PREFACE

The year of 1998 brought major changes for the institute. October saw the move to our newly completed building. A month earlier, the MEG group had relocated from the inner city area to a site outside Leipzig to ensure that future MEG measurements would be uncontaminated by environmental noise. The decision to move the MEG was taken after it became clear that passive and active noise cancellation techniques would not allow the generation of an adequate signal to noise ratio in the inner city of Leipzig. The relocation of the MEG group as well as that of the whole institute was implemented in an amazingly smooth manner thanks to the enormous commitment of the head of administration Ingrid Schmude and the head of the information technology group Helmut Hayd and their staff.

In May 1998, the institute underwent its first site visit and scientific evaluation by its international advisory committee or 'Fachbeirat'. Together with the advisory committee and the President of the Max Planck Society the decision was taken to enlarge the institute by the addition of a Junior Research Group to be established in 1999.

As in previous years, the scientific work carried out in 1998 centered around two main topics: the neurocognition of language and the neurocognition of memory, both in healthy and in neurologically impaired adults. The research undertakings were accompanied by developments in measurement techniques and experimental methods, as well as in signal and image processing and modelling.

To strengthen further the collaboration with the University of Leipzig, Yves von Cramon agreed to direct the Neuroscience Department of the Interdisciplinary Center for Clinical Research (IZKF) and Angela Friederici the Center of Advanced Studies (ZHS) of the University of Leipzig.

The present report provides an insight into the research objectives realized in 1998. Many of the achievements were made possible by the close cooperation between the two departments, Neurology and Neuropsychology, at the MPI of Cognitive Neuroscience in Leipzig.

Angela D. Friederici
D. Yves von Cramon

Leipzig, February 1999

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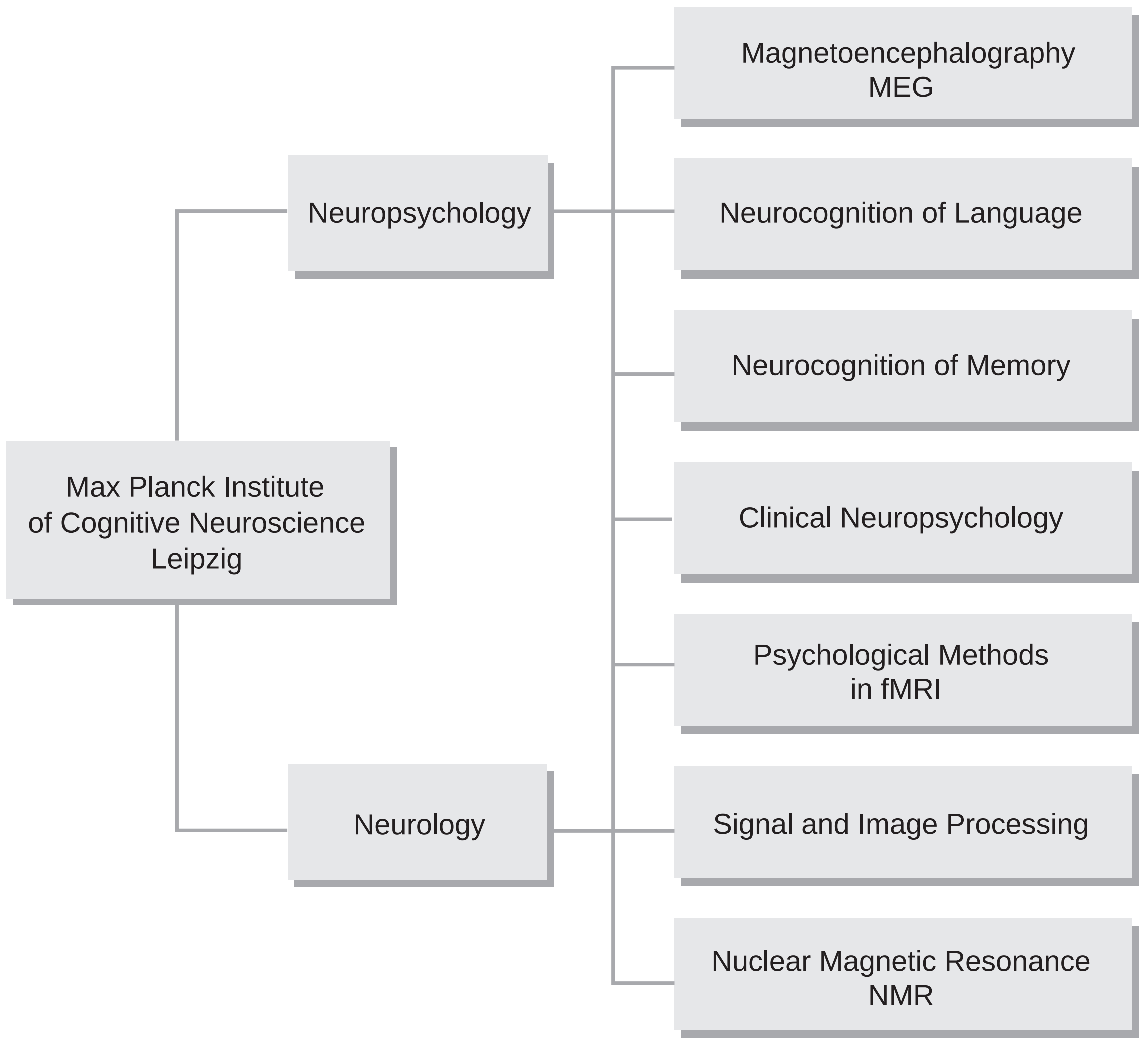
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Neurology
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Nuclear Magnetic Resonance
NMR

NEUROCOGNITION OF LANGUAGE 3.1

Language processing and its functional representation in the brain are major research areas in our institute. Psycholinguistic theorizing and neuropsychological and neurophysiological modelling, together with empirical data from both normals and from patients with circumscribed brain lesions, are considered in building a picture of the language-brain relationship. Measurements of language-related brain activity with high temporal resolution (EEG, MEG) and high spatial resolution (fMRI), are used to specify the processes and systems underlying language comprehension.

This year the research focused not only on syntactic and semantic processes and their possible interaction, but also on the impact of prosodic information during auditory sentence comprehension. By means of fMRI we were able to identify the *neuronal network of auditory sentence processing* and to specify the particular subcomponents responsible for phonological, semantic, syntactic and prosodic aspects of language processing (3.1.1, 3.1.2, 3.1.3). Furthermore, it was shown that the specific networks supporting semantic processing and syntactic processing are activated as a function of task demands even when processing single words (3.1.4).

The *temporal characteristics* of the activation of the different subprocesses can be explored by means of neurophysiological measures. A number of studies focused on *syntactic processes* trying to specify early processes of phrase structure building (reflected by the early negativity) and late processes of reanalysis and repair (reflected by late positivities) using depth electrodes (3.1.5), brain surface current density mapping (3.1.6) and spatio-temporal principle component analyses (3.1.7). The existence of the two syntactic processing components, i.e. the early negativity and the late positivity, was shown even in sentences containing no semantic information (3.1.8). The interesting question of the extent to which *prosodic information* affects syntactic parsing was investigated in a series of electrophysiological experiments (3.1.9, 3.1.10, 3.1.11). These indicate an immediate use of prosodic cues on initial syntactic structure building supporting the view that prosodic and syntactic information interact quite early during sentence processing. We identified a particular event-related brain potential component which was correlated with intonational phrase structure building based on prosodic cues. Additional linguistic analyses allowed a detailed description of the linguistic conditions under which certain prosodic cues are realized (3.1.12, 3.1.13). An *interface between the lexical and the syntactic level* of representation is instanced by the verb and its argument structure. The information about the number of arguments, the syntactic type of arguments (direct object/indirect object) and the semantic type of arguments (animate noun phrase/inanimate noun phrase) a verb can take must be processed online as elements of a sentence are encountered. German is particularly rich with respect to how it marks its arguments syntactically (by different cases) and at which point during sentence processing specific information becomes available (verb-first versus verb-second structures). By means of event-related brain potentials it was demonstrated that semantic information encoded in the verb elicits a classical N400 correlated with semantic processes whereas case marking information evokes components correlated with syntactic processes (3.1.14, 3.1.15). The presence of the particular syntactic components (early negativity, late positivity) is not independent of the stage in sentence processing at which case marking information becomes available (noun phrase after verb, i.e. verb-first, versus noun phrase prior to verb, i.e. verb-final). An interesting case is that of sentences in which the verb-stem occurs prior to its object arguments but its separable prefix in sentence final position. If the verb-stem is such that it can also function as a main verb with a verb-argument structure different from its prefixed variant, then additional processing demands will arise. The finding of a combination of an N400 and a late positive component at the sentence final separable prefix suggests that lexically triggered structural reanalysis takes place when the prefix is encountered (3.1.16). *Lexical-semantic processes were* investigated focusing on two issues. We first explored the question of how semantically ambiguous monomorphemic words and compound words are processed in subjects with different working memory spans (3.1.17, 3.1.18, 3.1.19). Secondly, we investigated the relation between the N400, specific priming effects and attentional parameters (3.1.20, 3.1.21, 3.1.22).

3.1.1 Towards the cerebral organization of speech: event-related brain responses to syntax, semantics and phonology

Friederici, A.D., Meyer, M. & von Cramon, D.Y.

Recent neuroimaging studies indicate that the processing of phonological information occurs in the left frontal cortex close to the border between Broca's area and the premotor cortex. The analysis of word meaning seems to correlate with an increase in local blood supply to a widely distributed cortical network including prefrontal and temporal cortices bilaterally. With respect to sentence processing, earlier neuropsychological models and brain imaging experiments emphasize the contribution of Broca's area to syntax mechanisms. More recent lesion studies report severe grammatical impairments during comprehension after damage to left inferior frontal regions or to the left temporal lobe.

The present study makes use of fMRI to specifiy the cerebral network involved in the processing of phonological, of syntactic and of lexical-semantic information during speech comprehension in a defined experimental setting.

In an event-related design 18 healthy subjects were presented with four types of auditory stimuli: (1) normal prose; i.e. sentences which are syntactically and semantically correct, (2) syntactic prose; i.e. a syntactically correct structure in which content words are replaced by phonologically legal pseudowords, (3) real word lists containing no syntactic structure, and (4) nonsense word lists; i.e. lists of phonologically legal pseudowords comprising no syntactic structure. These four conditions enable us to trace the brain's activation for the processing of primary syntactic aspects (2), primary semantic aspects (3), for the joint processing of semantic and syntactic aspects (1) and for the processing of phonological aspects (4).

Eight BOLD contrast image volumes were obtained in eight AC-PC parallel slices (thickness=6 mm, gap=2 mm) with gradient echo planar imaging (TR=2 sec, TE=40 ms) for each of the 144 single trials using a Bruker 3 Tesla scanner. Multisubject averaging revealed that the primary auditory cortex and the posterior parts of the superior temporal gyrus bilaterally were excited in all conditions, but were more strongly involved when considering only the sentence conditions. In contrast to word lists the processing of syntactic information evoked additional activation in the thalamus, in bilateral compartments of the temporal opercular cortex and most specifically in the left frontal opercular cortex.

Interestingly, in all conditions but the normal prose, salient hemodynamic responses in the superior-dorsal part of left Broca's area and the contralateral cortex could be detected. These presumably reflect phonological and lexical-semantic processing of legal and illegal function and content words. This finding indicates the involvement of additional resources in the left and right frontolateral cortex whenever the speech input deviates considerably from normal speech. Thus, the present data offer a systematic contribution to the functional specification of the cerebral network subserving language processing in general and auditory language processing in particular.

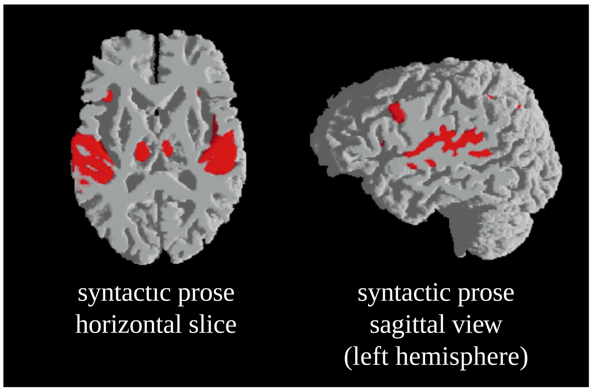

Figure 1.

Brain responses associated with prosodic processing in natural speech revealed by event-related fMRI

3.1.2

Meyer, M., Alter, K., Steinhauer, K., Friederici, A.D. & von Cramon, D.Y.

The most reliable finding in clinical neuropsychology on prosody appears to be a predominant contribution of the right hemisphere as opposed to the left hemisphere in both speech perception and production. According to several neuropsychological studies the right hemisphere and in particular the right temporal lobe is involved whenever prosodic aspects of language are concerned. To date there exists no systematic description of prosodic influence on normal language comprehension in healthy subjects provided by functional neuroimaging. However, Zatorre et al. (1992) have reported activation in the right prefrontal cortex (BA 45/46/9) while subjects are performing a pitch judgement.

