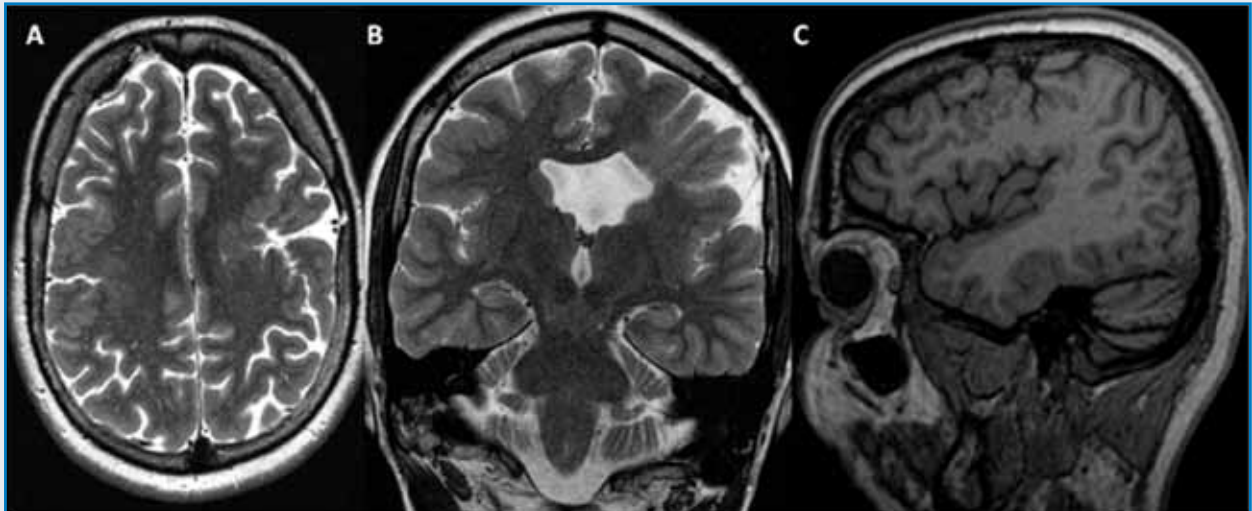


Figure 1a: Mapping motor function in a patient with epilepsy and bilateral pericentral polymicrogyria.

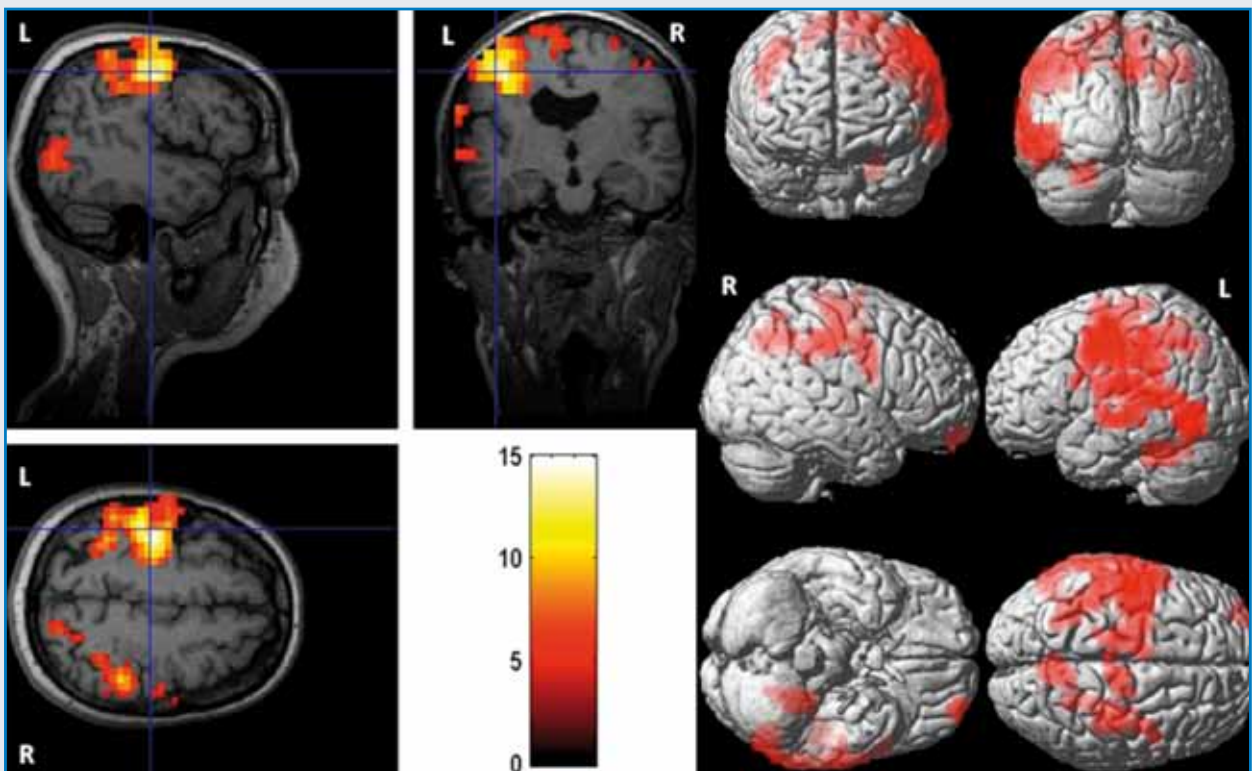
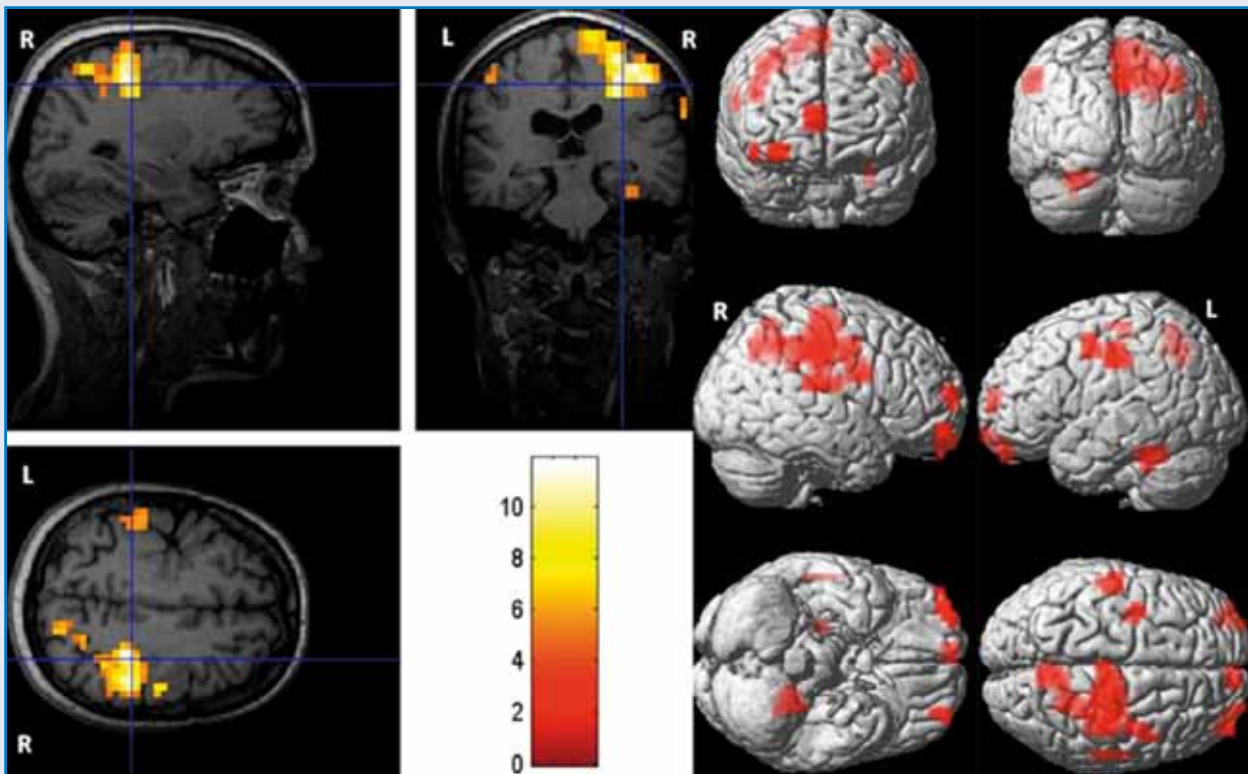


Figure 1b: Bilateral pericentral polymicrogyria: A – axial T2-weighted; B – coronal T2-weighted and C – sagittal T1-weighted images show bilateral polymicrogyria in pericentral area with schizencephalic cleft.

### Preoperative mapping of language systems

The aim of localizing language functions preoperatively is to minimize postoperative language deficits that can result from epilepsy surgery [13]. ‘Word generation’ tasks (also called fluency tasks) that require word retrieval in response to a verbal cue are most

task strongly activates the dominant inferior and dorsolateral frontal lobe, including prefrontal and premotor areas. Posterior language areas such as middle and inferior temporal gyri, fusiform gyrus, and angular gyrus are only weakly activated by the word generation task compared to a resting state or a word reading control [14 - 16].



**Figure 1c:** Finger-to-thumb opposition task performed on the right; BOLD signal is registered bilaterally in primary motor cortex (left > right). R – right, L – left.

fMRI studies comparing language lateralization in right-handed normal adults with epilepsy patients, observed that patients with epilepsy had a higher incidence of atypical (symmetric or right-lateralized) language dominance, which was particularly true for patients with left sided seizure foci [17, 18] (Figure 2). In one study there was a clear relationship between lateralization index and age of onset of seizures, with language tending to shift more toward the right hemisphere with earlier onset [19]. These observations are in agreement with Wada studies showing effects of side of seizure focus and age at onset on language lateralization [20].

### Wada test comparisons

There is a certain level of agreement between fMRI and Wada tests on measures of language lateralization [21 - 23]. fMRI offers a valid alternative to invasive Wada test for establishing language dominance, and it is likely that it will also replace the Wada test for assessing presurgical memory function in the nearer future. Some results are, however, conflicting due to differences in paradigms and analysis procedure [24]. Most of the studies, however, involved relatively small sample sizes (7-20 patients) and relatively few crossed-dominant individuals. The recent study on 60 patients with temporal lobe epilepsy aimed to determine whether preoperative language mapping using fMRI is

useful for predicting which patients are likely to experience verbal memory decline after left-sided anterior temporal lobe resection [14]. Preoperative language mapping with fMRI was compared with preoperative Wada testing for language and memory lateralization. Verbal memory decline occurred in over 30% of patients. Good preoperative performance, late age at onset of epilepsy, left dominance on fMRI, and left dominance on the Wada test were each predictive of memory decline. Preoperative performance and age at onset together accounted for roughly 50% of the variance in memory outcome ( $p < 0.001$ ), and fMRI explained an additional 10% of this variance ( $p \leq 0.003$ ). Neither Wada memory asymmetry nor Wada language asymmetry added additional predictive power beyond these noninvasive measures. It was suggested that preoperative fMRI is useful for identifying patients at high risk for verbal memory decline prior to left-sided anterior temporal lobe resection. Lateralization of language is correlated with lateralization of verbal memory, whereas Wada memory testing is either insufficiently reliable or insufficiently material-specific to accurately localize verbal memory processes.