The present study employed event-related fMRI to localize brain areas involved in the processing of linguistic prosody in spoken natural language. As German realizes prosody primarily by pitch variations, the design comprises four conditions which address the contribution of the pitch parameter (i.e., Fundamental Frequency, or F0). Two conditions (1 and 4) present grammatically correct and normally intonated sentences. Sentences of condition (1) employ a wide focus whereas sentences belonging to condition (4) are illegitimately narrowly focused. In (2), the pitch contour was completely flattened resulting in a monotonous, artificial sounding intonation while lexical information is still available. In (3), all segmented and lexical information has been filtered out whereas the pitch contour remains unaltered.

Participants were required to perform a prosodic comparison task. That is, they were required to decide whether the prosody of the current sentence was equivalent to that of the preceding sentence. Eight BOLD contrast image volumes were obtained from 12 subjects in eight AC-PC parallel slices (thickness=6 mm, gap=2 mm) with gradient echo planar imaging (TR=2 s, TE=40 ms) for each of the 144 single trials using a Bruker 3 Tesla scanner.

Data analysis revealed increased activation in the primary auditory cortex in all conditions, whereas the hemodynamic responses obtained from adjacent temporal language related areas and from the inferior frontal gyrus (pars triangularis) varied bilaterally depending on test condition (see figure below). The inferior precentral gyrus and the superior temporal cortex are more strongly involved bilaterally when considering the prosodically correct conditions only. Salient left and moderate right inferior frontal activation (pars triangularis) could be reported for all conditions except for delexicalized speech. Interestingly, in all conditions clusters in the right superior temporal gyrus were larger than those in the contralateral hemisphere. This finding suggests a particular influence of nonaffective prosodic aspects during the processing of speech.

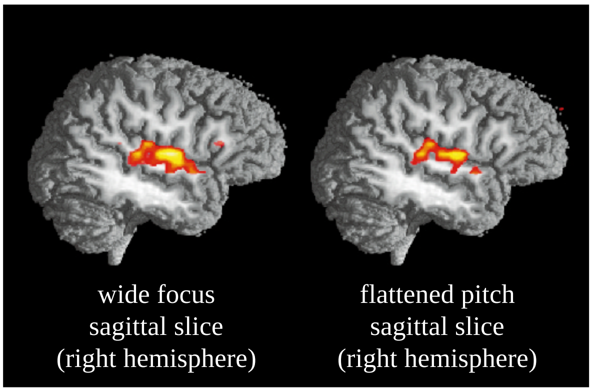

Figure 2.

3.1.3 Processing prosody only: event-related fMRI specifies comprehension mechanisms of delexicalized speech

Meyer, M., Friederici, A.D., Alter, K. & von Cramon, D.Y.

Data obtained in a recent event-related fMRI-study (3.1.1) identified the major components of cerebral speech organization: auditory stimuli (sentences and word lists) excited brain responses in the primary auditory cortices, in the superior temporal gyrus (planum temporale, temporal operculum) bilaterally, in the inferior frontal cortex (deep left frontal operculum, superior-dorsal part of Broca's area) and in subcortical regions (thalamus). Since the change in local blood supply during auditory speech comprehension was computed using a resting state (no speech presented, but scanner noise continues) baseline for data analysis, the language-specific cortices could not be separated exactly from the regions processing pure auditory stimuli. It is well known that auditory processing of sounds is subserved by Heschl's gyrus bilaterally. The current study was aimed at using natural language and deviant language stimuli to detect other areas related to language comprehension. This was achieved by means of an event-related approach.

The design comprises three conditions and allows the discrimination of language and sound processing. In one condition normal language information is presented, whereas in the other two conditions it is not. This is achieved by applying (1) normal sentences as natural language input, (2) sentences which are manipulated by a filtering procedure (delexicalization) and (3) jabberwocky sentences, as applied in a former study (3.1.1), as deviant language fillers.

To create stimuli entirely lacking in syntactic and semantic information, a unique filtering technique was used. The derived signal does not comprise any segmented or lexical information but conserves all prosodic parameters serving accentuation and prosodic phrasing, including pitch. Participants had to perform a syntactical judgment in that they were required to decide whether the sentence (either natural language or delexicalized speech) was realized in active or passive voice.

Eight BOLD contrast image volumes were obtained from 14 subjects in eight AC-PC parallel slices (thickness=6 mm, gap=2 mm) with gradient echo planar imaging (TR=2 sec, TE=40 ms) for each of the 108 single trials using a Bruker 3 Tesla scanner. Multisubject averaging revealed the primary auditory cortex and the posterior parts of the superior temporal gyrus (STG) bilaterally to be excited in all conditions. However, there was a greater involvement, especially in the left STG, for conditions (1) and (2).

For the case of the inferior frontal cortex the following pattern was observed: sentences comprising lexical and phonological information were found to elicit brain responses in the anterior part of the insula bilaterally and in the left frontal operculum. The processing of delexicalized information evoked a substantial increase in local blood supply in inferior frontal cortices (pars opercularis and pars triangularis) bilaterally.

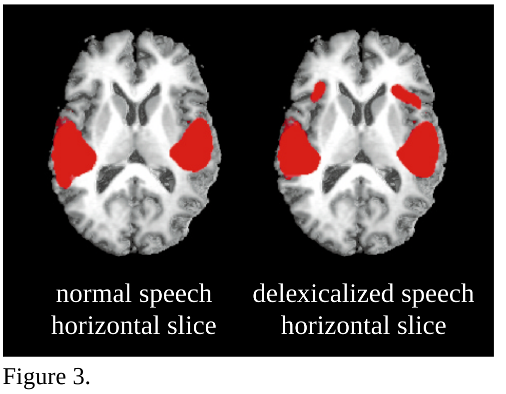

Figure 3.

3.1.4 Segregating semantic and syntactic processes during word perception

Friederici, A.D., Opitz, B. & von Cramon, D.Y.

The goal of the present study was to determine the brain regions involved in the processing of open class (content) and closed class (function) words. In contrast to previous work (Nobre et al., 1997) in which the factor word class was confounded with the factor concreteness, the present experiment crossed these factors systematically.

The stimulus material consisted of 80 content words (nouns) and 80 function words (prepositions), half of them being concrete and half abstract. In a first experiment the stimuli were presented visually on a computer screen and in a second one biaurally via headphones. In both experiments words were presented in 8 blocks with 20 words each. During a first run the words were blocked by concreteness and subjects required to judge the word class of the presented stimuli. In a second run words were blocked by word class and subjects required to judge concreteness. A physical judgment (visual experiment: spaced vs. non spaced print, auditory experiment: male vs. female voice) served as a baseline task. In both experiments gradient echo EPI images were collected from seven axial slices with a repetition time of 2.0 s. After baseline correction voxel-wise Pearson correlation of fMRI time series with a delayed box car reference wave-form was performed. After transforming of activation maps into stereotactic Talairach space, multisubject averaging was used to enhance the signal to noise ratio.

The results obtained in the auditory and the visual experiments were highly similar. When controlled for concreteness (syntactic judgment vs. physical baseline) content words only activated the Brodmann Area (BA) 44 in the left hemisphere (LH) whereas function words in addition to BA44 also activated the left BA45 and BA6. In the semantic judgment vs. baseline condition abstract words activated BA44/45 LH whereas concrete words gave rise to an increased fMRI signal in the BA6/4 LH in addition to BA44/46 LH. When comparing the semantic and the syntactic task directly we found a selective activation of left BA44 for the syntactic tasks and the additional involvement of BA45 and BA6 LH for the semantic task.

When open class and closed class words, controlled for concreteness, are processed with respect to either their syntactic or their semantic status, different patterns of brain activation are observed. The syntactic task predominantly activates Broca's area (BA44) in the LH, whereas the semantic tasks evoke a more extended activation including BA45/46.

3.1.5 Processing syntactic and semantic violations as revealed by ERP recordings from the medio-basal temporal lobes

Mecklinger, A.[1], Friederici, A.D.[1], Grunwald, T.[2], Pezer, N.[2], Penney, T.B.[1] & Elger, C.[2]

[1]Max-Planck-Institute of Cognitive Neuroscience, [2]Department of Epileptology, University of Bonn

In cooperation with the Department of Epileptology at the University of Bonn we continued to examine neuronal correlates of language comprehension by means of intracranial ERP recordings in patients with temporal lobe epilepsy. The patients listened to sentences that were syntactically and semantically correct or contained either a word category violation or a semantic selection violation. Both kinds of violations can be reliably dissociated electrophysiologically with scalp recorded ERPs. That is, syntactic violations evoke a biphasic ERP response, i.e. an Early Left Anterior Negativity peaking around 200 ms followed by a parietally distributed late positive component (P600).

Semantic violations give rise to a N400 component (Friederici et al., 1996). Bilateral depth electrodes were implanted in the medio-basal temporal lobes along the longitudinal axis with the amygdala as the target of the most anterior electrode. Electrode distance was 4 mm and electrode placements were verified by post-implant CT or MRI. Data were collected and analyzed from 11 patients. A syntactic violation evoked an early and a late positive component at recording sites within the hippocampus proper contralateral to the epileptogenic focus. The maximum peak of the early component was around 120 ms after word onset whereas the later component, similar to the MTL P300 (3.2.16), reached it maximum between 450 and 600 ms. In its temporal characteristics this dual component pattern resembles the biphasic scalp-recorded ERP response to syntactic violations. So far, no reliable intracranial ERP responses to the semantic selection violations have been obtained at any of the intracranial recording sites.

3.1.6 Processing of syntactic information monitored by brain surface current density mapping based on MEG

Knösche, T.R., Maess, B. & Friederici, A.D.

Magnetoencephalography offers a way of achieving the direct detection of neuronal activity and a temporal resolution comparable to that of ERP recordings. Spatial resolution is superior to that of EEG measurements, though inferior to fMRI. With this method, it may prove possible to assemble an approximate picture of the spatio-temporal organization of language processing in the brain which complements the findings of brain imaging studies. In the present study, we used a whole-head multichannel magnetometer allowing simultaneous registration from 148 sites (MAGNES WHS 2500, BTi) to monitor brain activity related to word category violations in auditorily presented sentences. Brain Surface Current Density (BSCD) mapping was used to identify brain regions with statistically different activation patterns between correct and syntactically incorrect language input.

The study was conducted with ten right handed female volunteers, who were native speakers of German. The experimental paradigm was identical to the one used by Friederici et al. (1993), and the stimulus material was taken from Hahne (1997), with the construction of 136 additional sentences. The brain surface current density mapping method (BSCD) was used to reconstruct intracranial current distributions related to the processing of the violating word in a standardized, Talairach-scaled brain model. These current densities were averaged to obtain the timecourse of the reaction and analyzed statistically in order to identify those brain regions that react specifically to syntactic violations.

The average MEG data show a prominent wave peaking at about 150 ms after violation onset which probably represents the same process as the early left anterior negativity (ELAN) found in ERP experiments. BSCD mapping located this early component in the normal and temporal frontal regions of both hemispheres. Another component that differentiates between the correct and incorrect sentences is a broad wave between 250 and 600 ms after violation onset. This late effect seems to be located mainly in the right hemisphere in temporal, frontal, and parietal regions. Between 250 and 450 ms, frontal and temporal sources in the left hemisphere also seem to participate.

This study shows that the activity associated with initial parsing is not only concentrated in left anterior regions as suggested by ERP results, but extends over a network involving both hemispheres. Later processes, possibly representing repair of the damaged structures, are located mainly in the right hemisphere.

This latter result can be linked to the fMRI finding of Meyer et al. (1998) demonstrating the involvement of the right hemisphere in the process of sentence repair.

3.1.7 ERP components elicited by syntactic disambiguation as revealed by spatio-temporal PCA

Friederici, A.D.[1], Mecklinger, A.[1], Spencer, K.[2], Steinhauer, K.[1] & Donchin, E.[2]

[1]Max-Planck-Institute of Cognitive Neuroscience, [2]Department of Psychology, University of Illinois, Champaign, USA

Sentences are labeled "Garden-path" if they are temporarily ambiguous and disambiguated towards the non-preferred structure by a particular word. Friederici (1997) examined the ERPs elicited by the disambiguating word in garden-path sentences. Subjects read German sentences containing a relative or a complement clause disambiguating either towards the preferred subject first or the non-preferred object first reading. Thus, the stimulus materials comprised subject and object relative clauses (SR and OR) and subject and object complement clauses (SC and OC). The ERPs were used to assess the time course and distinctness of the processes associated with these disambiguations. The ERPs were analyzed using peak amplitude measures and were consistent with Friederici's model (1998) of syntactic revisions. This model assumes two stages of the revision; diagnosis, i.e. the detection of the need for revising a current structure, and reanalysis, i.e. the actual computation of a new syntactic structure. Positive peaks at 300 ms and 600 ms varied as a function of sentence type (relative vs. complement) and structure (subject first vs. object first). To explore these peaks and their relation to other ERP components, and to take full account of the spatio-temporal database the data were reanalyzed using spatio-temporal Principal Component Analysis (Donchin et al., 1997).

First a "spatial" PCA was performed to analyze the covariance between electrode sites across time points. The spatial factors (or virtual electrodes) were subjected to a "temporal" PCA to examine the covariance between time points across each virtual electrode. This analysis revealed two spatial factors of interest with a centro-parietal and an occipital scalp distribution, respectively, as well as two temporal factors (TF) with high loadings at around 300 and 600 ms (TF1 and TF2). The statistical analyses revealed that for the occipital factor in the early time interval (TF1) the scores were larger for object relative than subject relative sentences. In the late time interval (TF2) the occipital factor showed higher loadings for object complements than for subject complements. For the centro-parietal factor larger factor scores for object complements than for subject complements were obtained in the late time interval (TF2). Given this pattern of results it is tempting to speculate that the occipital and the centro-parietal factors reflect electrophysiological activity associated with the two assumed stages of the syntactic revision process: diagnosis and reanalysis.

Processing syntax without semantics

3.1.8

Hahne, A. & Friederici, A.D.

Auditory ERP responses to correct and syntactically incorrect sentences containing word category violations were examined. In one condition, the sentences consisted of existing German words (word condition). In a second condition, the content words were replaced by pseudowords while maintaining morphological markers (pseudoword condition).

	word condition	pseudoword condition
syntactically correct	*Der Apfel wurde gepflückt.* [The apple was plucked.]	*Die Glabbe wurde gerottert.* [The wibon was rashed.]
syntactically incorrect	*Die Birne wurde im gepflückt.* [The pear was in the plucked.]	*Das Fiehm wurde im gerottert.* [The ploker was in the rashed.]

The word-pseudoword variation was presented to all subjects in all sessions. Sentences were presented auditorily. Participants performed a grammaticality judgment 1500 ms after the end of the sentence.

Syntactically incorrect sentences elicited nearly indistinguishable ERP patterns for the word and the pseudoword condition: an Early Anterior Negativity followed by a P600. The only reliable difference between the word and the pseudoword condition was observed for the syntactically correct sentences: real nouns in syntactically correct sentences elicited an N400 component whereas their place-holders in the pseudoword condition did not. These results support the notion that the syntactic ERP components, namely the Early Anterior Negativity and the P600, are independent of the word's lexical-semantic information.

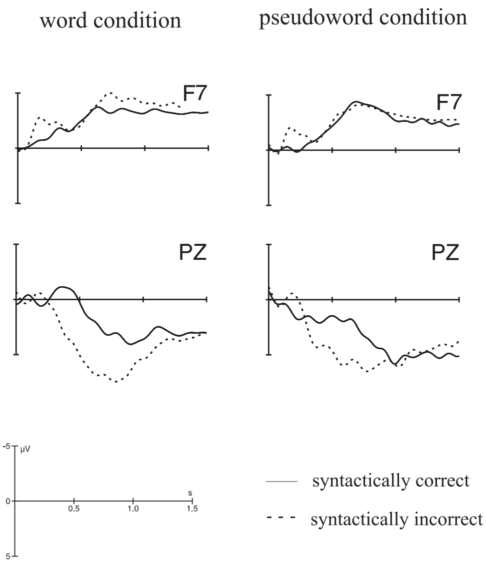

Figure 4. Grand average over 20 participants at F7 and Pz time-locked to the onset of the participle.

3.1.9 Brain potentials indicate immediate use of prosodic cues in natural speech processing

Steinhauer, K., Alter, K. & Friederici, A.D.

supported by DFG

We conducted two auditory event-related brain potential (ERP) studies demonstrating that accentuation and intonational phrasing guide the listener's initial syntactic sentence analysis. The new and consistent finding of a positive shift in the listeners' ERP at intonational phrase boundaries suggests a specific on-line brain response to prosodic processing.

The German sentence material consisted of 48 sentence pairs such as (A) and (B), where the bracketing indicates the respective intonational phrases (IPhs):

(A)	[*Peter verspricht*	*Anna zu arbeiten*]$_{IPh1}$	[*und das Büro zu putzen*]$_{IPh2}$
	(Peter promises	Anna to work	and to clean the office)
(B)	[*Peter verspricht*]$_{IPh1}$ #	[*Anna zu entlasten*]$_{IPh2}$	[*und das Büro zu putzen*]$_{IPh3}$
	(Peter promises	to support Anna	and to clean the office)

The noun phrase "*Anna*" is the object of the first verb "*verspricht*"/"promises" in (A) and therefore belongs to the first IPh. In contrast to (A), "*Anna*" is the object of the second transitive verb "*entlasten*"/"support" in sentence (B) and belongs to the second IPh.

Using a cross-splicing technique, we merged the acoustic signals of the first part of (B) and the second part of (A) between "*Anna*" and the infinitive marker "*zu*"/"to" in each of the 48 sentence pairs resulting in a third condition (C). If guided by prosodic cues, listeners were expected erroneously to attach the noun phrase "*Anna*" to the second verb which cannot take a direct object as its argument (e.g., * "to work someone").

(C) *	[*Peter verspricht*]IPh1#	[*Anna zu arbeiten*]IPh2	[*und das Büro zu putzen*]IPh3
	(Peter promises	to work Anna	and to clean the office)

In both experiments we found a large positive waveform at intonational phrase boundaries which we labeled *Closure Positive Shift* (CPS). As the grand average ERPs across both experiments (n=40) in Figure 5 illustrate, condition (A) displays a single CPS at its IPh boundary following the second verb "arbeiten". Conditions (B) and (C), in contrast, contain two IPh boundaries and thus display two such positive shifts.

As expected, the presence of an early IPh boundary preceding "*Anna*" in conditions (B) and (C) stopped further syntactic integration into the current first verb phrase and instead prepared an initial attachment of "*Anna*" to the second verb. This reversed parsing preference, triggered exclusively by prosodic information, successfully induced an initial misanalysis in the mismatch condition (C) and elicited an N400-P600 pattern of ERP components on the incompatible intransitive verb. We hypothesize that the N400 effect reflects a lexical re-access necessary to confirm the outright violation of the intransitive verb argument structure in (C). The P600, on the other hand, appears to indicate the subsequent structural revision concerning the attachment site of '*Anna*' as well as associated prosodic revisions.

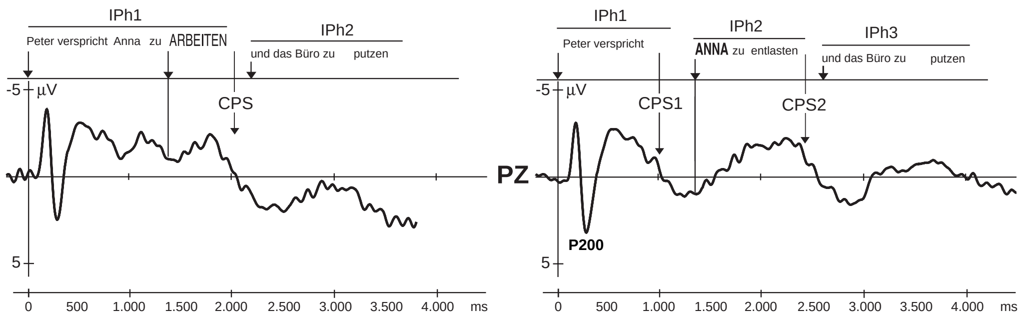

Figure 5. Grand average ERPs of both experiments (n=40) at the PZ electrode. The word onsets of the sentence examples are aligned to the time axis. Both conditions A (upper panel) and B (lower panel) display Closure Positive Shifts (CPS) at their respective IPh boundaries.

Don't blame it (all) on the pause: further ERP evidence for a prosody-induced 'garden-path' in running speech

3.1.10

Steinhauer, K.,
Alter, K. &
Friederici, A.D.

supported by DFG

An additional auditory ERP study was conducted in order to examine the processes underlying the *Closure Positive Shift* (CPS) at intonational phrase (IPh) boundaries in more detail. The German sentence material was adopted from our previous experiments (3.1.9).

(A)	[*Peter verspricht*	*Anna zu arbeiten*]$_{IPh1}$	[*und das Büro zu putzen*]$_{IPh2}$
	(Peter promises	Anna to work	and to clean the office)
(B")	[*Peter verspricht*]$_{IPh1}$	[*Anna zu entlasten*]$_{IPh2}$	[*und das Büro zu putzen*]$_{IPh3}$
	(Peter promises	to support Anna	and to clean the office)
(C")	*[*Peter verspricht*]IPh1	[*Anna zu arbeiten*]IPh2	[*und das Büro zu putzen*]IPh3
	(Peter promises	to work Anna	and to clean the office)

Sentence (A) consists only of two IPhs as opposed to three IPhs in (B) and (C). The additional IPh boundary in (B) and (C) was prosodically realized by a pause insertion before *"Anna"* ($p<0.0001$), as well as by a significant lengthening of the first constituent, i.e. *"Peter verspricht"* ($p<0.0001$). Furthermore, whereas a major accent occurs on the verb *"arbeiten"* in (A), accentuation is shifted to the noun phrase *"Anna"* in (B) ($p<0.0001$).

An important question is whether the CPS actually reflects prosodic phrasing or whether it is more directly related to the acoustic properties marking the IPh boundary. Since in written sentences terminal words preceding a pause are also associated with positive

ERP components (e.g. van Petten & Kutas, 1991), the most likely candidate for such direct correspondence was the pause insertion in (B) and (C) before *"Anna"*. Therefore in this study we carefully removed the entire pause in both conditions while preserving other intonational cues.

Both behavioral and ERP data for these conditions (B") and (C") confirmed that even without the pause the prosodic boundary was still perceived by the listeners (N=16) and still guided their initial parsing decisions (acceptability rates: 73.8% in B"; 10.9% in C"). Most importantly, we still observed the *Closure Positive Shift* (CPS) at the first boundary and also the N400-P600 pattern in condition (C"), as illustrated in Figure 6. These findings clearly support the notion that the CPS in fact reflects the processing of the boundary rather than the perception of a pause interrupting the speech input.

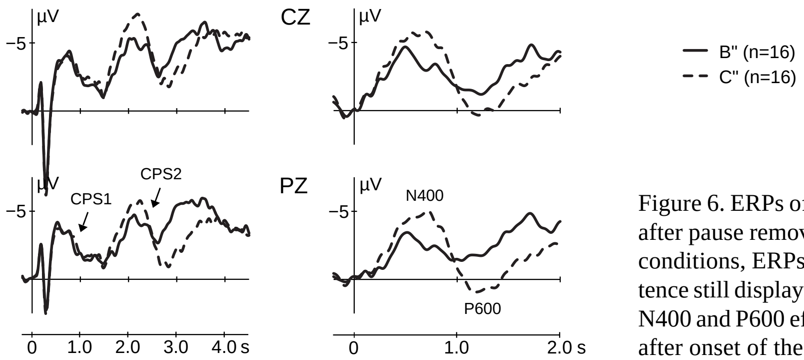

Figure 6. ERPs of conditions B" and C" after pause removal. Left panel: in both conditions, ERPs across the whole sentence still display two CPS. Right panel: N400 and P600 effects in condition (C") after onset of the critical second verb.

3.1.11 Are commas equivalent to prosodic boundaries in spoken language?

Steinhauer, K. & Alter, K.

supported by DFG

In previous experiments (Steinhauer et al., 1998; 3.1.9 and 3.1.10) we have demonstrated that prosodic boundaries in spoken sentences with different verb-argument structure are used to guide the listener's parsing. ERPs reflected both the processing of the prosodic boundaries (*Closure Positive Shift*, CPS) and the syntax-prosody mismatch (N400-P600). The same design has now been employed in the domain of written language using commas to mimic the prosodic cues for boundary marking.

(A) *Peter verspricht Anna zu arbeiten* *und das Büro zu putzen*
(Peter promises Anna to work and to clean the office)

(B) *Peter verspricht, Anna zu entlasten* *und das Büro zu putzen*
(Peter promises to support Anna and to clean the office)

(C) * *Peter verspricht, Anna zu arbeiten* *und das Büro zu putzen*
(Peter promises to work Anna and to clean the office)

(D) * *Peter verspricht Anna zu entlasten* *und das Büro zu putzen*
(Peter promises Anna to support and to clean the office)

As indicated by the performance data, commas in written language are almost as efficient as prosodic cues in spoken language.

The ERPs clearly demonstrate, however, that the underlying processing of boundaries in the visual modality (reflected by a negative slow wave) differs from that in the auditory modality (reflected by the CPS). This pattern furthermore confirms our assumption that the CPS is closely linked to prosodic rather than syntactic processing.

The larger P600 effect in the auditory modality suggests that the syntax-prosody mismatch was stronger than in the visual modality. This is compatible with our hypothesis that the P600 may reflect both structural and prosodic revisions.

3.1.10 De-accentuation: linguistic environments and prosodic realizations

Alter, K., Steinhauer, K. & Friederici, A.D.

It is generally maintained that prosody is an important determinant in speech processing. The term prosody is used here for both an abstract description of phonological properties of an utterance and their specific acoustic realizations.

We conducted a speech production study concerned with the prosodic realization of the syntactic and information structure in German. Exhaustive acoustic analyses of the speech data of seven uninstructed speakers were used to test the realizations of prosodic properties such as accentuation and intonation phrasing under different focus conditions.

The sentences had to be generated as answers to questions (Q/A-test) with either wide focus or narrow focus on the object (NP2) in a randomized order (n=30). All seven subjects were uninstructed with regard to the expected prosodic realizations. The speech corpus also contained filler sentences (30).