### Comparisons with cortical stimulation mapping

A number of studies have compared fMRI motor and language maps with the corresponding maps obtained using cortical stimulation mapping [11, 22, 25]. These

studies are of great potential interest because they permit a test of whether fMRI activation foci represent 'critical' language areas. The assumption underlying the cortical stimulation technique is that the temporary deactivation induced by electrical interference will identify any such critical areas. The reports comparing fMRI and cortical stimulation have encouraging results, although they involved relatively small samples (<15 patients). Methods for comparing the activation maps have tended to be qualitative and subjective rather than quantitative and objective, with a few exceptions [26, 22].

across subjects. Several factors make these comparisons particularly difficult to carry out. One problem is in matching the task characteristics across the two modalities. fMRI studies usually employ controls for non-linguistic aspects of task performance, whereas this is typically not true of stimulation mapping studies. For example, stimulation studies often focus on speech arrest, which can result from disruption of motor or attentional systems as well as language systems [28]. A second difficulty is the fact that many fMRI activation foci lay buried in the depths of sulci, which are not available for stimulation mapping. Thus, it is reason-

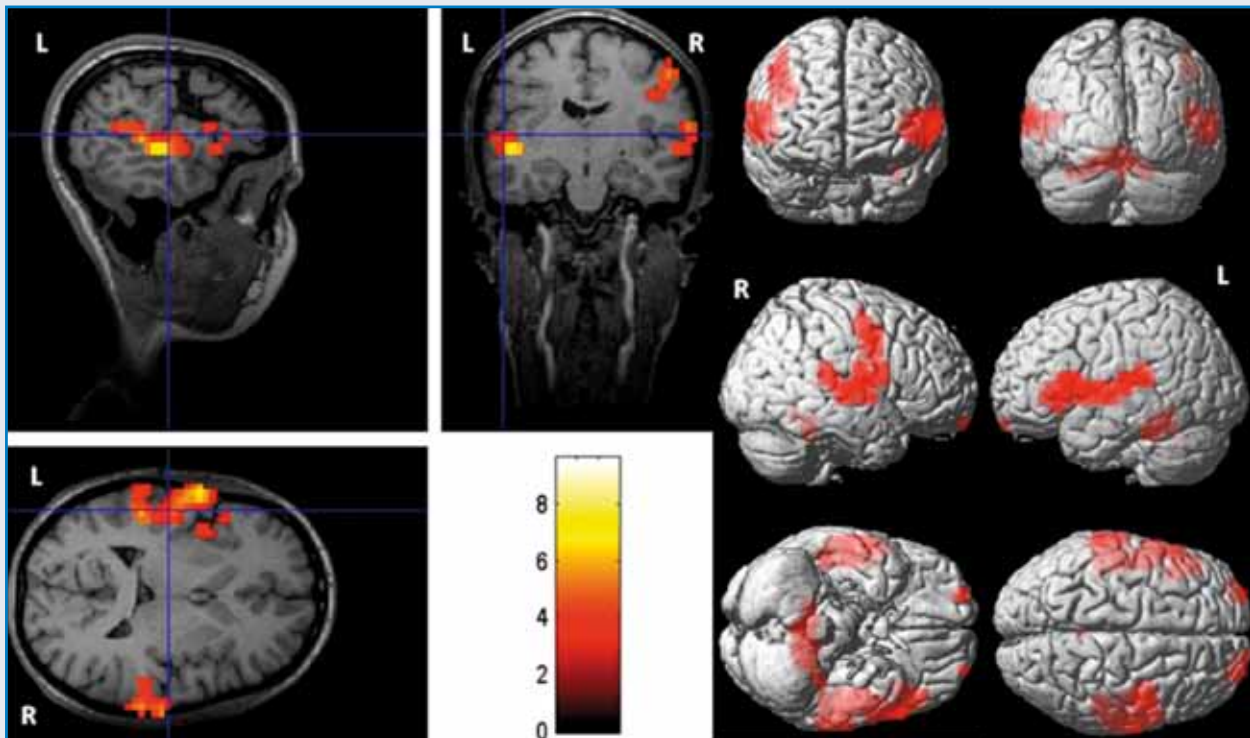


Figure 2: Mapping language in a patient with epilepsy and bilateral pericentral polymicrogyria. Word generation task; BOLD signal is seen bilaterally in Wernicke's area and on the left in Broca's area (predominantly left-sided activation). R – right, L – left.

In 14 patients, poor sensitivity of fMRI was observed for the naming and verb generation tasks (22 and 36%, respectively) in frontal and temporo-parietal areas. The specificity of fMRI was good in all conditions (97% for the naming task and 98% for the verb generation task). Better correlation (sensitivity, 59%; specificity, 97%) was achieved by combining the two fMRI tasks. Variation of the analysis threshold to  $P < 0.05$  increased the sensitivity to 66% while decreasing the specificity to 91%. Postoperative fMRI data (for the cortical brain areas studied intraoperatively) were in accordance with brain mapping results for six of eight patients. Complete agreement between pre- and postoperative fMRI studies and direct brain mapping results was observed for only three of eight patients [27].

Sensitivity and specificity were highly variable

able to expect that many foci of activation observed by fMRI simply will not be tested adequately during cortical stimulation mapping.

### Prediction of language outcome

A more meaningful measure of the validity of fMRI language maps, rather than comparison with Wada test or cortical stimulation mapping, is how well they predict postoperative language deficits. The ability of preoperative fMRI to predict naming decline was assessed in 24 consecutive patients undergoing left anterior temporal lobectomy (ATL) [29]. fMRI employed a semantic decision versus sensory discrimination protocol. All left ATL patients also underwent Wada testing

and intraoperative cortical stimulation mapping, and surgeries were performed blind to the fMRI data. Compared to a control group of 32 right ATL patients, the left ATL group declined postoperatively on the 60-item Boston Naming Test ( $p < 0.001$ ). Within the left ATL group, however, there was considerable variability; with 13 patients (54%) showing significant declines relative to the control group and the remainder showing no decline. Language laterality index based on fMRI activation in a temporal lobe region of interest was strongly correlated with outcome ( $r = -0.64$ ,  $p < 0.001$ ), such that the degree of language lateralization toward the surgical (left) hemisphere was related to poorer naming outcome, whereas language lateralization toward the nonsurgical (right) hemisphere was associated with less or no decline. The fMRI temporal lobe language laterality index showed 100% sensitivity, 73% specificity, and a positive predictive value of 81% for predicting significant decline. By comparison, the Wada language laterality index showed a somewhat weaker correlation with decline ( $r = -0.50$ ,  $p < 0.05$ ), 92% sensitivity, 43%

### The role of fMRI in planning epilepsy surgery

Although fMRI results increasingly influence diagnostic and therapeutic decision making in epilepsy surgery [30], it remains to be established how useful fMRI language activation maps will be for more precise planning of surgical resections. There are though some significant problems:

- inconsistencies in language maps produced by different activation protocols
- the failure to date to find an activation protocol that reliably activates the anterior temporal lobe, where the majority of epilepsy surgeries are performed
- an inadequate understanding of the specificity of fMRI activations. Thus, those who would use fMRI activation maps to decide which brain regions can be resected in an individual patient run two risks:
- resection of critical language zones that are 'not activated' because of insensitivity of the particular language activation protocol employed, resulting in

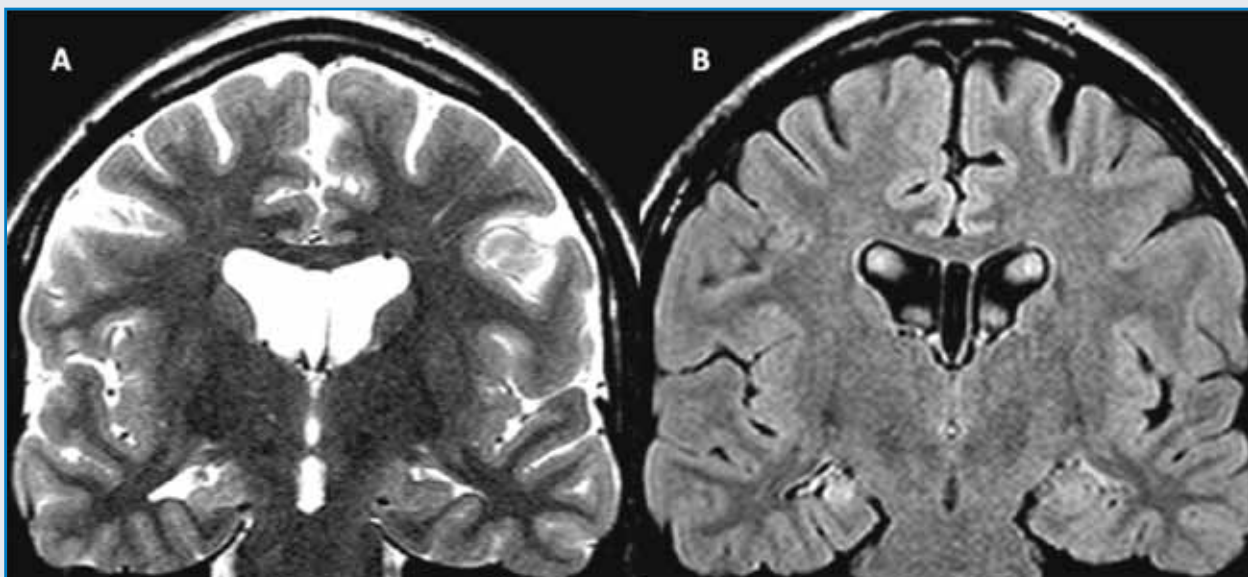


Figure 3: Mapping spatial memory in a patient with hippocampus sclerosis and epilepsy. Figure 3a: A – coronal T2-weighted and B – coronal FLAIR sequences showing sclerotic hippocampus on the right. R – right, L – left.

specificity and a positive predictive value of 61%. These results suggest that preoperative fMRI could be used to stratify patients in terms of risk for language decline. It is crucial to note, however, that these results hold only for the particular methods used in the study and may not generalize to other fMRI protocols, analysis methods, patient populations, or surgical procedures.

- postoperative language decline
- sparing of 'activated' regions that are actually not critical for language, resulting in suboptimal seizure control.

### Preoperative mapping of medial temporal lobe memory systems

While the Wada test has been the gold standard for preoperative lateralization of language and memory function, it is invasive and provides only a limited period of time for testing. Other problems associated

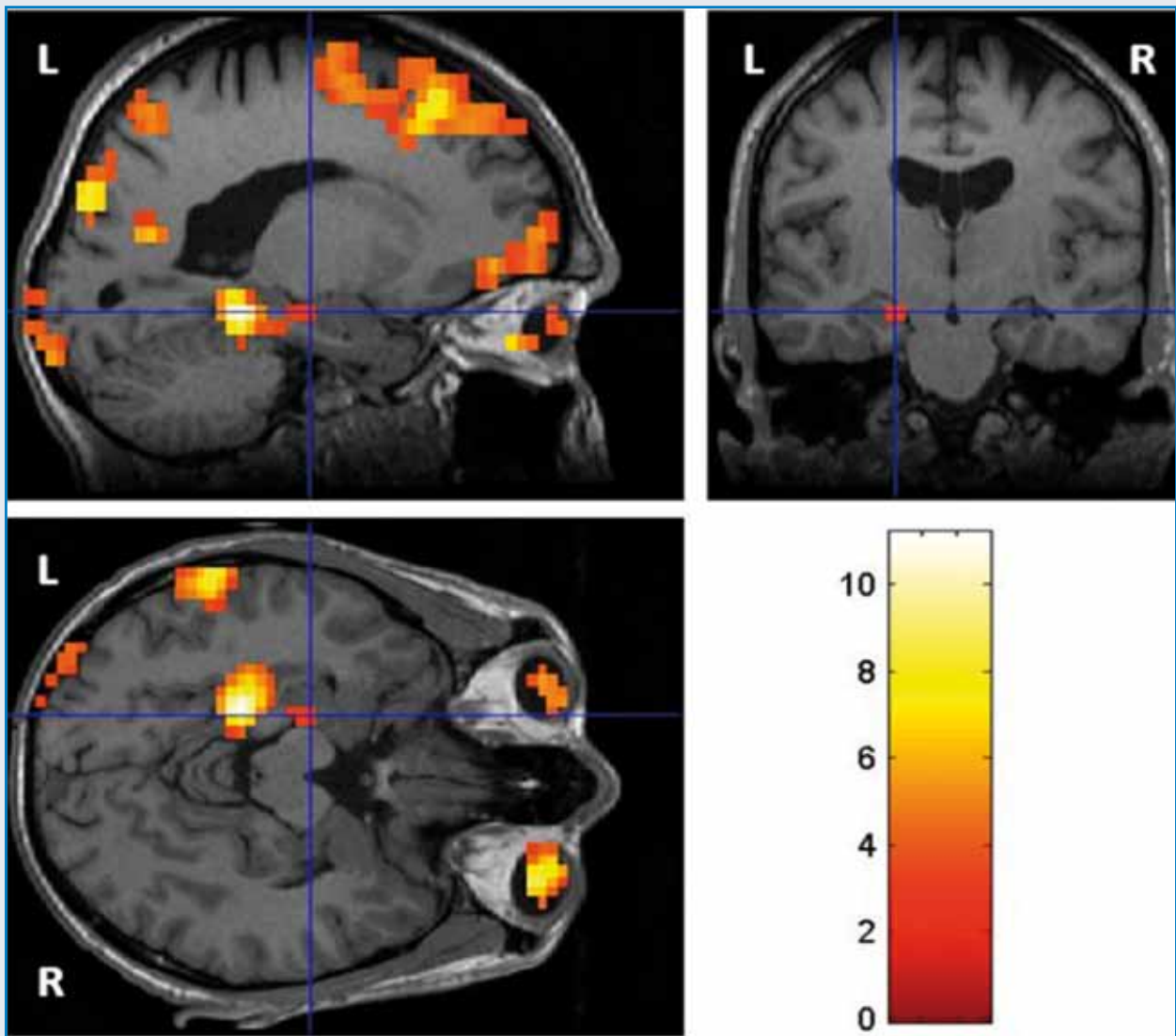


Figure 3b: Roland's hometown walking task. BOLD signal in left hippocampal-parahippocampal area. Healthy controls have fMRI signal in both hippocampal-parahippocampal regions.

with Wada testing include known injection-side order effects [31], variable cross-flow of amobarbital to the contralateral hemisphere, and the fact that the hippocampus is not actually supplied by the anterior circulation and is therefore deafferented rather than directly anesthetized during Wada testing. For these reasons, presurgical mapping of memory function in TLE is an obvious application for clinical fMRI. However, the hippocampus has been notoriously difficult to activate reliably. This may be at least partly attributable to difficulties in disengaging memory function for a control condition, as well as identifying a good active task. The hippocampus is also in a region of comparatively high static susceptibility, resulting in decreased sensitivity for BOLD fMRI. Episodic memory is typically engaged during fMRI by explicit or incidental encoding tasks, with subsequent recognition testing to verify encoding success [32].

Semantic language paradigm have shown activa-

tion in medial temporal lobe as well as a network of inferior prefrontal, lateral temporal, cingulate and cerebellar areas [33, 34]. In the majority of patients with mesial TLE hippocampal activation was also demonstrated. There was a significant difference in hippocampal activation between patients with left and right mesial TLE. Right TLE patients showed increased activity in the left hippocampal formation compared with left TLE patients. In contrast, patients with left TLE did not show increased activity in the right hippocampal formation compared with right TLE patients [35] (Figure 3). Some studies also compared fMRI memory lateralization with that obtained by Wada testing, demonstrating that memory lateralization by these two modalities agreed to a large extent [36, 32]. However, because fMRI examines endogenous function while the Wada test is fundamentally a lesion study, it is also reasonable to expect that these modalities may differ, and that the findings obtained with each modality may be complementary

rather than entirely duplicative [37]. Reductions in fMRI memory activation also appear to correctly lateralize seizure foci in the majority of cases, and some results also suggest that postsurgical amnesia correlates with fMRI activation ipsilateral to the resection [14, 38].

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### Summary

Patients with epilepsy may suffer from communication problems and interpersonal difficulties that have a significant bearing on their quality of life. Imaging and lesion studies have identified cerebral networks associated with social cognitive functions which are frequently affected in patients with temporal or frontal lobe epilepsies. Accordingly, recent studies have demonstrated impairments in social cognition in these patient groups using specific tasks involving emotional recognition and theory of mind (ToM). Within social cognition one can differentiate between more advanced social cognitive abilities, which require the understanding of complex mental conditions, and more basal processes such as the perception and expression of emotional information. The perception and expression of emotional information and ToM abilities have been investigated in numerous studies in a variety of patient groups and healthy persons using a number of experimental paradigms and tests. This paper broadly covers the most commonly used or representative tests of social cognition. Short descriptions and behavioural data from a variety of tests are presented in order to reveal their differences and to highlight recent developments and research perspectives.

Temporal lobe epilepsies (TLE) are often associated with behavioural disturbances such as psycho-social maladjustments and psychiatric co-morbidities including depression and social anxiety. However, since anxiety and distress related to epileptic seizures and their consequences, stigmatisation and discrimination as well as a lack of social support can be seen as causative variables in the development of psychiatric afflictions, it remains unclear to what extent psychosocial difficulties are caused by these factors and to what extent they are related to deficits in social cognitive functions and, accordingly, to lesions in structures associated with social cognition. The fact that psychosocial difficulties and psychiatric symptoms appear more often in mesial TLE compared to other chronic epilepsy syndromes supports the assumption of an association between mesial TLE and impairments in social cognition and offers an indication of a possible specific pathology associated with this epilepsy syndrome.

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Key words: Social cognition, temporal lobe epilepsy, theory of mind, emotion

### Zur klinischen Diagnostik von Defiziten der sozialen Kognition bei Patienten mit Epilepsie

Patienten mit Epilepsie leiden häufiger an interpersonellen Problemen und kommunikativen Schwierigkeiten als Patienten mit anderen chronischen Erkrankungen. Heute können wir davon ausgehen, dass zumindest bei Patienten mit fokalen Epilepsien frontalen und temporalen Ursprungs Strukturen in ihrer funktionellen Integrität beeinträchtigt sind, die für die soziale Kognition eine grosse Bedeutung haben. Der Funktionsbereich der sozialen Kognition umfasst komplexe Fähigkeiten der interpersonellen Zuschreibung mentaler Zustände wie auch basalere Prozesse der Emotionserkennung. Der Artikel stellt von den Autoren favorisierte neuropsychologische Testverfahren zur Diagnostik sozialer Fähigkeiten vor. Im zweiten Teil werden spezifische Ergebnisse aus Studien zur sozialen Kognition bei Patienten mit Temporallappenepilepsien präsentiert, die eine erhöhte Vulnerabilität dieses Funktionsbereiches belegen.

**Schlüsselwörter:** Soziale Kognition, Temporallappenepilepsie, mentale Zustände, Emotion

### Du diagnostic clinique de la cognition sociale chez les patients atteints d'épilepsie

Les patients atteints d'épilepsie souffrent plus souvent de difficultés d'interaction et de communication que les patients avec d'autres maladies chroniques. Aujourd'hui, nous pouvons partir du principe qu'en tout cas les patients avec des épilepsies focales d'origine frontale et temporale sont atteints dans l'intégrité de fonctionnalités qui sont d'une grande importance pour la cognition sociale. Le domaine fonctionnel de la cognition sociale englobe des facultés complexes d'attribution interpersonnelle d'états mentaux, ainsi que des processus plus basiques d'identification d'émotions. L'article présente des procédures de tests

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neuropsychologiques favorisés par les auteurs pour le diagnostic de facultés sociales. Dans la deuxième partie sont présentés les résultats spécifiques d'études de la cognition sociale sur des patients avec des épilepsies temporales qui corroborent une plus grande vulnérabilité de cette aire fonctionnelle.

**Mots clés :** Cognition sociale, épilepsie du lobe temporal, états mentaux, émotion

## Introduction

Social neuroscience is an emerging interdisciplinary field aimed at investigating the fundamentals of human social and emotional behaviour, the quintessence of which is the relationship between the brain and social interaction. Studies on the impact of neurological, psychiatric, and psychological conditions on human social behaviour contribute to our understanding of the complexity of social interactions and highlight important social and affective symptoms in brain disorders such as epilepsies which continue to be overlooked in clinical practice.

In patients with epilepsy non-social cognitive functions including memory, language and executive functions have been studied for many years, whereas social cognitive abilities have received little attention [1]. This is quite astonishing in light of what we know about the remarkable overlap between structures associated with social cognition and anterior brain structures which are frequently affected in patients with epilepsy. The paucity of research becomes more understandable when one considers the lack of readily apparent social deficits in the majority of patients with epilepsies [2].

Nevertheless, comprehensive clinical studies have revealed that psychosocial maladjustment is a serious problem in many patients with chronic epilepsies [3]. To what extent these maladjustments are caused by social burdens, stigma, and risk factors of active epilepsy, and to what extent they are due to dysfunctional social cognition, remains an open question [4, 5]. However, the fact that psychosocial maladjustment and psychiatric comorbidity are more frequent in certain focal epilepsies compared with other epilepsy syndromes may reflect a specific pathological association [6].

In the past, psychiatry and neurology have used different terms and concepts and differed in their diagnostic approaches, research and treatment methods. Their focus converges to some degree within the framework of the modern neurosciences. As such, social and affective neuroscience provides insight into behavioural disorders in patients with epilepsy via new unifying concepts that can be investigated by means of behavioural tests, structural and functional imaging as well as by neuropsychopharmacological interventions. These opportunities allow us to advance our understanding of brain diseases, how they affect behaviour and raise the

hope of new and more efficient therapeutic interventions.

## Social cognition

Many patients with epilepsy suffer from communication problems and interpersonal difficulties that have a significant bearing on their quality of life. Imaging and lesion studies have identified cerebral networks associated with social cognitive functions which are frequently affected in patients with temporal or frontal lobe epilepsies. Accordingly, recent studies have demonstrated impairments in social cognition in these patient groups using specific tasks involving emotional recognition and theory of mind [7-11].

Social cognition is a complex and extensive concept that comprises a wide spectrum of sub-processes at different levels of brain functioning [12]. It includes the perception, encoding, organising and accessing of a variety of relevant social information.

Social cognition is based upon the exchange of signals, whereby the processing of these signals can take place at the automatic and controlled level and is influenced by motivational aspects [13]. It is noteworthy that these processes rapidly act in different modalities in parallel and draw on implicit as well as explicit memories. Therefore, it is reasonable to assume that lesions in one or more widely distributed independent components may lead to greater or less severe impairments in social cognition.

Adequate social interactions are a prerequisite for normal human development from an anthropogenetical as well as ontogenetical point of view. Social cognition encompasses any cognitive process that involves conspecifics, either as a group or an individual. It encompasses the ability to build representations about others, oneself, and the relationships between oneself and others, and to apply them flexibly to execute social behaviour [13]. Therefore, the success of social interactions depends upon the ability to understand the cognitive and emotional processes of others [14].