1. Wide focus

What happens?
(A1) *Peter* [*verspricht*]verb_1 *Anna zu* [*ARBEITEN*]verb_2
(Peter promises Anna to work)

What happens?
(B1) *Peter* [*verspricht*]verb_1 *ANNA zu* [*entlasten*]verb_2
(Peter promises to support Anna)

2. Narrow focus on NP2

TO WHOM does Peter promise to verb_2?
(A2) *Peter* [*verspricht*]verb_1 *ANNA zu* [*ARBEITEN*]verb_2 [intrans]
(Peter promises Anna to work)

WHO does Peter promise to verb_2?
(B2) *Peter* [*verspricht*]verb_1 *ANNA zu* [*entlasten*]verb_2[intrans]
(Peter promises to support Anna)

In (A2), the narrow focus of the question context requires the accentuation of the NP2 instead of the verb_2 which normally carries the accent with wide focus (cf. A1). Thus, the intransitive verb_2 in (A2) but not in (B2) becomes de-accentuated with narrow focus.

In (A2) the verb_1 is shorted and the NP2 'Anna' is lengthened. Two production strategies seem to be involved: (1) To reach the target - namely the narrowly focused constituent - as fast as possible and (2) to mark the prominence on NP2 by lengthening this constituent.
With respect to the de-accentuation from (A1) to (A2), we find the expected pitch pattern realized by different strategies:

(1) in (A2) the NP2 'Anna' is marked by a rising F0-contour, verb_2 is flattened
(2) rhythmical changes by producing early peaks in (A2) and reducing peak-to-peak distances between the sentence initial rise and the focused one
(3) pitch accent differences by a higher sentence onset pitch range in (A1) compared with (A2)
(4) producing a higher pitch range on NP2 in (A2).

3.1.13 Exploiting syntactic dependencies for German prosody: evidence from speech production and perception

Alter, K.[1], Matiasek, J.[2], Steinhauer, K.[1], Pirker, H.[2] & Friederici, A.D.[1]

[1]Max-Planck-Institute of Cognitive Neuroscience, [2]Department of Natural Language Understanding, Austrian Research Institute for Artificial Intelligence, Vienna

German syntax allows for verbal constructions with superficially similar surface structure but different prosodic patterns which are due to differences in the argument structure of the verbs involved. In order to help the listener to arrive at the correct argument attachment and to avoid garden-path effects the production of the correct prosodic structure in these cases is highly important. In our study, the speech signals of 48 temporarily ambiguous sentence pairs (Steinhauer et al. 1998) were analyzed exhaustively and the distinguishing prosodic parameters were identified. In cooperation with the Austrian Research Institute for Artificial Intelligence in Vienna we could show that the prosodic information was immediately decoded and used to guide initial parsing in 20 hearers. Based on the findings of this multidimensional analysis we propose a method to implement this kind of syntax-prosody mapping in a concept-to-speech system that realizes the involved prosodic cues.

In the speech production experiment we found a very strong correspondence between tone-accent placement and phrasing on the one hand and syntactic dependencies on the other. In the perception experiment employing neurophysiological measures the importance of these prosodic cues for auditive processing was verified.

Based on the experimental findings, a syntax-prosody mapping that realizes the essential prosodic cues has been incorporated into the Vienna concept-to-speech system. We showed that in a language generation system employing declarative resources and integrating syntactic and phonological processing this kind of syntax-prosody mapping brings a better speech synthesis quality.

3.1.14 Verb-argument structure processing: the influence of verb-specific and argument-specific constraints

Frisch, S. & Friederici, A.D.

So far, ERP research on verb-argument structure and subcategorization violations has not yielded a very homogeneous pattern of results. Rösler et al. (1993) reported a negativity at 400 ms post stimulus onset with a left anterior maximum, followed by a small late positivity. Osterhout et al. (1994) found an N400-like negativity at posterior electrodes, also followed by a late positivity. Hagoort et al. (1993), in contrast, did not find any component associated with verb subcategorization violations.

In two ERP studies, we investigated the time course of the integration of different types of verb-argument structure information. We compared (a) correct sentences with sentences with a violation of either (b) information about the *number* of arguments (two NP arguments but only one-place verb) or (c) information about the *form* of the object argument (case marking violations). Furthermore, we addressed the question of whether these processes are dependent on the availability of verb information prior to the NP arguments. We therefore varied the sequence of verb and NP arguments. That is, we realized both violation types in NP-NP-V (Experiment 1) as well as in V-NP-NP (Experiment 2) structures.

In Experiment 1 (NP-NP-V structures), ERP patterns on the critical word (verb) showed a biphasic pattern in both violation conditions compared to the correct condition: an N400 followed by a P600 in the number of arguments condition (b), and a more lateralized Left Anterior Negativity (LAN) followed by a P600 in the case marking violation condition (c). In Experiment 2 (V-NP-NP structures), the number of arguments condition (b) again showed a biphasic N400-P600 pattern on the critical item (second NP), whereas case marking violations (c) evoked a P600 only.

The finding that the LAN for case marking violations only occurred in NP-NP-V structures suggests that this component reflects an increased difficulty in integrating syntactic information from the lexicon (such as verb subcategorization information) into an ongoing sentence representation. This integration is only necessary in Experiment 1, where the verb has to fit into a sentence structure already built up (which, in this case, contains subject and object NP argument). If, however, the verb has already been processed in the prior context as in Experiment 2, then only a check between its lexical-syntactic information concerning the case marking of the arguments and the overt case marking of the incoming object NP is required.

3.1.15 Effects of overt case information on the processing of pronominal arguments

Jacobsen, Th.[1, 2] *& Friederici, A.D.*[2]

[1]*Department of Psychology, University of Leipzig,* [2]*Max-Planck-Institute of Cognitive Neuroscience*

Jacobsen (University of Leipzig) and Friederici continued their work on effects of case-marking. In contrast to English, morphological case is marked overtly in German. This event-related brain potential (ERP) experiment investigated effects of type of verb complement (accusative or dative) on the processing of overtly accusative or dative-marked personal pronouns. The verb, as the case assignor, preceded the personal pronoun which served as the object-NP, realizing a case-violation between the case required by the verb (accusative or dative) and the case marking on the pronoun in half of the sentences. The other half consisted of correct sentences. The following types of sentences were used.

(1) Accusative
Correct *Er wußte, sehen würde Nina* ihn *erst, wenn sie geht.*
(He knew, see would Nina him only, when she leaves.)

(2) Accusative
Incorrect **Er wußte, sehen würde Nina* ihm *erst, wenn sie geht.*
(He knew, see would Nina him only, when she leaves.)

(3) Dative
Correct *Er wußte, helfen würde Nina* ihm *erst, wenn sie geht.*
(He knew, help would Nina him only, when she leaves.)

(4) Dative
Incorrect **Er wußte, helfen würde Nina* ihn *erst, wenn sie geht.*
(He knew, help would Nina him only, when she leaves.)

A64-channel EEG was recorded while participants (N=16) read the 200 sentences in a word-by-word SVP setting at 500 ms a word in a fully counter-balanced design without fillers. Grammatical acceptability judgments were used to ensure sentence reading. The ERPs for the case-marked pronouns revealed effects of case violations. In contrast to the correct conditions, both syntactically incorrect conditions elicited more negative-going wave forms in the time window between 300 and 480 ms after stimulus onset, that were broadly distributed and non-lateralized. Violations of the accusative, linguistically labelled *structural case*, resulted in a larger negativity at frontal sites than the dative, linguistically labelled *inherent case*. There was no reliable P600 observed. Current linguistic theories hold that inherent cases are semantically interpretable whereas structural cases are not. The distributional difference between the two linguistically distinct violation conditions could indicate that different neural substrates are involved.

3.1.16 Processing of verbs: ERP-studies with separable complex verbs

Urban, S. & Friederici, A.D.

When a word is perceived in a sentential context several types of information have to be accessed in a mental lexicon. With reference to verbs, these types have been described as follows: verbal category, subcategorization frame, predicate argument structure and verb argument structure. The question remains as to whether all these theoretically separable parts of information are encoded as mental representations (i.e. as entries added to a verb) or whether the language processor (parser) uses the informational types of the verb in a serial order.

As a first step towards this representational and processing issue we dissociate verbs which can be used either intransitively (1) (e.g. *er lächelte)* or as Separable Complex Verbs (1) (e.g. *Er lächelte ... an*), from those which are either obligatory transitive (3) or intransitive (2) and (4).

1) *Er lächelte den Arbeiter an und ... /* He smiles the worker at and ...

2) * *Sie lebte den Bauherrn an und ... /* She lived the constructor at and ...

3) *Er alarmierte den Detektiv und ... /* He alarmed the detective and ...

4) * *Er zeltete den Wald und ... /* He camped the forest and ...

With the help of the on-line measurement of event-related brain potentials (ERPs) we tried to isolate the processing steps which occur when the system encounters these different verb types. Two questions concerning the incrementality of the comprehension process are considered in the present study. First, at which point in time during sentence processing does the system assess the verbal information concerning transitivity? Second, does the parser immediately assign an initial structure when encountering a verb even if it is ambiguous (intransitive/transitive) or is it open for a possible transitive interpretation? If the parser assigns an intransitive reading as an initial structure when encountering the verb (*lächelte*) a revision would be necessary at the particle (*an*).

In an ERP-experiment participants were asked to give a grammaticality judgment after having read the sentences in a word-by-word manner. The resultant ERP-pattern for sentence type (1) was dominated by a P300 like component followed by a P600 at the position where the particle appeared. A similar P300-P600 pattern has been observed at the point of disambiguation for sentences containing a temporal syntactic ambiguity and has been interpreted as reflecting two steps in a revision process, diagnosis and reanalysis (Friederici, 1998). The present ERP pattern may be a reflection of these processes triggered by the particle.

Working memory and processing of semantically ambiguous words: inhibition or activation?

3.1.17

Gunter, Th.C., Wagner, S. & Friederici, A.D.

Some recent studies in psycholinguistics show evidence for a strong interaction between working memory (WM) and language processing. There is, however, a discussion about the underlying mechanisms used in working memory. Some behavioral experiments lend support to a model assuming an activation mechanism (activation of relevant information, Miyake et al., 1994), whereas others indicate an inhibition mechanism (suppression of irrelevant information at the lexical level, Gernsbacher & Faust, 1991, and at the syntactic level; Friederici et al., 1998). This study was designed to disentangle this issue by measuring ERPs during the processing of sentences containing an ambiguous word. Particular differences between high and low span subjects (as measured by the Daneman & Carpenter reading span test) are of importance.

32 subjects read German sentences (10 words long) containing an ambiguous word at the second position, followed by a nominal predisambiguation at 5th and final disambiguation per verb at 6th position. Presentation was word-by-word. After every sentence a probe detection followed. 88 experimental and 88 filler sentences each containing one ambiguous word were used. Semantic variation with respect to the different meanings of ambiguous words appeared as follows:

A. *Der Ton wurde vom Sänger gesungen, als* ... (The note was by the singer sung, when ...)
—> dominant predisambiguation, dominant disambiguation

B. *Der Ton wurde vom Töpfer gebrannt, weil* ... (The clay was by the potter glazed, because...)
—> subordinated predisambiguation, subordinated disambiguation

C. *Der Ton wurde vom Sänger gebrannt, obwohl* ... (The clay was by the singer glazed, although ...)
—> dominant predisambiguation, subordinated disambiguation

D. *Der Ton wurde vom Töpfer gesungen, während* ... (The note was by the potter sung, while ...)
—> subordinated predisambiguation, dominant disambiguation

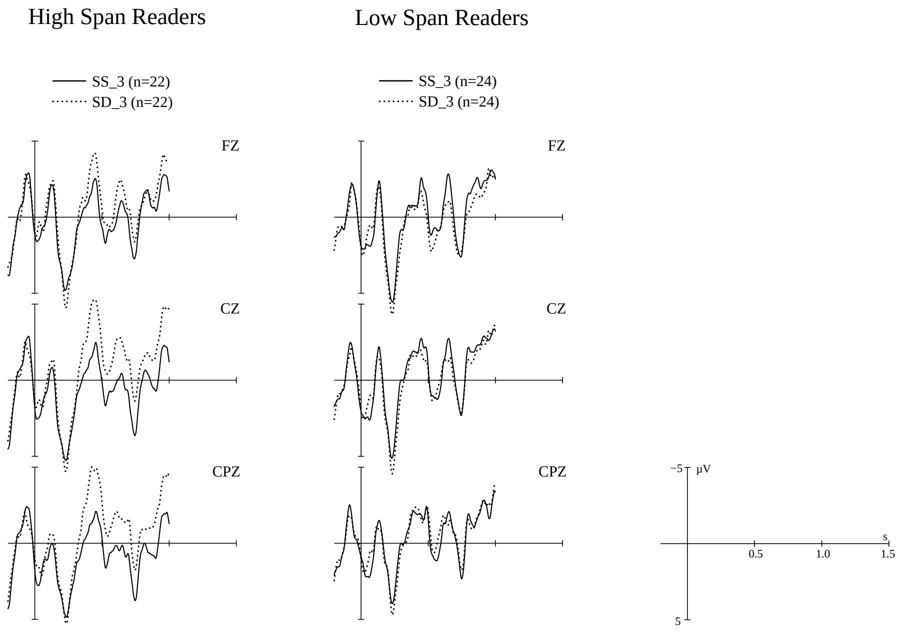

Figure 7. Switch from subordinated to dominant for high and low reading span subjects

There was a slight difference between high and low span readers in processing the noun at the 5th position. High span readers showed a bigger N400 component for the subordinated meaning than low span readers. This indicates that the subordinate meaning is inhibited to a larger extent in the high span subjects. In instances where there was a switch from the subordinate to the dominant meaning between 5th and 6th positions in the sentence (see figures) it was found that subjects with high WM-capacity suppressed the irrelevant meaning very quickly, whereas subjects with a smaller WM-capacity had difficulties in inhibiting the dominant meaning. The results seem to support the inhibition model.