## Basal social-cognitive processes

Within social cognition one can differentiate between more advanced social cognitive abilities, which require the understanding of complex mental conditions, and more basal processes such as the perception and expression of emotional information.

Processing of emotional information plays an important role in many aspects of cognition [15], including decision-making [16], memory, and attention [17]. Furthermore, understanding other people requires relevant information from different modalities which may provide social information about others including speech, facial expression, prosody, lexical information, gaze

direction, gestures and posture. Besides the predominant meaning gleaned from visual information, olfactory, auditory and tactile sensations can also influence processing of social signals [12]. However, the majority of studies have explored the processing of facial expressions because of longstanding research traditions and well established test materials [18].

Brain damaged patients who exhibit impaired emotional processing, but who are otherwise neuropsychologically intact, show marked deficits in social behaviour and in their interpersonal relationships [16]. Emotional agnosia, also called expressive or social emotional agnosia, can be seen as an emotion perception deficit and refers to a form of agnosia in which individuals are unable to perceive facial expressions, body language and intonation, thus making it impossible for them non-verbally to perceive people's emotions and limiting their social interactions. Social-emotional agnosias are commonly observed following amygdala and right cerebral lesions, particularly those involving the temporal lobe [19].

Although not a form of agnosia in the narrow sense of the word, alexithymia may be difficult to distinguish from, or even co-occur with, emotional agnosia. Whereas emotional agnosia refers to the inability to recognize affect in others (oriented towards others), alexithymia refers to the inability to recognize affect in oneself (oriented towards oneself). Peter Sifneos introduced the term to describe people who appeared to have impairments in understanding, processing, or describing their own emotions [20].

Despite the importance of emotional expression and processing of emotional information, there are only a few measures available to assess these functions, most of which are not standardised [21] or cross-culturally validated.

More detailed information about measures of basal social cognitive functions is provided in the following sections covering methodological issues and imaging.

## Theory of mind (ToM)

Humans are by far the most talented species in reading the minds of others. This implies that we constantly make assumptions about the intentions and beliefs of others which form the framework of our complex interpretations of human behaviour in daily life. These mentalistic interpretations often seem trivial to us to the point that we fail to perceive them as meaningful, not to mention consider them part of an intuitive psychological theory. Nevertheless they represent a fundamental aspect of social cognition which has been coined theory of mind (ToM) [22]. ToM is thought to be the proximate mechanism enabling humans to find their way in complex, collaborative social networks.

The terms empathy, social intelligence, and perspective taking are, along with ToM, related abilities and concepts and were often used as equivalents in the

literature as well as in everyday speech. Therefore, social cognition is not equivalent to ToM since there are a number of cognitive abilities which fall within the realm of social cognition which do not involve ToM operations in the narrow sense of the word, e.g. social reasoning and decision making, the recall of knowledge regarding social schemata and moral judgment [23].

According to numerous findings, ToM is considered a specific cognitive domain that needs to be delineated from general intelligence and from executive functions. There are many studies in which social cognition has been shown to be dissociable from general intelligence. For example, Baron-Cohen and Jolliffe [24] showed that very high functioning adults (HFA) with autism or Asperger's syndrome (AS), despite being of normal or above average IQ, were nevertheless impaired on a subtle theory of mind test. A further example of this dissociation is seen in Down's syndrome where intellectual function is impaired, but individuals perform well on theory of mind tasks [25].

In another study, Baron-Cohen et al. [26] used a revised version of the "Reading the mind in the eyes Test" (Eyes Test) and administered this test to a group of adults with AS or HFA. Again, there was no significant correlation between IQ and the performance in the Eyes Test, confirming that this is independent of general (non-social) intelligence. Using the "Mind in the Voice" Task, which extends the aforementioned test into the auditory domain, Rutherford et al. [27] found that individuals with AS/HFA have difficulty extracting mental state information from vocalizations. Here, too, no significant correlation was found between verbal IQ and performance on the voice task for either the AS/HFA group or the noncollege control group.

Apart from theory of mind, memory, attention, executive functions (including planning of action), motivation and decision making equally contribute to the cognitive and behavioural outputs in social interactions. ToM should be considered a complex neuropsychological function that can be selectively disturbed, but which is correlated with distinct cognitive abilities, in particular executive functions [28].

The first precursors of ToM, including the imitation of intended actions [29] and the distinction between one's own and others' desires and their relation to emotions [30] can be observed already at the age of eighteen months. Also, the beginning of the pretend play [31], joint attention skills and the development of the ability to attribute wishes and emotions to others [32] can be considered as an important milestone in the development of a ToM.

By the age of about three to four years children gain the cognitive prerequisite for the comprehension of another person's belief (e.g. that he or she has a false assumption about a certain fact) and thereby the ability to represent mental conditions independent of reality and to derive action predictions from attributions of mental states. This ability requires a conceptual understanding

of the mental conditions of another human being [33].

The comprehension of false beliefs in children can be investigated with the help of so-called „first-order false belief tests“, the most prominent of which include the „Sally-Anne Task“ [34], the „Maxi-Task“ [35] and the “Smarties-Task” [36]. The development of an understanding that someone can have a false belief about a false belief begins a bit later towards the age of 6 years [37], while the understanding of different perspectives appears between the ages of 12 and 17 [38].

The ability to attribute second-order or embedded mental states (e.g., he thinks that she thinks) is a very socially relevant achievement in the development of a theory of mind. Being able to represent what one person thinks about what a second person thinks allows us to understand not only another’s belief about the world (a first-order belief) but also to understand that person’s concern about yet another person’s belief about the world (a second-order belief). This sort of reasoning is necessary for any sophisticated understanding of the subtleties inherent in social interactions. Perner [39] argued that it is at the level of second-order reasoning that social interaction can be understood as an interaction of minds where people are concerned about each other’s mental states. Typical second-order false belief tasks are the Ice-Cream Van Task [37] or the second-order Sally-Anne Task [34].

Tests which go above and beyond simple attribution performances are also called „higher-order“ or „advanced“ ToM tests and require the understanding of complex mental states (what does X think or feel?) or also the comprehension of mental states in role-taking activities (e.g. does X also really mean what X says? Why does X behave thus?). The inferences one makes regarding others’ mental states include knowledge regarding their thoughts and beliefs (“cognitive ToM component”) as well as knowledge and empathic understanding of their emotional states and feelings (“affective ToM component”).

## Methodological issues

### Testing social cognition

The perception and expression of emotional information and ToM abilities have been investigated in numerous studies in a variety of patient groups and healthy persons using a number of experimental paradigms and tests. The following list of selected tests is not intended to be exhaustive, but broadly to cover the most commonly used or representative tests. Short descriptions and behavioural data from a variety of tests are presented below in order to reveal their differences and to highlight recent developments and research perspectives.

## Selected tests of basal processes of social cognition

### *Ekman faces*

#### *Test description.*

Influenced by the work of the psychologist Sullivan Tompkins, Ekman was the first to apply quantitative methods in an effort to clarify the question of the biological basis of emotional facial expression. He showed that facial expressions of emotions are not culturally determined, but universal across human cultures and, thus, biological in origin. Expressions he found to be universal included anger, disgust, fear, joy, sadness and surprise. Ekman and Friesen [18] developed the Facial Action Coding System (FACS) to taxonomise every conceivable human facial expression. The FACS has since become the most widely used and validated series of photographs in facial expression research. These photographic representations have been applied in a variety of tests requiring identification, matching, sorting or rating of facial expression of emotions.

#### *Behavioural data.*

While initially the question of lateralisation of emotional facial expression perception was pursued [40], the amygdala has increasingly attracted attention with advances in imaging technology. Primarily it was assumed that the perception of fearful expressions depended on the structural and functional integrity of both amygdalae [41]. However, subsequent studies have shown that not only facial expressions of fear, but also the perception of other emotions, are affected after bilateral amygdalar lesions [42, 43] and that unilateral lesions can also result in deficits [44, 45]. Disturbances in the perception of emotions from facial expressions have also been reported in patients with Traumatic Brain Injury (TBI) [46], in frontotemporal dementia [47] as well as in patients with frontal and temporal lobe epilepsy [7, 9, 48, 49].

### *Comprehensive Affect Testing System (CATS)*

#### *Test description.*

Most studies on social cognition have used visual stimuli, but it is clear that real-life social interactions necessarily draw on additional modalities. Audition provides important social signals in addition to language. Accordingly, the intonation of speech – prosody – can signal various emotions, and is recognised using some

of the same structures that we use for recognising facial expressions [50]. Froming et al. [51] took this issue into account and developed a computerised measurement of visual and auditory emotional processing of the six basic emotions (Comprehensive Affect Testing System, CATS). The CATS consists of thirteen subtests assessing facial identification, emotion matching with and without verbal denotation, emotional tone or prosodic processing with and without verbal denotation, and with conflicting or congruent semantic content.

#### *Behavioural data.*

The CATS has been administered to patients with Asperger's syndrome (AS) and comparisons between these patients and healthy controls on CATS subtest results revealed general impairments in the comprehension of facial and prosodic information in the AS group [51]. Recently, Rocca et al. [52] applied the CATS to a group of patients with schizophrenia and healthy controls and found that controls performed better on all subtests, the only exception being an affect discrimination task. Data collection is in progress with different groups of patients with brain damage.

### **Selected tests of theory of mind**

Various experimental paradigms exist for evaluating ToM-skills. However a truly theoretically based differentiation of relevant aspects and dimensions of the ToM-construct and its test psychological considerations remain absent.

According to the conceptual classification of a "cognitive" and an "affective" ToM component (with overlaps with empathy), some tests require the attribution of epistemic mental conditions such as knowledge, attention or beliefs while other tests investigate the attribution of affective mental conditions e.g. "feel happy" or "want something" [53]. According to Shamhay-Tsoory and Aharon-Peretz [54], performance on second-order false belief tasks requires cognitive components of ToM while "higher-order" or "advanced ToM tests" such as the faux-pas test [55] require both components. The attribution of intention assumes the recognition of whether an action was executed intentionally or accidentally and can be considered as a further type of attribution, although its inclusion under the attribution of epistemic mental conditions seems to be reasonable as well.

Apart from the classification of ToM tests according to their type of attribution, they also differ with regard to the stimulus modality they employ. While some contain verbal material such as stories and subsequently demand adequate language comprehension, complex visual stimuli are applied in other tests (dynamic and non-dynamic); rarely have verbal and visual material

been combined.

### ***Moving Triangles***

#### *Test description.*

Heider and Simmel [56] conducted an experimental study over 65 years ago that can be seen as the starting point of attribution theory research. In their experiment healthy subjects were asked to interpret a short film sequence (2.5 min) in which three geometric shapes (a big and a small triangle and a circle) move around at different speeds. Another shape in the field is a rectangle which also acts as door that can be opened and closed. All in all, Heider and Simmel's [56] study contained three experiments. In the first experiment subjects freely described what they saw after watching film sequences twice. In a second experiment, subjects were asked to interpret the movements of the figures as human actions and to answer structured interview questions after presentation of the film. In the third experiment the video was shown in reverse and subjects took part in a short, structured interview. The authors observed that people attributed intentions and desires to moving geometric shapes if these actions are of adequate complexity.

#### *Behavioural data.*

Klin [57] developed the Social Attribution Task (SAT), a new cognitive procedure based on Heider and Simmel's cartoon animation and applied it to a group of individuals with autism, with Asperger's syndrome (AS), and normally developing adolescents and adults. The SAT is adapted for presentation to developmentally disabled individuals by minimising factors thought to promote ToM task performance but that are absent in real-life social situations. Furthermore, it includes a coding system to examine and quantify different aspects of the subject's social cognitive responses. Both clinical groups showed significant deficits in making social attributions.

Based on the classic Heider and Simmel [56] paradigm, Abell et al. [58] aimed to design novel stimuli whose properties of motion would evoke mental state attributions. Protagonists of the new test were two shapes (a big red and a small blue triangle) moving around the screen, which on most trials contained an enclosure. Mental state attributions were restricted to pure movement and interaction in the absence of vocal or facial expression. In their study they presented three different types of animation sequences: random movement in which no interaction occurs (e.g. bouncing), goal-directed (G-D) interactions that elicit attributions of simple actions (e.g. fighting) and ToM interactions

that elicit attributions of mental states to the agents (e.g. tricking). The G-D and ToM condition consisted of four animations each, while the random condition had two animations. The computerised animations were presented to high-functioning children with autism, children with general intellectual impairment, normally developing 8-year olds and adults. The authors found that high-functioning children with autism frequently used inappropriate descriptions when characterising the ToM animations. Castelli et al. [59] used twelve silent animations, four of each of the three types of animations, and here as well the autism group gave fewer and less accurate descriptions of the ToM animations.

Finally, Heberlein and Adolphs [60] used a video of the original Heider and Simmel [56] film in a single case study and found that a patient who acquired bilateral focal damage during childhood failed to attribute social intent to the moving geometrical objects in the normative manner.

### **Cartoon task**

#### *Test description.*

Recent research in social cognitive neuroscience has begun to define subcomponents of ToM. One important differentiation is that of “affective” versus “cognitive” ToM, although different terms have been used to describe these and related concepts [61]. This differentiation was taken into account in the “Yoni” paradigm, which was introduced by Shamay-Tsoory et al. [62] and is based on a task previously described by Baron-Cohen and Goodhart [63]. It is a computer-controlled test for the assessment of cognitive and affective ToM-performances. In this test the mental state of the main character has to be inferred from the situational context on the basis of verbal cues, eye gaze and facial expression. There are three main conditions: cognitive, affective and physical, each requiring either a 1st or 2nd order inference. The cognitive and affective conditions require mental inferences, while the physical condition serves as a control condition and requires a choice based on the physical attributes of the character. In each of the 64 trials a face named Yoni is shown in the middle of a computer screen with four coloured pictures in each corner that either belong to a semantic category (e.g. animals, fruits) or show faces. In the upper range of the screen an incomplete sentence about what Yoni is referring to is presented and subjects are required to decide as quickly as possible which of the four stimuli in the corners best completes the sentence.

#### *Behavioural data.*

Using the Yoni-paradigm Shamay-Tsoory and colleagues [62] were recently able to demonstrate selective deficits in affective as opposed to cognitive ToM in various patients groups. In Shamay-Tsoory, Aharon-Peretz and Levkovitz’s [64] study the performance of patients with schizophrenia was compared to that of patients with localised lesions in the ventromedial (VM) or dorsolateral prefrontal cortex (PFC), patients with non-frontal lesions, and healthy controls. The authors found that patients with schizophrenia and those with VM lesions were impaired on affective ToM tasks, but showed no difficulties in the cognitive ToM conditions. Support for a selective impairment in schizophrenia for the ability to attribute affective mental states comes from another study in which patients with schizophrenia made significantly more errors in the affective conditions as compared to healthy controls [62]. A modified version of the Yoni-paradigm which included additions to the ToM task of gloating, envy and identification trials (“fortune of others” emotion task) was used with patients with AS and HFA [65] as well as in patients with localised, well-defined brain lesions of various aetiologies [66]. The authors showed that, whereas individuals with AS and HFA had no difficulties with first- and second-order ToM tasks, they were impaired in their ability to identify envy and gloating.

In a study with patients with different localised lesions, Shamay-Tsoory and Aharon-Peretz [54] were able to demonstrate that affective and cognitive ToM processing depends in part on distinct anatomical substrates. While the ventromedial prefrontal cortex (VMPFC) seems to have a special role in processing affective ToM, cognitive ToM may involve both the VMPFC and dorsal parts of the prefrontal cortex. Furthermore, recognition of envy and gloating is impaired in patients with ventromedial prefrontal damage [66].

### **Reading the mind in the Eyes Test**

#### *Test description.*

There are only a few tests which examine ToM skills in adults. So-called “higher-order” or “advanced ToM tests” go far beyond simple attributions and can only be used to study adolescents and adults of normal intelligence, e.g. “Reading the mind in the Eyes Test” (Eyes Test) [24, 26]. The subject’s task is to choose which of four words best describes what the person in the picture, that shows only a pair of eyes, is thinking or feeling (e.g. terrified, upset, arrogant, annoyed) [26].

### *Behavioural data.*

The Eyes Test has enjoyed wide use and has demonstrated reduced test performance in patients with psychiatric diagnoses including autism and AS [24, 26, 67] and in patients with schizophrenia [68].

Further, patients with unilateral or bilateral amygdalar lesions [44, 53], with frontotemporal dementia [69] as well as with frontal lobe epilepsy [48] have been found to have impaired performance in the Eyes Test. Farrant et al. [48], however, presume that the discovered deficits in the frontal variant of frontotemporal dementia (fvFTD) and FLE group are in fact caused by the emotional component rather than ToM itself.

All in all, findings from this widely used test show it to be sensitive for detecting specific ToM impairments in populations that have been found to have deficits in other ToM tests.

## **Faux pas Test**

### *Test description.*

The Recognition of Faux pas Test [55, 67] is another ToM test for adults and estimates the ability to recognise and understand a social faux pas. It was designed to evaluate mentalising abilities in individuals with high functioning autism who are able to pass second-order false belief tests. A faux pas is understood as a statement in which the speaker accidentally offends or insults another person. For example, person “A” complains to person “B” about a wedding present without realising that he is talking to the person from whom he received it. The Faux pas Test measures several ToM components by including deductions concerning epistemic mental conditions as well as affective mental conditions [53, 55]. As verbal materials, in the form of rather complex stories, are used in this task, it makes fairly high verbal demands of the individual.

### *Behavioural data.*

Baron-Cohen et al. [67] administered an age-adapted version of the Faux pas Test to a group of younger subjects (mean age = 12 years old) with HFA/AS and found that they had difficulties using mental state knowledge and had difficulties in detecting the faux pas. Unlike the children with HFA/AS in the Baron-Cohen et al. study [67], adults with AS in Zalla et al.’s study [70] and the two adolescents with AS in Shamay-Tsoory et al.’s case-study [71] reported that something awkward or wrong was perpetrated in the faux pas stories; they were generally unable to provide correct justifications in terms of reasons and intentions and failed to attribute emotions to others.

The adult version of this test has also been applied to patients with orbitofrontal and amygdalar lesions [53, 55], TBI [72], patients with mesial temporal lobe epilepsy [10], patients with Parkinson disease [73], patients with fronto-temporal dementia and patients with Alzheimer disease [69]; all of whom had difficulties recognising that a faux pas had been committed.

## **Strange Stories**

### *Test description.*

The Strange Stories Test is concerned with the comprehension of nonliteral statements in hedged expressions, metaphors, irony, sarcasm and bluff [74]. In this test subjects are confronted with a set of stories requiring the attribution of complex mental states. There are two conditions in this test consisting of two sorts of materials: social stories, which have to do with mental states and physical stories which have to do with physical behaviour. There are eight examples of each of these two sorts. Subjects were asked to read these stories and answer a question after each passage.

### *Behavioural data.*

Happé [74] used such a set of stories to test able autistic, mentally handicapped and normal children and adults in their understanding of story characters’ thoughts and feelings. Subjects with autism had difficulties understanding the protagonists’ intentions and made context-inappropriate mental state attributions. By contrast, they had no difficulty understanding the physical events in the stories or understanding stories not involving mental states. These results were replicated in other studies of patients with HFA and AS [24, 75, 76].

Shaw et al. [77] reported deficits in a number of advanced ToM tests, including Happé’s strange stories, in a group of subjects with early damage to the amygdala. These patients made significantly fewer fully accurate mental state attributions compared to a group of patients with late damage to the amygdala and healthy comparison groups.

## **Imaging of social cognition**

Tasks which demand social cognitive abilities appear to activate a consistent set of brain regions. Experiments using imaging techniques have found underlying neural processes in different frontal and temporal localised brain regions [55, 78] including particularly the medial frontal cortex (MFC), inclusive the anterior cingulate cortex (ACC), the superior temporal sulcus (STS) at

the temporal parietal junction (TPJ), the temporal poles (TP) and the amygdala.

#### *Medial frontal cortex (MFC) and anterior cingulate cortex (ACC).*

For a better understanding of its role in social cognition, one can functionally divide the MFC into a posterior rostral region (prMFC, associated with cognitive processes) and an anterior rostral region (arMFC, associated with emotional processes), as well as into an orbital region (oMFC, associated with the monitoring of task outcomes). While the prMFC is thought to be engaged in monitoring the value of possible future actions, the oMFC guides behaviour regarding the evaluation of possible consequences. The arMFC appears to be activated by a wide range of social cognition tasks that involve thinking about the psychological attributes of people regardless of whether the person was the self, another person, or whether judgments pertained to dispositions or mental states [78]. Thus, activations of the arMFC and ACC were found for the perception of oneself as well as one's own mental conditions [79, 80] and for the thinking about the mental states of others [81]. Based on this knowledge and results which have revealed involvement of the ACC in the control of the attention [82], Gallagher and Frith [83] proposed that the activated parts of the ACC could govern the attention allocated to mental conditions. Thus, the ACC could correspond to the „decoupling“ mechanism which was suggested by Leslie [84] and which differentiates hypothetical conditions from reality [85].

#### *Superior temporal sulcus (STS).*

Activation in the area of the STS has consistently and robustly been reported in many studies. It is assumed that the STS represents rather elementary processes involved in a variety of ToM tasks and that the posterior STS is particularly sensitive to biological motion [86]. Overall, the results point to the participation of the STS in the perception of purposeful actions and their attribution as self-caused or other-caused [87, 88].

Temporal parietal junction (TPJ). The TPJ appears to be involved in reasoning about the contents of another person's mind [89]. In particular, it has been proposed that the right TPJ is selectively involved in representing the beliefs of others [90]. However, this remains a controversial issue as this region has also consistently been activated during spatial reorienting of visual attention [91].

#### *Temporal pole (TP).*

The TP may be involved with the retrieval of memory contents, especially autobiographical memories and memories for faces [83]. Accordingly, the studies which presumably made only negligible demands on the memory or imagination of the test participant were unable to find any activation in the temporal pole [81, 92]. Olsen et al. [93] reviewed the literature in both non-human primates and humans and their findings indicated that the TP has some role in both social and emotional processes including face recognition and ToM.

#### *Amygdala.*

The amygdala-complex is considered to have a central role in the perception and processing of socially relevant information [94, 95], emotional learning [96] and memory [97]. The amygdala was shown to react to angry and fearful faces [98], be involved in gaze monitoring [99], and is crucial for the recognition of social emotions. Furthermore, there is converging evidence that amygdala structures and their connecting complex of neural systems are at the core of the ability to interpret the mental states of others [53, 100]. In their current overview of results from different functional imaging studies of the brain basis of ToM skills, Carrington and Bailey [101] found the amygdala to be less consistently activated. However, its influence on social and emotional reactions [102] clearly indicates involvement of the amygdala in certain ToM functions.