3.1.18 Processing compounds with a semantically ambiguous first component: an ERP-study

Wagner, S. & Gunter, Th.C.

In German, it is possible to generate millions of compound words. Every noun can be combined with any other noun as long as there is no semantic mismatch. Which mechanisms underlie the processing of German compounds? How does lexical access of these words function? Ambiguous words can help shed light on these issues. Swinney et al. (1976) suggests that an ambiguous word activates all its meanings for several hundred milliseconds after access. Facilitatory priming effects should therefore be measurable within a small time-window after lexical access. When a compound word with two parts starts with an ambiguous part, and such a compound is accessed in two stages, one would expect that at least directly after the processing of the first (ambiguous) part, both meanings of that part are present in semantic memory. Since semantic decomposition of an ambiguous part is finished at the end of the compound, one should not expect to find facilitation or N400 effects at that point for the irrelevant meaning.

Sixty two-part German compound words were used. The first part was an ambiguous word whereas the second part disambiguated the first one as used in the subordinated meaning. (i.e. '*Ballkleid*', Ball-dress, note that a disambiguation towards the dominant meaning would arise in the word '*Ballspiel*' [ball game]). These compounds were presented in a cross-modal-priming-paradigm as primes. Targets were presented visually and were either related to the dominant meaning of the ambiguous component or unrelated to either the compound or its parts. For each target, the subjects had to make a lexical decision. In a first session, the targets were presented at the end of the first part (i.e. in the middle of the compound word). In a second session the targets were presented at the end of the compound. 35 subjects were examined per session.

Both sessions showed a behavioral priming effect. The ERPs measured during the lexical decision showed an clear N400-effect (the targets related to the dominant meaning evoked a smaller N400 than unrelated targets) in the first session whereas no ERP-differences were found in the second session.

These findings give strong evidence for a decomposition-parsing-mechanism for non-phrasal or idiomatic compounds. They also suggest that behavioral and ERP-data reflect different processes. Whereas the RT-results indicate that the dominant meaning of the ambiguous word is active in working memory at both measuring points, the ERP-data show that during the disambiguation the irrelevant meaning has probably been inhibited.

3.1.19 Semantic representation and processing of German compounds: a RT study

Isel, F., Gunter, Th.C. & Friederici, A.D.

The present study examined the nature of semantic representations for disyllabic German compounds which contain two morphemes. The question we addressed was whether compounds have their own representation in the mental lexicon, or if they can be accessed through the entry for their initial or for their final constituents. Two experiments were run using the cross-modal (auditory-visual) semantic priming paradigm.

Experiment 1 was designed to study the level of activation of the first morpheme. Measures of reaction times were realized at the acoustic offset of compounds. Four categories of compounds were used: (1) Fully transparent "T-T" (each morpheme was semantically related to the compound: "*Weinglas*"), (2) Fully opaque "O-O" (no semantic relation between the morphemes and the compound: "*Luftschloss*"), (3) Partially opaque "T-O" (only the first morpheme was semantically related to the compound: "*Geldwäsche*"), and (4) Partially opaque "O-T" (only the second morpheme presented a semantic link with the compound: "*Flohmarkt*").

Results showed a facilitatory priming effect for the transparent morphemes of fully transparent compounds (20 ms) and for the opaque morphemes of partially opaque compounds (12 ms). The facilitation observed for the processing of the opaque morphemes was not expected. The absence of any facilitation for the processing of the first transparent morphemes contained in partially opaque compounds suggested that the residual activation found for the transparent morphemes of fully transparent compounds was due to the propagation of activation between the compound and the first morpheme and between the second morpheme and the first morpheme.

Experiment 1: Mean lexical decision times (ms)

	T-T	O-O	O-T	T-O
Related	485	486	487	483
Unrelated	505	486	499	487
Priming eff.	+ 20*	0	+ 12**	+ 4

* p< .0001; ** p< .01

Experiment 2: Mean lexical decision times (ms)

	T-T	O-O	O-T	T-O
Related	499	503	496	499
Unrelated	510	501	496	502
Priming eff.	+11	- 2	0	+ 3

Experiment 2 was aimed at studying the level of activation of the first morpheme when the propagation of activation was diminished. In order to decrease a potential propagation of activation, the visual targets appeared at the acoustic offset of the first morpheme.

No significant facilitation of the first morpheme was apparent. These results suggest that at the acoustic offset of the first morpheme the semantic form of this morpheme was not sufficiently activated to trigger a recognition process. Moreover, they confirm that the facilitation observed in Experiment 1 was essentially due to propagation of an activation between semantically related nodes.

Taken together, our results suggest that the German compounds are probably not decomposed in order to be accessed. Unlike the prefixes in prefixed words, the first morphemes of German compounds are not extracted to allow the isolation of "head" which could serve as access code to the compounds.

Comparing semantic and repetition word list priming: an event-related potential study

3.1.20

Kotz, S.A.

Previous ERP priming studies have associated the effect of semantic and repetition priming with an attenuation of the N400 amplitude (Kotz, 1998; Kotz, et al., 1992). The current experiment examined whether priming as a function of word type (associative vs. semantic) and repetition priming tap into the same underlying processing mechanisms. This should be reflected in either an additive or interactive N400 effect.

ERPs were recorded from seventy-four electrode sites comparing auditory word list associative/semantic and repetition priming. In the first list, sixteen subjects listened to associatively and semantically related primes and targets (CAT-DOG vs. LOCK-CHAIN), unrelated primes and targets, and pseudowords. After a lag of twenty minutes the same subjects heard a second word list. While all target types from the first list were repeated, they were preceded by a 'reversed' prime type (e.g. a previously presented related or unrelated associative target was now a semantic target). In both tasks, subjects were asked to make a lexical decision about each word.

Two main results can be reported. First, in an initial word list presentation both associative and semantic word types elicit an N400 component (Figure 8). However, the strength, latency and distribution of the ERP priming effects differ. Second, the repetition priming effect dissociating old and new targets does vary as a function of word type (Figure 9).

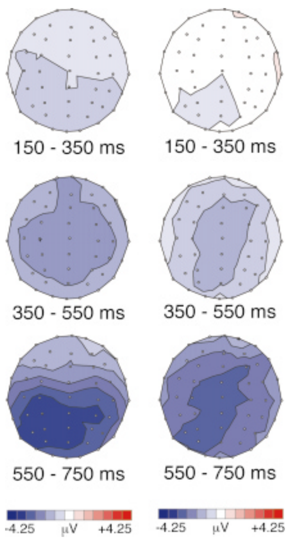

Figure 8.

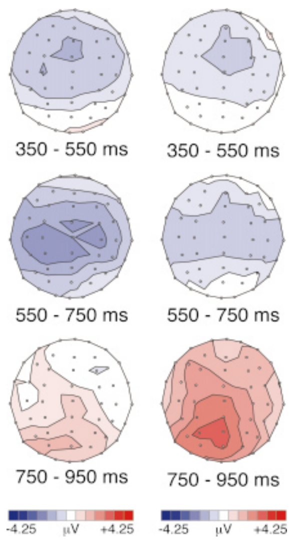

Figure 9.

In conclusion, it appears that in the first presentation priming paradigm the time course of activation differs between associative and semantic word types. Furthermore, the distributional differences of the N400 priming effect indicate that the underlying neural processes differ as a function of word type relation. The attenuation of the N400 component followed by a positivity in the repetition priming condition varied as a function of word type. This result suggests that 'partial repetition' of different word type relations is sensitive to specific contextual inter-item processing.

3.1.21 A dipole analysis of the N400 word type priming effect

Kotz, S.A. & Knösche, T.R.

There is sufficient evidence that the distribution of the N400 component in semantic paradigms varies as a function of modality and task. While these distribution differences speak for the possible existence of multiple generators of the N400, there is converging evidence from intracranial recordings (Nobre & McCarthy, 1995), lobectomy patients (Rugg et al., 1991) and PET studies (Martin et al., 1996) that one of the generators of the N400 lies in the anterior medial temporal lobe.

We set out to explore further whether distributional differences reflected in surface recordings of the N400 component are based on more than one generator. Utilizing the sequential word list priming paradigm we found distributional differences between the priming effects of word associations and purely categorical relations in both the visual and auditory modalities. While both word priming effects were found bilaterally at centro-parietal electrode sites, there was additional bilateral activation at frontal electrode sites for categorical relations. However, the effect was more enhanced at right frontal sites.

In order to qualify systematic differences between the associative and the categorical conditions, single fixed dipole fits were carried out in a time window of length 100 ms around the peak of the N400 component. Electrodes (72-setup) with obvious artifacts were excluded from the procedure. A spherical model of the head was employed to account for volume conductor effects. The positions and orientations of the dipoles were compared using the two-tailed paired t-test.

Comparing the visual and auditory modalities, no significant difference in the positions of the dipoles could be found. However, in the auditory modality the dipoles were tendentially pointing to the left hemisphere while in the visual modality they were oriented to the right hemisphere. This difference was significant ($p<.02$), but could also reflect a lateralization of the source position.

Comparing the associative and semantic conditions we found no differences in position or orientation in the auditory modality. However, there was an effect of position (anterior) in the visual semantic condition (18.5 mm, $p<.04$). Further analyses of the associative and semantic conditions in both modalities are currently underway.

Spatial selective attention and semantic categorization: an event-related potential study

3.1.22

Kotz, S.A. &
de Filippis, M.

Previous studies propose that the processing nature of the N400 in spatial selective attention and semantic priming reflects semantic integration. We explored further the effects of spatial selective attention on semantic categorization. In Experiment 1, ERPs were recorded from 32 electrode sites to words presented in the left and right visual field, while subjects maintained central eye fixation. 24 subjects responded to words with an underlined letter "e" in the attended visual field. In Experiment 2, subjects responded to animal names with an underlined letter "e" in the attended visual field. When no semantic categorization is required there should be no N400 effect, but a modulation of the P1-N1 complex in the attended visual field. When semantic categorization is required, there should be an enhanced P1-N1 complex followed by an N400 in the attended visual field.

In Experiment 1, we found an enhanced P1-N1 complex, but no N400 in the attended visual field. In Experiment 2, we found a P1-N1 effect followed by a frontocentral negative-going waveform 500 to 800 ms poststimulus onset in the attended visual field. Independent of the P1-N1 attention effect there was a centroparietal negative-going waveform (500-800 ms) in the unattended visual field. These preliminary results indicate that the focus of spatial attention can influence both the attended and unattended activation of the N400 component. This suggests that the activation of the N400 component can vary as a function of the relative spatial closeness or distance of the items in the attended and unattended visual field.

This research program examines memory systems and processes and their functional representation in the brain. In accordance with recent developments in memory research, memory is regarded as process specific. That is, memory performance is examined in terms of specified processes such as encoding, storage and retrieval. Furthermore, memory is considered to be comprised of multiple systems, such as working memory, semantic and episodic memory. Behavioral measures, electrophysiological measures (ERPs, gamma-band oscillations), measures of hemodynamic brain activation (fMRI) and neuropharmacological measures are used to examine memory-related brain activation patterns with a sufficiently high temporal and spatial resolution.

One major focus of this research program is on working memory, a brain system that enables temporary storage and manipulation of information necessary for the guidance of goal-directed behavior. Working memory can be separated into executive control processes that allow the coordination of lower level cognitive functions and content specific maintenance processes that enable storage of information. The ongoing research focuses on the functional characteristics and neuronal correlates of maintenance processes and executive processes of working memory. We examine the neuronal networks underlying the maintenance of object and spatial information (3.2.1) and of spatial and rhythmic information (3.2.2) by means of fMRI and event-related potential measures. One study (3.2.3) was designed to investigate the neuronal correlates of feature binding and their potential relevance for working memory maintenance processes. We furthermore try to specify the interaction of executive control and active maintenance processes in working memory using memory coordination (3.2.4, 3.2.5) and interference (3.2.6) as experimental paradigms.

Another research focus is on the neurocognitive systems underlying memory retrieval. Memories are considered as bound features comprising particular episodes that are distributed across different parts of the brain. We assume that memory retrieval is a constructive process by which features of a past experience are reactivated to form coherent representations of the past. To gain insight into these memory mechanisms and the underlying brain activation patterns we examine ERP correlates of object retrieval using incidental and intentional memory tasks (3.2.7, 3.2.8). Two other projects focus on the effects of encoding instructions (directed forgetting, depth of encoding) and on retrieval mechanisms using neuropharmacological and ERP measures (3.2.9, 3.2.10). The brain mechanisms underlying true and false recognition memory judgments are examined by ERPs and fMRI measures recorded in identical experiments (3.2.11, 3.2.12). A similar combined fMRI/ERP approach is used to obtain insights into frontal and temporal lobe contributions to deviancy and novelty processing in the auditory domain (3.2.13, 3.2.14). The lateralization of verbal memory processes in incidental memory tasks is examined by means of fMRI data in (3.2.15). Using depth electrode recordings in epileptic patients we try to specify the contribution of the hippocampus to feature binding processes (3.2.16). One project focuses on the temporal lobe mechanisms engaged in face processing (3.2.17).