#### *Task-related imaging.*

Functional imaging studies on social cognition have used classical ToM tasks (introduced in the preceding section) as well as tasks involving the processing of faces.

Using positron emission tomography (PET) Morris and his colleagues [103] were the first to document a specific activation of the amygdala during the presentation of faces with systematically varied expressions (Ekman Faces). Thus, a modulation of the neural activation took place depending on the valence and intensity of the emotion. The left amygdala registered significantly more neuronal activity looking at fearful faces than looking at happy faces. Whalen and his colleagues [104] were able to confirm this finding. They also noticed a significantly stronger activation looking at fearful faces in comparison to neutral or angry ones. Baron-Cohen et al. [67] was even able to show, using fMRI, that patients with autism and Asperger's Syndrome (AS) did not show amygdala activation in comparison to healthy controls while making mentalistic inferences from the eyes (Eyes Test). These results are in accordance with histopathological studies demonstrating gray matter abnormali-

ties in the amygdala and surrounding temporal areas [105].

Functional imaging has also been used to study the detection of mental state information in Heider and Simmel's [56] animations of moving geometric shapes. Castelli et al. [88], using positron emission tomography, presented an animated sequence in which two triangles interacted with each other. The more strongly the observers attributed mental conditions to the triangles, the stronger the activity in the MPFC, temporal pole and STS. Schultz et al. [106] utilised an analogous task and noticed activations in the same areas when using fMRI. In both of these studies where mentalising was determined by the movements of abstract shapes, the activity in the temporal pole extended into the amygdala and some activity could also be seen in the fusiform gyrus. Each study required explicit mentalising whenever the test persons were asked to characterise the mental states of another person or to make decisions according to the mental states of others. The only exceptions were studies using passive viewing of animations.

To our knowledge there is only one study to date which has linked structural abnormalities to impaired social cognitive abilities using faux pas tasks [107]. Herold et al. [107] used voxel-based morphometry (VBM) to compare data of patients with schizophrenia to healthy individuals and found that the poor faux pas performance of patients with schizophrenia correlated with gray matter reduction in the left OFC and right TP. These results correspond to those recently found in a study by Shamay-Tsoory et al. [108] who revealed that the pattern of ToM deficits in patients with schizophrenia resembled those seen in patients with ventromedial PFC lesions.

A PET study of ToM in autism [109] employed a story comprehension task (Strange Stories), replicating a prior study in normal individuals [110]. The authors found displaced and diminished mPFC activation in subjects with autism. However, due to small sample size (six subjects with autism) and relatively poor spatial resolution of PET imaging, these results should be considered preliminary.

### Social cognition in temporal lobe epilepsy

Mesial temporal lobe epilepsy (MTLE) is the most prevalent focal epilepsy. It is characterized by recurrent seizures which originate from mesial temporal structures, most frequently within the hippocampus. Therefore, hippocampal sclerosis represents the most common pathological substrate in MTLE [111]. Neuropsychological examinations often uncover memory impairments which are usually material-specific to the side of ictal onset [112]. Resective surgery can be highly effective in obtaining seizure freedom in medically intractable patients with MTLE, but bears a significant risk of memory and language impairments. Accord-

ingly, performances on measures of memory, language, and executive functions have been studied extensively pre- and postoperatively in this patient group. But despite knowledge that cerebral networks associated with social cognitive functions are frequently affected in patients suffering from temporal lobe epilepsies, investigations into social cognitive abilities have been scarce [1]. This paucity of research could be due to the lack of readily apparent social deficits in temporal lobe epilepsy patients [2].

At the same time, TLE is often associated with behavioural disturbances such as psycho-social maladjustments and psychiatric co-morbidities including depression and social anxiety [3]. However, since anxiety and distress related to epileptic seizures and their consequences, stigmatisation and discrimination as well as a lack of social support can be seen as causative variables in the development of psychiatric afflictions [4, 5], it remains unclear to what extent psychosocial difficulties are caused by these factors and to what extent they are related to deficits in social cognitive functions and, accordingly, to lesions in structures associated with social cognition. The fact that psychosocial difficulties and psychiatric symptoms appear more often in MTLE compared to other chronic epilepsy syndromes [6] supports the assumption of an association between MTLE and impairments in social cognition and offers an indication of a possible specific pathology associated with this epilepsy syndrome. Of course, there are other epilepsy syndromes, such as frontal lobe [48] or juvenile myoclonic epilepsy [113], which may also be at risk of social cognitive impairments, but these have only rarely been investigated and we therefore focus below on TLE.

Several studies of basal aspects of social cognition suggest that the recognition of basic emotions in facial expressions is frequently impaired in TLE-patients [7-9, 11, 49]. In particular, patients with early seizure onset within the right, non-speech dominant, hemisphere showed pronounced difficulties in the recognition of fearful faces [7, 9]. Also, the early-onset right MTLE-HS patients in Hlobil et al.'s [114] study were impaired in their ability to recognise fear when compared to other MTLE patients and control subjects, indicating that age of damage is an important factor determining this ability.

Moreover, impairments in the recognition of basic emotions with negative valence have also been reported in temporal lobectomy patients with amygdala damage on the basis of facial and vocal expressions [115]. The patients in Shaw et al.'s [49] study who underwent a left anterior temporal lobectomy for medically intractable epilepsy which incorporated the entire amygdala, evaluated fearful facial expressions in a more normative manner. By contrast, in right-sided MTLE patients the operation did not have any effect on the level of impairment.

Apart from impairments in the recognition of basic emotions (considered to be a prerequisite for a ToM),

deficits in emotional memory [116] and in ToM abilities [10] have been associated with MTLE.

Abnormalities in higher-order social cognition were directly attributed to MTLE in a study by Schacher et al. [10]. The authors compared patients with MTLE to patients with epilepsy not originating within the MTL and healthy controls in their ability to detect a social faux pas. They used a shortened version of the Faux pas Test [53], consisting of three short prose passages, and found that MTLE patients performed significantly worse in this test than patients with epilepsy other than MTLE (extra MTLE) and healthy controls. This finding was not accounted for by variables such as age, age at seizure onset, duration of epilepsy, text comprehension or IQ and, thus, corroborate earlier findings that ToM abilities are mainly independent of other cognitive functions [85]. Considering that the epilepsy control group exhibited no impairments in the ToM task, the authors concluded that the observed deficit comprised a specific impairment in focal epilepsies with lesions in the ToM-network.

The question of the role of the amygdala and the affective functions which it mediates is still under debate [77]. The amygdala has been associated with ToM processes in numerous studies [94], whereby it appears to be of particular importance in the attribution of affective mental states [14]. To detect a social faux pas, as required in Schacher et al.'s [10] study, one has to be able to understand the emotional condition of another person. In patients with MTLE, the amygdala are often part of the epileptogenic zone and in about a quarter of patients with hippocampal sclerosis (HS), the ipsilateral amygdala shows volume reduction or even atrophy [117, 118]. Furthermore, neuropathological findings in temporal lobe epilepsy patients point to variable degrees of neuronal cell loss and astrogliosis in the amygdala [119, 120].

Disagreement remains as to what degree the amygdala merely supports the development of ToM abilities [77, 85, 121] or whether it additionally represents an important part of the neural network which underlies ToM processing abilities [53, 122-124]. The majority of authors agree with the latter supposition, which receives support in particular from lesion studies that indicate a clear connection between uni- and bilateral lesions of the amygdala and deficits in ToM [53, 125].

Apart from these behavioural studies, imaging studies have also been conducted that have detected amygdalar dysfunctions. Using an animated fearful face-paradigm in their fMRI study, Schacher et al. [126] showed that ipsilateral amygdala functioning is impaired in the majority of patients with mTLE. In contrast, the paradigm resulted in symmetrical bilateral amygdala activation in healthy volunteers.

Bonelli et al. [127] used a fearful face paradigm to study the role of the amygdala in the processing of emotions in patients with mTLE and to examine whether this may be a potential preoperative predictive marker

for emotional disturbances following surgery. Healthy control subjects looking at photographs of fearful faces demonstrated left lateralised amygdala activation, while right-sided TLE patients showed bilateral amygdala activations. Left-sided TLE-patients, however, had significantly reduced activations of either the left or right amygdala in comparison to the control group and the right-sided TLE-patients. During scanning, subjects in Bonelli et al.'s [127] study were instructed to make judgments of whether photographs of faces were pleasant or unpleasant, a task in which patients with right-sided MTLE were previously shown to have impairments as compared to left-sided MTLE patients and healthy controls [7, 9]. In Bonelli et al.'s [127] study, the left-sided MTLE patients displayed on average bilaterally reduced fMRI amygdala reactivity. Inspections of scatter plots revealed, however, considerable interindividual variability in the asymmetry of amygdalar responses, even in patients with left-sided MTLE.

Structure-function analyses have also shown an association between impairments in the recognition of facial expressions, especially of fear [9], and reduced fMRI activity in patients with early onset right-sided TLE [7]. In addition, an association has been observed between fear recognition deficits and the duration of epilepsy as well as the amount of decrease in amygdalar volume [128, 129].

In sum, the majority of studies suggest that the degree of impairment and which aspects of social cognition are impaired is influenced by amygdalar pathology in addition to mediating factors such as the age at which and side of which a lesion was acquired, age at seizure onset, the expansion of the symptomatogenic zone as well as the functional deficit zone.

## Conclusions

Today, we remain unsure as to whether we should consider deficits in social cognition as defining symptoms of the MTLE syndrome. However, the current state of research convincingly demonstrates that a considerable number of patients with MTLE demonstrate impairments in social cognition. These impairments may have a devastating impact on interpersonal relationships, social functioning and quality of life and may promote the occurrence of the frequently reported comorbid symptoms of depression and anxiety. Yet, aspects of social cognition are not often part of the psychiatric or neuropsychological assessment of patients with epilepsies. We strongly recommend the expansion of cognitive assessment batteries to include tests of social cognition. As acute difficulties in social cognition are not necessarily evident in brief interactions between physician and patient; and these symptoms are often subclinical in nature and, therefore, psychometrically difficult to ascertain, it is important to develop sensitive and standardised instruments to analyse social cognition in different modalities. Identifying deficits in social cognition would allow for the development more specific treatment strategies aimed at improving social-cognitive abilities in terms of training or within the scope of postoperative rehabilitation. As intact social-cognitive skills are of everyday relevance in that they allow for adequate social functioning in interpersonal relationships as well as in wider society, further insights into social cognition in epilepsy patients are required.

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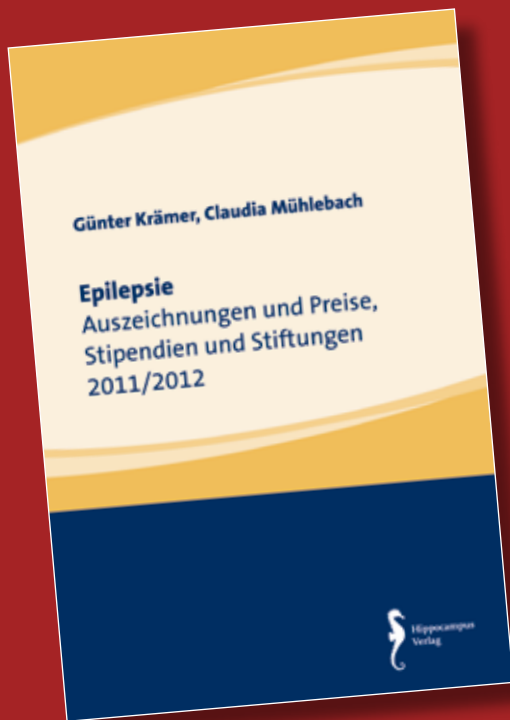


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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DVD „L’ombre du loup   Im Schatten des Wolfes“

### Ich (wir) möchte(n):

- Einzelmitglied der Epilepsie-Liga werden und bezahle mindestens 50 Franken jährlich.
- Kollektivmitglied der Epilepsie-Liga werden und bezahlen mindestens 100 Franken jährlich.



## Epilepsie-Preise

Gerne machen wir Sie auf die Broschüre „Epilepsie. Auszeichnungen, Preise, Stipendien und Stiftungen 2011/2012“ von Günter Krämer und Claudia Mühlebach aufmerksam. Darin finden Sie alle Informationen (Termine, Bedingungen), die Sie für eine Bewerbung benötigen. Bitte weisen Sie mögliche Anwärter in Ihrem Umfeld auf die Broschüre hin. Diese können Sie auf [www.epi.ch](http://www.epi.ch) unter Publikationen herunterladen oder bei [info@epi.ch](mailto:info@epi.ch) bzw. der Geschäftsstelle der Epilepsie-Liga, Seefeldstrasse 84, Postfach 1084, 8034 Zürich, bestellen.

Bitte frankieren

Absender/in

Name   Vorname	
Strasse   Nr.	
PLZ   Ort	
Telefon	
eMail	

### Schweizerische Liga gegen Epilepsie

Seefeldstrasse 84  
Postfach 1084  
CH 8034 Zürich

### Ausschreibung – Forschungsförderung

#### Förderung der wissenschaftlichen Forschung im Bereich der Epilepsie (vorwiegend Starthilfen) durch die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga)

Die Epilepsie-Liga unterstützt wissenschaftliche Projekte im Bereich der Epileptologie im Gesamtbetrag von

**CHF 20'000.—**

pro Jahr. Insbesondere soll die Erforschung von Ursachen und Behandlungen der Epilepsie gefördert werden.

Stipendien für Aus- oder Weiterbildung oder Auslandsaufenthalte werden nicht ausgerichtet. Hingegen können Reise- und Aufenthaltskosten (ohne Salär) für Kurzaufenthalte (maximal einige Wochen) finanziert werden, sofern sie dem Erlernen von Methoden dienen, welche im Rahmen eines unterstützten Projektes in der Schweiz eingesetzt werden.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

**Termin für die Einreichung von Gesuchen: 31. Dezember 2011**

Formulare und Wegleitung für Gesuchstellende können angefordert werden bei:

Schweizerische Liga gegen Epilepsie  
Seefeldstrasse 84 | Postfach 1084  
8034 Zürich  
Tel. 043 488 67 77 | Fax 043 488 67 78  
info@epi.ch

#### Bitte vormerken

Die nächste Mitgliederversammlung findet am 4. Mai 2012 von 13.30 bis 14.30 Uhr anlässlich der Gemeinsamen Tagung der SGKN, SNG und SLgE in Lugano statt.

## Vorschau Epileptologie 1 | 2012

### Epilepsie und Schlaf II

#### Elektrophysiologie und Schlaf

*Corinne Roth und Johannes Mathis | Bern*

#### Epilepsie und Schlafqualität

*Heidemarie Gast | Bern*

#### Schlafentzug in der Epilepsiediagnostik

*Dominique Flügel | St. Gallen*

#### Kataplexie und epileptische Sturzanfälle

*Ramin Khatami | Barmelweid*

#### Nächtliche hypermotorische Epilepsie und ihre Differenzialdiagnose

*Claudio Bassetti | Lugano*

#### Epilepsy and Sleep-Disordered Breathing

*José Haba-Rubio and Andrea Rossetti | Lausanne*

#### ESES

*Susi Strozzi | Bern*

#### Nächtliche nicht epileptische Bewegungsstörungen im Schlaf

*Georg Kaegi und Stephan Bohlhalter | St. Gallen und Luzern*

### Ausschreibung – Promotionspreis

**Die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga) vergibt alle 3 Jahre einen Preis in Höhe von**

**CHF 10'000.—**

**für die beste Dissertation auf dem Gebiet der Epileptologie.**

Bewerbungen sind aus allen Fachbereichen und Berufsgruppen möglich und erwünscht, sowohl aus Grundlagen- als auch klinischen Fächern. Eine Altersbeschränkung erfolgt nicht.

Das Preisrichterkollegium setzt sich aus drei Vorstandsmitgliedern der Epilepsie-Liga zusammen, das bei Bedarf zusätzlich externe Gutachter hinzuziehen kann. Es trifft seine Entscheidung in geheimer Wahl.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Die Preisverleihung erfolgt jeweils im darauf folgenden Jahr anlässlich der Jahrestagung oder Mitgliederversammlung der Epilepsie-Liga.

Bewerbungen sind **bis zum 31.12.2012** an die **Geschäftsstelle der Epilepsie-Liga** (Seefeldstrasse 84, Postfach 1084, 8034 Zürich) einzureichen und müssen beinhalten: vier Exemplare der abgeschlossenen und beim Dekanat eingereichten Dissertation, vier Exemplare einer Stellungnahme des Doktorvaters (dabei kann es sich auch um das entsprechende Gutachten für die Dissertation handeln).

### Mise au concours – Soutien de la recherche

Promotion de la recherche scientifique dans le domaine de l'épilepsie (surtout sous forme d'aide initiale) par la Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie)

La Ligue contre l'Epilepsie soutient les projets scientifiques dans le domaine de l'épileptologie par un montant total de

**CHF 20'000.—**

par an, la priorité étant accordée aux projets cherchant à élucider les causes et à mettre au point des traitements de l'épilepsie.

Aucune bourse ne sera octroyée pour la formation de base ou continue ou pour des séjours à l'étranger. En revanche, la prise en charge de frais de voyage et de séjour (sans salaire) est possible pour les séjours de courte durée (quelques semaines au maximum) lorsque ces séjours servent à apprendre des méthodes appliquées dans le cadre d'un projet bénéficiant de soutien en Suisse.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Délai de remise des demandes :

**31 décembre 2011**

Les formulaires, ainsi que le guide pour les candidats peuvent être demandés à l'adresse suivante :

Ligue Suisse contre l'Epilepsie  
Seefeldstrasse 84  
Case postale 1084  
8034 Zurich  
Tél. 043 488 67 77  
Fax 043 488 67 78  
info@epi.ch

### Mise au concours – Prix de promotion

La Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie) décerne tous les 3 ans un prix d'un montant de

**CHF 10'000.—**

pour la meilleure dissertation dans le domaine de l'épileptologie.

Tous les domaines spécialisés et tous les groupes professionnels couvrant les disciplines fondamentales ou cliniques sont invités à soumettre leur candidature. Aucune limite d'âge n'a été fixée.

Le jury décernant le prix se compose de trois membres du comité directeur de la Ligue contre l'Epilepsie. Il peut être complété au besoin par des experts externes. La décision est prise par vote secret.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Le prix est toujours décerné l'année suivante dans le cadre de l'assemblée annuelle ou générale de la Ligue contre l'Epilepsie.

Les dossiers de candidature doivent parvenir au Secrétariat de la Ligue contre l'Epilepsie (Seefeldstrasse 84, case postale 1084, 8034 Zurich) jusqu'au

**31.12.2012**

et comporter les pièces suivantes :

- quatre exemplaires de la dissertation achevée et remise au décanat,
- quatre exemplaires d'une prise de position du directeur de thèse (il peut par exemple s'agir de l'expertise concernant la dissertation).

## Call for Patients with Rare Epilepsy Syndromes including Dravet Syndrome

### EuroEPINOMICS Outreach scheme

EuroEPINOMICS is a large European research consortium consisting of four Collaborative Research Projects, which aims to identify novel epilepsy genes and genetic variants predisposing to epilepsy and drug response, and to unravel their molecular pathways ([www.esf.org/euroepinomics](http://www.esf.org/euroepinomics)).

The CRP "Genetics of rare epilepsy syndromes" (RES) aims to decipher the genetic basis of Rare Epilepsy Syndromes by bringing together the expertise of epileptologists with access to large patient cohorts and molecular genetics teams with a vast experience in locus and gene identification.

In order to support emerging research groups and support existing in areas with lacking infrastructure, the RES consortium has created the EuroEPINOMICS Outreach scheme. The purpose of the scheme is to provide basic genetic testing for patients by including patients in the RES genetic research pipeline.

Within this scheme, the RES consortium currently offers SCN1A testing for patients with Dravet Syndrome starting 01.11.2011 until 01.02.2012 and array CGH analysis for patients with non-lesional epileptic encephalopathies. Currently, 20 patients from Switzerland can be tested free of charge for SCN1A within the next three months through the Department of Molecular Genetics, Antwerp, Belgium (Prof. Peter De Jonghe). This current call for patients will be coordinated by Dr. Johannes Lemke, Switzerland. Prerequisites for testing patients include (1) a detailed epilepsy history reminiscent of typical Dravet Syndrome, (2) inclusion of both parents into the study prior to testing ("complete trios") and (3) parental consent for genetic testing including genome-wide studies for further research studies. For other non-lesional epileptic encephalopathies (Ohtahara Syndrome, West Syndrome, Myoclonic Astatic Epilepsy, Lennox-Gastaut-Syndrome etc.), array CGH testing can be provided through the consortium and – in selected cases – whole exome sequencing. The RES consortium may refuse testing for patients based on lacking or inadequate phenotypic information, inavailability of parents or lack of consent.

Please contact Dr. Lemke for patient trios with Dravet Syndrome or other epileptic encephalopathies to be included in the RES scheme to arrange for patient consent and testing.

**Dr. med. Johannes Lemke, Oberarzt Humangenetik  
Universitätsklinik für Kinderheilkunde, Inselspital,  
CH-3010 Bern  
Tel. +41 (0) 31 632 0210  
Fax +41 (0) 31 632 9484  
E-Mail: [johannes.lemke@insel.ch](mailto:johannes.lemke@insel.ch)**

Prof. Peter de Jonghe

Project Leader EuroEPINOMICS RES

### **Kahn-Preis Epileptologie**

Zur Unterstützung wissenschaftlicher Arbeiten von jüngeren Forschenden aus dem gesamten Gebiet der Epileptologie stellt die Jubiläumsstiftung der Bank Hugo Kahn für Epilepsieforschung einen Betrag von

bis zu 10'000 Franken

zur Verfügung. Der 1998 initiierte Preis kann sowohl zur Anerkennung bereits abgeschlossener Arbeiten als auch zur Unterstützung laufender Erfolg versprechender Projekte aus klinischen oder theoretischen Fachgebieten eingesetzt werden. Das Höchstalter für Gesuchstellende beträgt 45 Jahre.

Einzureichen bis: Ende Mai 2012.

### **Prix Kahn de l'Epileptologie**

Pour soutenir les jeunes chercheurs dans leurs travaux sur tous les domaines de l'épileptologie, la Fondation érigée par la Banque Hugo Kahn met à la disposition de la recherche sur l'épileptologie un montant

jusqu'à 10'000 francs.