3.2.1 Functional MRI evidence for domain specific visual working memory systems

Mecklinger, A.[1], Bosch, V.[1], Bentin, S.[2] & von Cramon, D.Y.[1]

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Neuroimaging studies in humans show that prefrontal, premotor and parietal cortical regions constitute a working memory network that supports the active retention of information. We used fMRI to examine the influence of information content and memory load on the neuroanatomical and functional characteristics of this network. Subjects performed a modified delayed matching-to-sample task that allowed the examination of content-specific retention processes, independently of perceptual and encoding processes. In Experiment 1, S1 consisted of two non-verbalizable abstract objects at two spatial locations in a simulated 3D space. Subjects had to decide if either object or spatial information of the S2 was the same as in S1 or not. The relevant type of information was indicated by a task cue presented in the S1-S2 interval. In a third control condition the cue indicated a memory-free perceptual task. Within the 4 s cue-S2 interval the hemodynamic response was measured. In Experiment 2, either three human faces or two butterflies were used as stimuli during a 6 s cue-S2 interval. Here, the cue indicated a memory or a perceptual task.

In both experiments, memory performance was statistically indistinguishable. The memory tasks activated similar cortical regions to those activated during control tasks. These areas included posterior parietal (banks of the intraparietal sulcus), premotor and prefrontal regions (banks of the inferior precentral and inferior frontal sulcus). The activation pattern was left lateralized for objects and faces and more bilateral, with a tendency to the right hemisphere for spatial locations. Furthermore, the frontal activation pattern for the non-verbalizable objects (Experiment 1) and the butterflies (Experiment 2) had a larger anterior extension along the inferior frontal sulcus than that for spatial locations and faces. Longer retention times (in Experiment 2) elicited a larger proportion of prefrontal and premotor activation, whereas the posterior parietal activation was not affected by retention duration.

Consistent with previous studies, these results indicate that working memory networks show content-specific hemispheric weightings when comparing object and spatial working memory. Moreover, the larger frontal activation pattern for abstract objects and butterflies suggests that these objects are retained within working memory in a different way. It is an open question whether this frontal effect is due to the type of information per se or rather is a function of different object characteristics.

In conclusion, the results suggest a functional segregation of the network components with posterior parietal areas being more involved in visuo-spatial processes of retention and the premotor/prefrontal regions being more concerned with mnemonic aspects of working memory.

3.2.2 Cortical timing functions investigated by event-related potentials (ERP) and functional magnetic resonance imaging (fMRI)

Schubotz, R., Friederici, A.D. & von Cramon, D.Y.

In the first study, ERPs were recorded during the presentation of several repetitions of a sequence of visual stimuli, which incorporated both a temporal rhythm and a spatial pattern. The subject was required to compare the stimuli with an initial rhythmic or spatial pattern set and to indicate either rhythmic or spatial deviants is a go/no-go response mode. A third task requiring the subjects to monitor for brief flickers at the onset of a new item presentation served as a perceptual baseline condition and controlled for attentional, preparatory and expectancy effects. Only no-go trials were used for signal analysis. As expected, rehearsal-related slow ERP activity was pronounced over frontal sites during monitoring of temporal structures, and over parietal sites during monitoring of spatial structures. Attentional and preparatory activity could be dissociated electrophysiologically from timing functions, which were recorded exclusively during the rhythm task and which were reflected by enhanced negative SPs over frontal sites. Thus, non-specific effects of attention and preparation reflected by CNV components in all tasks could be functionally dissociated from specific electrophysiological activity corresponding to mnemonic timing functions.

The second study set out to investigate cortical contributions to perceptual and mnemonic timing functions without including task related motor requirements. fMRI was used to scan 10 subjects while they monitored visual or auditory rhythms in a go/no-go paradigm. 6 gradient echo EPI images were obtained simultaneously from 10 axial slices (6 mm thickness, 2 mm spacing) for each trial using a 3 Tesla MRI scanner and event-related stimulus design. To rule out any motor response contribution only no-go trials were used for signal analysis. Significant BOLD activation was found for both presentation modalities bilaterally in the premotor cortex (including SMA) (1), the frontal operculum including Broca's area and the homologue on the right side (2), the ascending and descending branch of the intraparietal sulcus (IPS) (3), and the basal ganglia (4). These findings are consistent with the view that a queue of time-

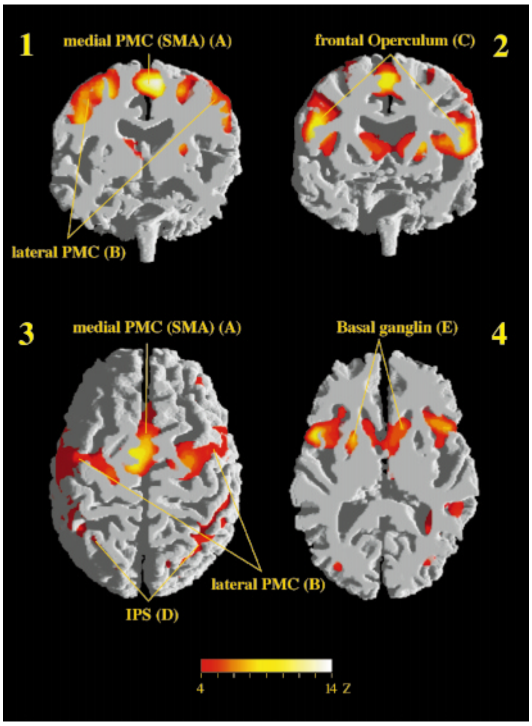

Figure 1.

ordered motor commands is formed in the medial premotor cortex before voluntary movements are executed via the primary motor area. The bilaterality of activation supports the view that the premotor activation does not reflect motoric effector recruitment, but a supramodal mnemonic representation of sequences that fit into a precise timing plan.

3.2.3 Gamma responses and ERPs in a visual classification task

Herrmann, C.S. & Mecklinger, A.

We examined event-related potentials (ERPs) and gamma range EEG activity in a visual classification task. Ten subjects counted silently the occurrence of rare Kanizsa squares (targets) among Kanizsa triangles and non-Kanizsa figures (standards). The stimuli are depicted in the left column of the figure below. By applying a time-frequency analysis to the data and selectively calculating topographical maps of certain frequencies, we were able to find three different types of gamma responses to Kanizsa figures: an early phase-locked gamma response at 40 Hz in the N100 time range, late phase-locked gamma activity (200-300 ms) at 40 Hz and a continuous phase-locked gamma response at 80 Hz due to the monitor refresh frequency. The two 40 Hz responses were significantly higher for Kanizsa figures than for non-Kanizsa figures and within the Kanizsa figures higher for the target figure than for the non-target. The phase-locking of these two responses, which had previously also been detected as non-phase-locked activity, may be attributed to the flicker frequency of the monitor.

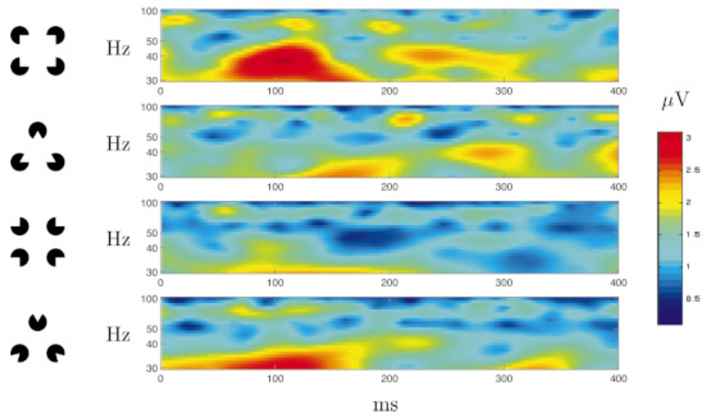

Figure 2. Average of the phase-locked time-frequency planes (WTAvs) for electrode FC4 over nine subjects.

Figure 2 shows the phase-locked time-frequency diagram for electrode FC4 over all subjects. Between 50 and 150 ms a phase-locked 40 Hz component is visible for the averaged Kanizsa square (early 40 Hz), between 200 and 300 ms another phase-locked 40 Hz component (late 40 Hz) emerges for both Kanizsa figures and spurious 80 Hz activity is intermittently present over the whole interval.

With these results, we were able to show that gamma activity is not only modulated by the binding process of illusory figures but also by the appearance of a target stimulus. In a future experiment we plan to investigate the changes in gamma activity when the task is altered to require the detection of one of the non-Kanizsa figures. According to our hypothesis, the early 40 Hz component should then be recorded for the non-Kanizsa target only.

3.2.4 Dissociating the neural correlates of working memory components: an fMRI study

Gruber, O., Bublak, P. & von Cramon, D.Y.

The concept of working memory describes complex operations which have been hypothesized to include distinct functional components such as temporary storage and executive processing of relevant information. Recent functional neuroimaging studies have revealed a widely distributed neural network subserving the performance of working memory tasks. However, in most of these studies the experimental conditions and statistical comparisons activated non-selectively brain regions participating in working memory. It was thus impossible to achieve an isolation of neural structures according to their relative functional contribution to different components of working memory.

In the present study, we varied the demands on some of these components, i.e. on storage, rehearsal and manipulation processes. Experiments incorporated: (1) a modified digit-ordering task demanding "online"-maintenance as well as manipulation of relevant information, (2) a result-matching phase requiring predominantly the maintenance component of working memory, (3) an appropriate forced-choice control condition which matched both activation conditions with respect to visual input and motor output processing. Seven healthy right-handed volunteers underwent functional magnetic resonance imaging (fMRI) at 3 Tesla (Bruker Medspec 30/100). Gradient echo-planar image series (repetition time = 2 s, echo time = 40 ms, flip angle = 90°, voxel size = 3x3x5 mm^3) were obtained in 16 slices covering the entire cerebrum.

When contrasting result-matching with the forced-choice control, averaged group analysis showed significantly increased brain activity right-accentuated in inferior frontal and posterior parietal areas which seemed to correspond to active maintenance processes. On the other hand, in direct comparison with result-matching, digit-ordering evoked strong activation left-lateralized in frontal, parietal and premotor regions as well as in the right cerebellum which appeared to be related to manipulation and rehearsal. These findings suggest that brain structures which subserve executive performance in general are dissociable by imposing different demands on more specific sub-processes of working memory. Moreover, in five of our volunteers the results of individual analyses support a "process-specific" model of lateral frontal lobe organization which predicts that whilst the ventrolateral prefrontal cortex subserves the "online"-maintenance of relevant information, the dorsolateral prefrontal cortex is involved in manipulation.

Future work will attempt to explain the observed lateralization effects and individual differences in brain activity, to dissociate additional constituents of executive processing (e.g., inhibitory control) and to assess the functional interactions among the physiological processes underlying working memory and executive functions.

3.2.5 Effects of propranolol and atenolol on executive functions in working memory

Mottweiler, E., Bublak, P. & Müller, U.

Beta-blockers are mainly used to treat hypertension and coronary heart disease. Different frequencies of central nervous system side-effects have been reported (McAinsh & Cruickshank 1990, Gleiter & Deckert 1996) and attributed to either liposolubility that facilitates crossing the blood-brain-barrier or β_1-selectivity (Table 1). Cognitive side-effects are especially critical in patients with stroke and persisting hypertension. The aim of this study was to assess the cognitive side-effects of beta-blockers with differing liposolubility on executive functions in working memory.

Substance	lipophilicity (distribution coefficient)	brain / plasma -ratio	t_{max} [hours]	elimination $t_{1/2}$ [hours]	β_1 / β_2-ratio
Atenolol	0.015	0.2	3	6-10	1.7
Propranolol	20.2	26.0	1.5	3-4	0.3

Table 1**.** Pharmacological characteristics of atenolol and propranolol (from Cruickshank & Prichard 1988).

The effects of two beta-blockers, atenolol 50 mg (hydrophilic) or propranolol 25 mg (high liposolubility), and placebo administered to young healthy volunteers (n=16 per drug condition, age 19-27) in a randomized double-blind design were compared. The task (3.3.7) consists of a memory coordination task that requires short-term maintenance and differing degrees of manipulation of a digit list for guiding a sequence of simple actions (2AFC-responses).

Between subjects repeated measures ANOVAs with the factors drug (2) and manipulation (3) revealed significant increases of reaction time (RT) with increasing executive demand (main effect manipulation: $p<0.001$). There were no significant drug effects on errors. There was, however, a marginally significant slowing of execution time with increasing manipulation after propranolol administration (interaction manipulation x drug: $F_{1,30}=3.36$; $p=0.077$) but not after atenolol administration ($F_{1,30}=0.21$; $p=0.647$) (Figure 3). The manipulation costs were significantly lower after propranolol than for placebo ($t_{30}= -1.83$, $p<0.05$). The drug-induced decreases in heart rate and blood pressure were significant after both atenolol ($p<0.001$ and $p<0.003$, respectively) and propranolol ($p<0.05$ and $p<0.03$, respectively) as compared to placebo. There were no significant drug effects on paper-pencil tests of attention (d2, ZVT) or in the mood questionnaires (STAI-X1, Bf-S).