Le prix créé en 1998 peut récompenser des travaux déjà achevés ou venir en aide aux projets prometteurs en cours dans des domaines spécialisés cliniques ou théoriques. La limite d'âge des candidats pouvant postuler a été fixée à 45 ans.

A soumettre jusqu'à: fin mai 2012.

### **Kahn Prize for Epileptology**

To support the work of young researchers in their work in all areas of epileptology, the Foundation set up by the Banque Hugo Kahn has made the sum of

up to 10,000 Swiss francs

available to epileptology research. The prize, created in 1998, can pay for work already done or can help promising projects currently under way in specialist clinical or theoretical areas. The age limit for candidates wishing to apply is 45.

To be submitted by: the end of May 2012.

Bewerbungen und Vorschläge sind bis Ende Mai 2012 unter Beifügung der entsprechenden Unterlagen in vierfacher Ausfertigung einzureichen an:

Schweizerische Liga gegen Epilepsie  
Dr. med. Günter Krämer, Präsident  
Postfach 1084  
Seefeldstrasse 84  
CH 8034 Zürich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
info@epi.ch

Preisrichterkollegium: Dr. med. Günter Krämer, Zürich (Vorsitz), Prof. Dr. med. Paul-André Despland, Montreux, und Prof. Dr. med. Theodor Landis, Genève.

Les candidatures et les propositions de candidats accompagnées d'un dossier en quatre exemplaires sont à soumettre jusqu'à fin mai 2012 à :

Ligue Suisse contre l'Epilepsie  
Dr. Günter Krämer, Président  
Case postale 1084  
Seefeldstrasse 84  
CH 8034 Zurich  
Tél. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
info@epi.ch

Collège des juges: Dr. Günter Krämer, Zurich (présidence), Prof. Dr. Paul-André Despland, Montreux, et Prof. Dr. Theodor Landis, Genève.

Candidates and applications from candidates accompanied by four copies of their file should be submitted by the end of May 2012 to:

Swiss League Against Epilepsy  
Dr. Günter Krämer, Chairman  
P.O. Box 1084  
Seefeldstrasse 84  
CH 8034 Zurich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
info@epi.ch

Panel of Judges: Dr. Günter Krämer, Zurich (chairman), Prof. Dr. Paul-André Despland, Montreux, and Prof. Dr. Theodor Landis, Geneva.

**2012**

7.1.2012 | Berlin, Deutschland

**4. Berliner Epilepsie-Parkinson-Seminar**

Information: Prof. Dr. Bettina Schmitz,  
Vivantes Humboldt Klinikum, Berlin, Deutschland,  
Tel. 0049 / 30 / 130122245,  
Fax 0049 / 30 / 130122247,  
e-mail: bettina.schmitz@vivantes.de

26.1.2012 | Lausanne, Hôtel Alpha-Palmiers

**4ème journée romande d'épileptologie**

Information: Marine Veyre,  
Tel. 0041 / 21 / 821 46 80

26.-28.1.2012 | Brno, Tschechien

**2nd Course on Epilepsy Surgery**

Information: Prof. Dr. Cigdem Özkara,  
Cerrahpasa Medical School,  
Department of Neurology,  
Istanbul, Turkey,  
Tel./Fax 0090 / 212 / 6330176,  
e-mail: cigdemoz@istanbul.edu.tr,  
tarabova@ta-service.cz

8.-10.2.2012 | München, Deutschland

**46. Münchner EEG-Tage**

Information: PD Dr. Oliver Pogarell und Dr. Dipl. Psych.  
Susanne Karch, Klinische Neurophysiologie, Klinik für  
Psychiatrie der Ludwig-Maximilians-Universität Mün-  
chen, Nussbaumstr. 7, 80336 München, Deutschland,  
Tel. 0049 / 89 / 51605541,  
Fax 0049 / 89 / 51605542,  
e-mail: anmeldung@eeg-tage.de,  
www.eeg-tage.de

29.2.-3.3.2012 | Stuttgart, Deutschland

**52. Jahrestagung der Deutschen Gesellschaft für Epileptologie e.V. (DGfE)**

Information: Prof. H. Lerche, Abt. Neurologie,  
Epileptologie, Univ. Tübingen, Hertie-Inst. für klin.  
Hirnforschung, Hoppe-Seyler-Str. 3, 72076 Tübingen,  
Deutschland  
Tel. 0049 / 7071 / 2982057,  
Fax 0049 / 7071 / 295260,  
e-mail: holger.lerche@uni-tuebingen.de,  
www.dgfe.info

8.-11.3.2012 | Wien, Österreich

**6th World Congress on Controversies in Neurology (CONy)**

Information: ComtecMed, 53 Rothschild Boulevard, PO  
Box 68, Tel Aviv, 61000, Israel,  
Tel. 00972 / 3 / 5666166,  
Fax 00972 / 3 / 5666177,  
e-mail: Info@comtecmed.com,  
www.comtecmed.com/CONy

14.-17.3.2012 | Graz, Österreich

**10. Jahrestagung der Österreichischen Gesellschaft für Neurologie**

Information: Tanja Weinhart, ÖGN Sekretariat,  
Garnisongasse 7/22, 1090 Wien, Österreich,  
Tel. 0043 / 1 / 512 / 809119,  
e-mail: weinhart@oegn.at

15.3.2012 | Solothurn

**Fachveranstaltung der Schweiz. Liga gegen Epilepsie**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
e-mail: info@epi.ch,  
www.epi.ch

15.3.2012 | Solothurn

**Publikumsveranstaltung der Schweiz. Liga gegen Epilepsie**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
e-mail: info@epi.ch, www.epi.ch

22.-25.3.2012 | Manila, Philippinen

**9th Asian & Oceanian Epilepsy Congress (AOEC)**

Information: 9th AOEC, ILAE/IBE Congress Sekretariat,  
7 Priory Hall, Stillorgan, Dublin 18, Ireland,  
Tel. 00353 / 1 / 2056720,  
Fax: 00353 / 1 / 2056156,  
e-mail: manila@epilepsycongress.org

22.-25.3.2012 | Sevilla, Spanien

**2nd International Conference on Neurology and Epidemiology (ICNE)**

Information: GL events, Package Organisation, 10 quai Charles de Gaulle, 69463 Lyon Cedex 06, Frankreich, Tel. 0033 / 4 / 78176176, Fax 0033 / 4 / 78176257, e-mail: elma.zerzaihi@gl-events.com, www.neuro-conference.com, www.neuro-conference.com/2012/unsubscribe.html

24.3.2012 | Zürich

**Frühjahrssymposium**

Information : Schweiz. Epilepsie-Zentrum, Bleulerstrasse 60, 8008 Zürich, Tel. 0041 / 44 / 3876302, Fax 0041 / 44 / 3876396, e-mail : leonie.mueller@swissepi.ch

28.-31.3.2012 | Prag, Tschechien

**2nd International Congress on Epilepsy, Brain and Mind**

Information: GUARANT International spol. s r.o., Opletalova 22, 110 00 Prag 1, Tschechien, Tel. 00420 / 284 / 001444, Fax 00420 / 284 / 001448, e-mail: ebm2012@guarant.cz, www.epilepsy-brain-mind2012.eu

19.-22.4.2012 | Münster, Deutschland

**38. Jahrestagung der Gesellschaft für Neuropädiatrie  
9. Fortbildungsakademie**

Information: Intercongress GmbH, Karlsruher Str. 3, 79108 Freiburg, Deutschland, Tel.0761 / 696990, Fax 0761 / 6969911, e-mail: neuropaediatrie@intercongress.de, www.intercongress.de

21.-28.4.2012 | New Orleans, USA

**64th Annual Meeting of the American Academy of Neurology**

Information: American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116, USA, Tel. 001 / 651 / 6952717, Fax 001 / 651 / 6952791, e-mail: memberservice@aan.com, www.aan.com

May 2012 | Beirut, Lebanon

**Epilepsy Course 2012**

3.-5.5.2012 | Lugano

**Gemeinsame Jahrestagung von SGKN/SNG/SLgE**

Information: IMK Institut für Medizin und Kommunikation AG, Harald F. Grossmann, Executive Partner, Münsterberg 1, 4001 Basel, Tel. 0041 / 61 / 2713551, Fax 0041 / 61 / 2713338, e-mail: harald.grossmann@imk.ch

6.-10.5.2012 | Eilat, Israel

**11th Eilat Conference on New Antiepileptic Drugs (Eilat XI)**

Information: Target Conferences Ltd, PO Box 29041, Tel Aviv 61290, Israel, Tel. 00972 / 3 / 5175150, Fax 00972 / 3 / 5175155, e-mail: eilatxi@targetconf.com, www.eilat-aeds.com/XI

20.-23.5.2012 | Lyon, Frankreich

**5th International Epilepsy colloquium: Pediatric Epilepsy Surgery**

Information: Congrex Deutschland GmbH, Hauptstrasse 18, 79576 Weil am Rhein, Tel. 0049 / 7621 / 98330, Fax 0049 / 7621 / 78714, e-mail: weil@congrex.com, www.ruhr-epileptologie.de/5th-international-epilepsy-colloquium

24.5.2012 | Bern

**133. Epilepsie-Kolloquium**

Information: regula.kunz@insel.ch

1.6.2012 | Bern

**Epilepsie-Laienveranstaltung**

Information: regula.kunz@insel.ch

8.-13.7.2012 | Rostock, Deutschland

**The 6th Baltic Sea Summer School on Epilepsy**

Information: Petra Novotny, Prof. Peter & Jytte Wolf Foundation for Epilepsy, e-mail: petra.novotny@wolfstiftung.org, www.epilepsiestiftung-wolf.de/7.html

16.8.2012 | Basel

**Fachveranstaltung der Schweiz. Liga gegen Epilepsie**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
e-mail: info@epi.ch, www.epi.ch

16.8.2012 | Basel

**Publikumsveranstaltung der Schweiz. Liga gegen Epilepsie**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
e-mail: info@epi.ch, www.epi.ch

8.-11.9.2012 | Stockholm, Schweden

**16th Congress of the European Federation of Neurological Societies (EFNS)**

Information: Kenes International, 17 Rue du Cendrier,  
PO Box 1726, 1211 Geneva 1,  
Tel. 0041 / 22 / 9080488,  
Fax 0041 / 22 / 7322850,  
e-mail: efns2012@kenes.com,  
www.kenes.com/efns2012 oder  
www.efns.org/efns2012

9. – 12. 9. 2012 | Gargnano/Gardasee, Italien

**24. Praxisseminar über Epileptologie**

Information: Stiftung Michael,  
Münzkamp 5, 22339 Hamburg, Deutschland,  
Tel.: 0049 / 40 / 5388540,  
Fax: 0049 / 40 / 5381559,  
e-mail: stiftungmichael@t-online.de  
www.seminargargnano.de

15.9.2012 | Zürich

**Herbstsymposium**

Information : Schweiz. Epilepsie-Zentrum,  
Bleulerstrasse 60, 8008 Zürich,  
Tel. 0041 44 387 63 02  
Fax 0041 44 387 63 96  
e-mail : leonie.mueller@swissepi.ch

26.-29.9.2012 | Hamburg, Deutschland

**Jahrestagung der Deutschen Gesellschaft für Neurologie (DGN) 2012**

Information: Congrex Deutschland GmbH,  
Joachimstaler Str. 12, 10719 Berlin, Deutschland,  
Tel. 0049 / 30 / 8871085550,  
e-mail: dgn@congrex.com, www.congrex.de,  
www.dgn.org



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becker@epi.ch

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bd@screenblue.de, www.screenblue.de

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