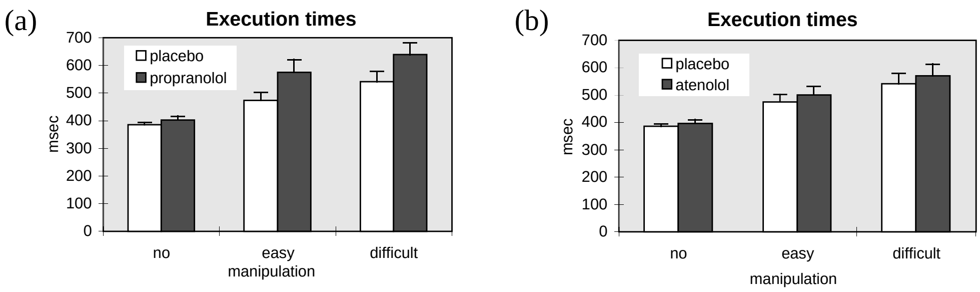

Figure 3. Effects of propranolol (a) and atenolol (b) on execution time as compared to placebo.

These results support our hypothesis that executive functions in working memory are affected by propranolol (lipophilic) but not by atenolol (hydrophilic). Since both beta-blockers induced a slowing of heart rate and a decline of blood pressure, peripheral effects do not explain the divergent cognitive effects. We conclude that the observed effect on working memory is due to the higher liposolubility of propranolol presumably mediated via cortical beta-receptors.

Interference-control in visual working memory

3.2.6

Ungerer, K., Mecklinger, A. & Bublak, P.

According to Baddeley working memory is comprised of two types of processes: active maintenance and executive control. One function of executive control is to select task-relevant information and to inhibit task-irrelevant information (interference-control). Evidence for reduced ability to inhibit irrelevant information was obtained in populations such as elderly people (Chao & Knight, 1997) and schizophrenic patients (Beech et al., 1989). These results are in agreement with the assumption that efficient inhibitory processes require intact prefrontal functions.

In a series of experiments we examined the mechanisms of interference-control in young and healthy adults with a modified visual S1-S2-paradigm. Hierarchical structured stimuli (c.f. Walker et al., 1993) divisible into four categories and with two relevant features (upper and lower part) were used. Three interference stimuli, which were presented in the retention phase between S1 and S2, consisted either of an unstructured point pattern (*m* - mask), or of stimuli from different (*d*) or the same (*s*) categories compared to S1. Potential inhibitory mechanisms were investigated by ignored repetition trials (*IR*) where one interference stimulus was also presented as S2.

Error rates were lowest in the mask condition, but shortest reaction times were obtained for condition *s*. *IR* trials showed higher error rates than in the control conditions in which S2 had not previously been presented as an interference stimulus.

The higher error rates in *IR* trials suggest a contribution of episodic memory retrieval rather than inhibitory mechanisms to processing of interference stimuli (Neill & Valdez, 1992). Presumably the two relevant stimulus features are processed actively and separately. Identical features appearing in both S1 and interference stimuli enhance memorization of the feature whereas similiar but non-identical features disturb the retention process. Figure 4 illustrates this model by an example of condition *d* with *IR*-manipulation: the upper similiar feature weakens and the lower identical feature strengthens the representation of S1 in memory. In this framework false positive answers might have occurred because of a diffuse representation of the upper feature (difference of S1 and S2) and a clear representation of the lower feature (identitiy of S1 and S2) leading to higher error rates in *IR* trials. The assumption of active processing of interference stimuli agrees with neurophysiological studies by Miller et al. (1996) in which single cell recordings revealed repetition mechanisms in infero-temporal neurons whereas neurons of the prefrontal cortex were involved in the processing of interference stimuli related to task-relevant behavior.

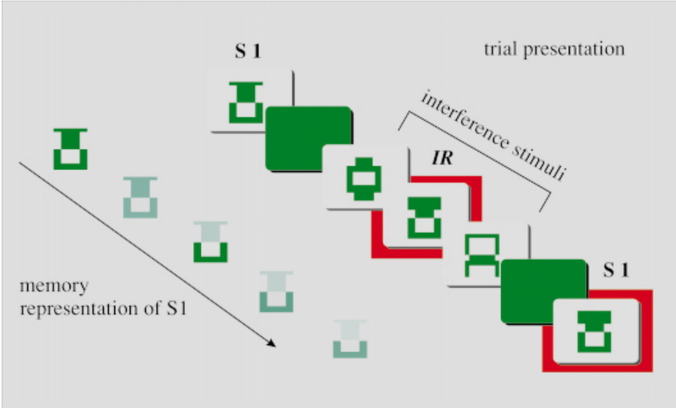

Figure 4. An example of condition d with IR-manipulation. The stimuli presented on the screen are presented in the upper row, the lower row illustrates the presumed representation of S1 in memory. This representation changes by watching the interference stimuli leading to a false positive answer.

3.2.7 The effect of encoding and retrieval conditions on object representation: evidence from ERPs

Penney, T.B.[1], Mecklinger, A.[1], Hilton, H.J.[2] & Cooper, L.A.[2]

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In a series of experiments we recorded ERP responses to studied and non-studied line drawings of possible and impossible 3D objects under conditions of incidental (Experiments 1 & 2) or intentional encoding (Experiment 3) and incidental or intentional retrieval. The incidental retrieval task was an object decision task in which subjects indicated whether a briefly presented (50 ms) object could exist as a 3D object in the real world (possible vs. impossible judgment) and the intentional retrieval task was an old/new recognition task.

The encoding task emphasized structural features in Experiment 1 and semantic features in Experiment 2. In both the object decision and the recognition tasks in Experiment 1, the studied possible objects evoked more positive going waveforms than the non-studied possible objects. This positive difference was localized more frontally and was earlier in the recognition task than in the decision task. There were no ERP differences between studied and non-studied impossible objects, in spite of a significant effect of study on behavior. Although in Experiment 2 behavioral performance in the object decision task for the possible objects was equivalent to that in Experiment 1, there was no ERP effect. In addition, there was no behavioral or ERP effect for the impossible objects in the object decision task. In the object recognition task there was a frontally localized old/new effect for the possible objects, but no effect for the impossible objects.

In Experiment 3, subjects were explicitly told to remember each possible and impossible object and a series of encoding - test blocks were used to reduce memory load relative to Experiments 1 and 2. Recognition memory performance was substantially better than in Experiments 1 and 2 and there was a frontally localized old/new ERP effect for both the possible and the impossible objects.

The ERP results from the object decision task support a model of object representation which claims that the brain encodes global structural descriptions of objects only when structural features are emphasized at encoding. Hence, we obtained an ERP repetition effect for the possible objects in Experiment 1 but not Experiment 2. There is no repetition effect for the impossible objects because their structure can not be encoded globally. The frontal effect in the recognition tasks probably reflects a facilitation of search in episodic memory. The fact that the recognition effect was present for both types of object following intentional encoding but only for possible objects following incidental encoding suggests that this effect can be strategically modulated.

3.2.8 Possible and impossible objects evoke frontal and parietal ERP differences in an immediate repetition paradigm

Penney, T.B., Mecklinger, A. & Neßler, D.

ERP waveforms to repeated words, faces and objects are more positive than first presentations, but there is no such difference for orthographically illegal non-words, scrambled faces, and nonsense patterns. We examined ERPs to initial and repeated presentations of line drawings of structurally possible and impossible objects in a target detection task. In Experiment 1, the non-target objects were possible and impossible geometric figures and the targets were real-world objects or combinations of parts of real-world objects. In Experiment 2, the non-target objects were real-world objects and the targets were geometric figures.

At frontal sites the repeated possible and impossible non-target items, in both experiments, evoked a more positive ERP waveform (250-350 ms) than did first presentations. In contrast, at parietal sites the repeated non-target items, in both experiments, evoked a more negative ERP waveform (300-600 ms) than did first presentations. The topographic distribution of this parietal repetition effect was different from the target P300 effect.

The brief frontal positivity to repeated items may reflect a facilitation of conceptual or lexical access during object categorization. The polarity of the parietal repetition effect was the reverse of what is usually found with stimulus repetition, although it is consistent with some earlier work using visual stimuli. It may reflect a facilitation of a perceptual representation or activation of an episodic memory trace.

3.2.9 Dopaminergic modulation of intentional forgetting

Müller, U., Mecklinger, A. & Ullsperger, M.

The catecholaminergic modulation of prefrontal cognitive functions has been comprehensively investigated in monkeys over the last two decades (Brozoski et al. 1979; Arnsten, 1998) but so far only preliminarily in humans. There is now converging evidence that working memory is regulated via cortical dopamine (mainly D1) and noradrenaline (mainly a2) receptors. Recent evidence from monkey (Lidow et al., 1998) and human research (Kimberg et al., 1997) indicates an inverted U-shaped relationship between working memory performance and prefrontal levels of dopamine and noradrenaline. To investigate the dopaminergic modulation of intentional forgetting and retrieval processes, presumably mediated by the prefrontal cortex (3.2.10), we used a modified version of the item method directed forgetting (DF) paradigm (Zacks et al. 1996).

A total of 32 healthy volunteers (mean age 23.6 years) participated in this experiment, which had been approved by the regional ethical committee. Each subject received either placebo or 0.1 mg of pergolide, a dopamine agonist, on two separate test days. Half of the subjects were pretreated with 300 mg of sulpiride, a centrally active dopamine antagonist. The other half received only domperidone, a peripherally active dopamine antagonist. The DF paradigm was performed as previously described (Annual Report 1997, pp. 52-54) with 6 blocks of 30 categorically ordered words, presented consecutively on a PC screen. After a 2.5 s delay half of the words were cued as to-be-remembered (TBR) and the other half as to-be-forgotten (TBF). There was an immediate recall at the end of each block and a final recognition task requiring "old/new" and "recollect/know" decisions.

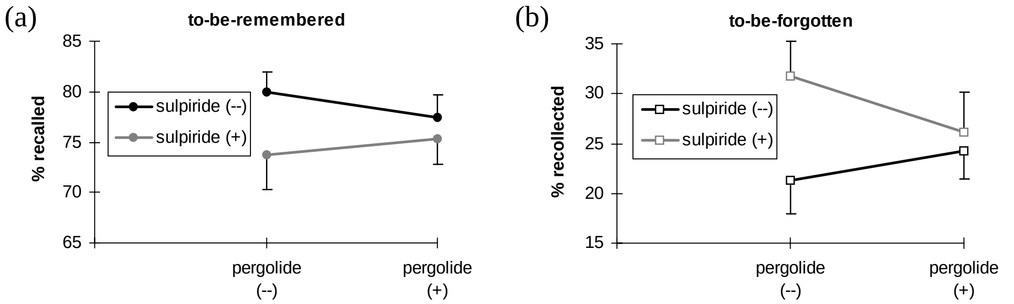

Figure 5. effects of sulpiride (dopamine antagonist) and pergolide (dopamine agonist) on immediate recall and recollection rates in the directed forgetting paradigm.

The main pharmacological finding was a significant interaction between sulpiride (DA antagonist) pretreatment and pergolide (DA agonist) treatment (F=4.78; p=0.03) for the efficacy of intentional forgetting (Figure 5). The performance of the pretreated group improved (more efficient forgetting as indicated by lower recollection rates) and that of the group without sulpiride pretreatment deteriorated (better recollection of TBF items) after pergolide as predicted by the inverted U-shaped model (Figure 6).

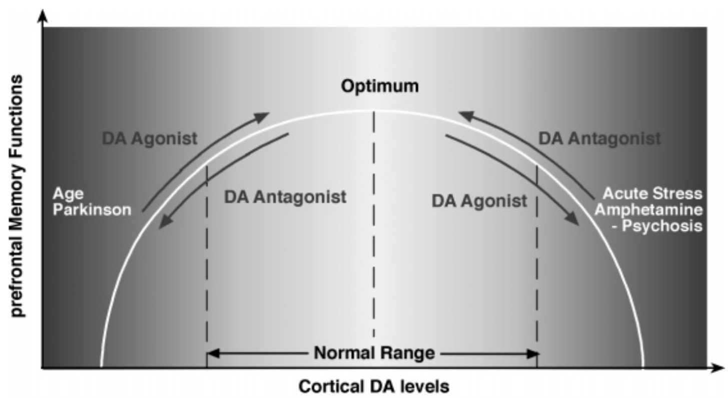

Figure 6. Effects of dopamine (DA) agonists and antagonists on prefrontal memory functions (modified from Lidow et al., 1998).

This is the first pharmacological study in healthy volunteers that corroborates previous findings in monkeys of a bi-directional dopaminergic modulation of prefrontal memory processes in humans using an antagonist/agonist design. Optimal cortical dopamine levels seem to be necessary for optimal cognitive functioning, under- and overstimulation of cortical dopamine receptors will impair cognitive functioning. Further studies must address the topological and receptor specificities of dopamine actions in distinct cortical and subcortical areas.

3.2.10 An electrophysiological test of directed forgetting: differential encoding or retrieval inhibition?

Ullsperger, M., Mecklinger, A. & Müller, U.

In recent years several behavioral and pharmacological studies using a directed forgetting paradigm have been performed at our institute. In the present study we used event-related potentials (ERPs) to examine electrophysiological correlates of directed forgetting. In particular we addressed the question of whether differential memory performance for items that have to be forgotten and items that have to be remembered is due to differential encoding or to retrieval inhibition of ‘forget items’.

In Experiment 1 subjects were presented with semantically categorized word lists. By means of a cue shown after each word subjects were instructed either to remember or to forget the item. In a subsequent delayed recognition test ERPs were recorded from 61 scalp sites.

Recognition performance was significantly lower for ‘forget’ than for ‘remember’ words (directed forgetting effect). ERPs revealed phasic frontal and parietal positive-going old/new effects for remember items (TBR), whereas forget items (TBF) elicited only a frontal old/new effect. Moreover, both item types evoked a late right frontal positive slow wave being more pronounced for forget items, suggesting that these items are associated with a larger amount of post-retrieval processing (Figure 7).

In Experiment 2 we examined whether or not the same retrieval-related ERP pattern as in Experiment 1 can be obtained by a deep vs. shallow encoding instruction. The same single word cueing method and the same stimulus material were used and memory encoding was manipulated by cueing subjects to process the words either deeply or shallowly. Similar retrieval-related activity in Experiments 1 and 2 would support the differential encoding model of directed forgetting.

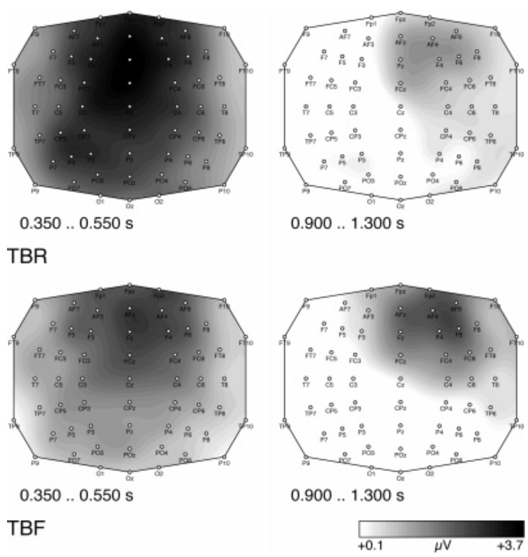

Figure 7. Spherical spline maps illustrating the scalp topography of the differences between ERPs to recognized and new items. Upper row: to-be-remembered, lower row: to-be-forgotten words.

Recognition performance was significantly lower for shallowly than for deeply encoded items. Both deeply and shallowly encoded words elicited phasic frontal and parietal old/new effects followed by a right frontal positive slow wave. However, in contrast to remember and forget items these effects differed only quantitatively, i.e. the amplitudes of the early frontal and parietal old/new effects were smaller for shallowly encoded words. Importantly, the right frontal positive wave was not more pronounced for items which had undergone shallow encoding (Table 2).

Taken together, these results suggest that differential depth of encoding alone cannot account for the effects of directed forgetting. They are more consistent with the view that items followed by an instruction to forget become inhibited and less accessible, and thus are more difficult to retrieve. Particularly the increase of the late right frontal positivity for recognized forget words might reflect an electrophysiological correlate of the larger amount of post-retrieval processing necessary to 'overcome' the inhibition of those items.

	directed forgetting			levels of processing		
	to-be-remembered		to-be-forgotten	deeply encoded		shallowly encoded
early midfrontal effect	++	>	+	++	>	+
parietal effect	++	>>	0	++	>	+
late right frontal effect	**+**	<	**++**	**++**	≥	**+(+)**

Table 2. Patterns of mean differences of ERP amplitudes elicited by recognized and new items (old/new effects) in both experiments (+/++: positive/highly positive old/new effect, 0: no old/new effect)

3.2.11 Remembering events that never happened: dissociable ERP response for true and false recognition memory

Neßler, D., Mecklinger, A. & Penney, T.B.

The examination of false memories can provide insights into the cognitive and neuronal aspects of memory retrieval. Although historically this approach was rarely considered in memory research, there are now many psychological studies of memory illusions. However, so far only a few ERP studies on false memories have been conducted. Some of them used the Deese-paradigm, in which subjects made old/new decisions about previously studied words (old), semantically related but nonstudied words (lures) and other nonstudied words (new). These studies failed to show any differences between the ERPs to randomly presented old words (hits) and lures. These results must be interpreted with caution because semantic associations between old words and lures were not bidirectionally symmetric. In another study (Rubin et al., in press), in which lures were recombinations of studied syllables, false alarms to lures elicited different ERP responses from those corresponding to hits.

We examined ERP responses to randomly intermixed old words, new words and lures in a list learning paradigm. In the study phase we presented words from different categories (e.g. furniture, fruits), which were used as old words in the test phase. Lures were drawn from the same semantic categories, whereas new words had no associations to studied words.

In the first experiment, old responses to lures were slower than old responses to old words and new responses to new words. The false alarm rate to lures was 30%. ERP responses to old words were more positive than to new words between 400 and 700 ms at frontal and at parietal sites. Interestingly no such old/new effects were obtained for lures, which were not distinguishable from correctly classified new words in this early time interval. In a later time interval (800-1600 ms), however, old words as well as lures evoked right frontal positive slow waves relative to new words, an effect which previous studies have attributed to post-retrieval monitoring processes. Though the absence of old/new effects to lures in the 400 to 700 ms time range suggests that no episodic retrieval takes place, these words are nevertheless subject to post-retrieval processes such as the recovery of context information from the study episode. Between 400 and 600 ms at frontal sites, correctly rejected lures elicit more negative going waveforms than false alarms to lures, presumably reflecting the successful classification of semantically related words.

Frontal lobe contribution to veridical and false recognition memory judgments — 3.2.12

Mecklinger, A., Neßler, D., Penney, T.B. & von Cramon, D.Y.

Functional neuroimaging studies have shown that the prefrontal cortex, predominantly on the right side, and the medial temporal lobes play an important role when information is retrieved from episodic memory. However, most previous PET and fMRI studies of memory retrieval have been limited by the requirement to test different item types in different blocks. Here we used event-related fMRI to examine brain activation during true recognition of previously studied words and false recognition of semantic associates. In a list learning paradigm subjects listened to 150 words from different semantic categories. The subsequent test phase had interstimulus intervals of 6.75 s and the subjects saw randomly intermixed studied words, new words and semantic associates of the studied words (lures). During the test phase echo planar images were acquired from 16 axial slices (TE=40 ms; TR=2.25 s). The false alarm rate to lures was 30% and thus considerably higher than the base false alarm rate of 9%. Response times were larger for lures than for correct old and new responses. Relative to new words correctly recognized old words activated the middle frontal gyrus and the nucleus accumbens in the basal forebrain. Subjects with low hit rates did not show basal forebrain activation to hits but rather activations along the banks of the cingulate sulcus. Lures activated the banks of the cingulate sulcus and correctly classified new words were accompanied by left prefrontal cortex activation. These results provide evidence for dissociable prefrontal brain activity for correct and false recognition. They also support the prominent role of prefrontal brain regions and possibly also the basal forebrain in recollecting old information. The cortex along the cingulate sulcus may play a role in discrimination processes requiring effort.

3.2.13 The functional neuroanatomy of auditory deviancy and novelty processing: integrating ERP and fMRI results

Opitz, B., Mecklinger. A., Friederici, A.D. & von Cramon, D.Y.

We continued our work on identifying the neural mechanisms underlying processing of deviant and novel auditory information. The ERP approach is necessarily approximate in identifying functionally relevant brain regions, because neural sources can only be estimated from the two-dimensional scalp topography using inverse methods like dipole modelling. Conversely, neuroimaging methods, despite their capability of localizing brain structures underlying cognitive functions with high spatial resolution, do not in most cases provide the adequate temporal resolution to make inferences about the processes that operate in the subsecond range.

In an effort to overcome the intrinsic limitations of both approaches, previously recorded ERP and fMRI data (Opitz et al., Annual Report 1997, pp. 67-68) were integrated by means of a neuroanatomically constrained source analysis. The fMRI provides the number and locations of possible generators of scalp recorded ERP components that are active in specific time intervals. Therefore, dipoles were kept fixed in location according to the fMRI results and their orientations were modelled in order to fit the topographic distribution of specific ERP components. The specificity of the dipole model in accounting for the variance of a particular ERP component was estimated by keeping dipole locations and orientations fixed and calculating the time course of dipole strength and goodness of fit over an ERP interval ranging from 100 ms before to 600 ms after stimulus onset.

The MMN, an ERP component elicited by deviant tones in a repetitive auditory stimulus sequence was associated with bilateral fMRI activation in the transverse temporal gyrus. Inverse solutions for dipole orientation provide evidence for a substantial contribution of these structures to deviancy processing. When the same stimuli had to be counted (targets) they elicited a P300 component in the ERP and led to an increased fMRI signal in both superior temporal gyri (STG) and the neostriatum. This ERP component could be modelled by two dipoles in the STG. In contrast, novelty detection was associated with the generation of a novel P3 component in the ERP. When the stimuli were attended to, only identifiable novels (e.g. dog barking) evoked an N4-like negativity. The fMRI responses showed bilateral foci in the STG anterior to those areas activated by targets. Subjects showing a strong N4-effect in the ERP had an additional fMRI activation in the right prefrontal cortex. The results of the combined analysis suggest that the activity of this prefrontal brain structure is delayed relative to processes underlying novelty detection.

This study demonstrates that combined analyses of fMRI and ERP provide a new approach for disentangling temporal aspects of neural activation in a distributed network underlying deviancy and novelty processing.

Lateralization of fMRI activity during retrieval varies as a function of encoding condition

3.2.14

Opitz, B., Mecklinger, A., Friederici, A.D. & von Cramon, D.Y.

An important question relating to the neural basis of memory is that of which brain regions are involved in retrieval from episodic memory. According to the HERA model right prefrontal structures mediate retrieval of episodic memory irrespective of information type. Here we examined retrieval-related activity in an intentional memory task for two types of nonverbal auditory stimuli; meaningful and non-meaningful novel sounds. We found that lateralization of retrieval-related prefrontal fMRI activity depends on encoding condition.

15 subjects were presented with novel sounds embedded in a sequence of tones. In the study phase different groups of subjects were required to judge either the loudness of sounds or to decide whether or not a sound could be verbally described. The subsequent test phase consisted of a recognition test. During the entire experiment echo planar images (TE=40 ms, TR=1 s) were acquired from eight axial slices.

Recognition performance was significantly above the level of chance for both encoding conditions and item types. In the study phase the right dorsolateral and inferior prefrontal cortices (PFC) were activated in both conditions. In the VERBAL condition additional activation of the left inferior PFC was obtained. Retrieval-related fMRI activity varied as a function of encoding condition: in the LOUDNESS condition we detected an activation focus in the right inferior PFC while in the VERBAL condition an activation in the left dorsolateral PFC was observed. When meaningful and non-meaningful novel sounds were examined separately item-specific fMRI activations were obtained in the test phase only. In the test phase of the VERBAL condition both novel types consistently activated the left inferior PFC, whereas in the test phase of the LOUDNESS condition the retrieval of meaningful but not non-meaningful novel sounds gave rise to an activation of the right inferior PFC.

These findings indicate that the right dorsolateral PFC is engaged in encoding of nonverbal auditory information independent of encoding condition. Furthermore, the lateralization of PFC activity during retrieval of nonverbal material depends on the availability of verbal codes, with left hemispheric involvement for verbally and right hemispheric activation for non-verbally coded information. Moreover, the differential activation of the right PFC by meaningful and non-meaningful novel sounds in the test phase of the LOUDNESS condition suggests that only the retrieval of the nonverbal conceptual-semantic information carried by a stimulus engages the right PFC.

Lateralization of verbal memory based on an incidental memory retrieval task

3.2.15

Hund-Georgiadis, M., von Cramon, D.Y., Lex, U. & Mecklinger, A.

Lateralization of language functions plays an important role in the benefit-risk evaluation of presurgical decision making in patients with tumors and epileptic foci in the vicinity of eloquent cortices. Presently, the invasive WADA-test is the Gold Standard of language lateralization. The latter includes - given the brief examination time available

- testing of certain language modalities such as spontaneous speech, semantic encoding, syntactic encoding and sometimes verbal memory. An unanswered question is whether the different components of speech show homogeneous lateralization effects. So far, no comprehensive study of lateralization effects of verbal memory is available. In a recent study Wagner et al. (1998) found an influence of remembering and forgetting of verbal stimuli on the magnitude of functional activation in left prefrontal and temporal cortices. It remains unclear however, whether these effects are due to general language or memory processes or are confounded effects. The current study was designed to establish a paradigm suitable for studying lateralization effects of verbal memory in normal controls and patients. 13 right-handed healthy control subjects underwent functional MR-imaging. Each subject performed three tasks in the scanner. In a word classification task 120 words had to be classified as abstract or concrete (semantic encoding). A shape and color recognition task served as a distractor. During an incidental memory task, 180 words had to be classified as 'new' or 'old', with reference to their presence in task 1.

Functional MRI-recording was performed using Echo Planar Imaging (EPI), (twelve axial slices, slice thickness 7 mm, TR 2 sec, TE 40 ms, matrix 128x64). fMRI data were analyzed with the BRIAN-Software (Kruggel & Lohmann, 1995). Data analysis included single subject and group analysis. The medial temporal cortex was considered as the main region of interest, besides prefrontal and temporal cortices.

As expected and in agreement with our previous work, the semantic encoding task was associated with activation of the bilateral inferior frontal gyrus. The degree of lateralization in this ROI was different across subjects. Furthermore, activation in the second temporal gyrus and the supramarginal gyrus was apparent. During the incidental memory task the overall activation was smaller than that is the semantic encoding task. Less activation was seen in language related areas. However, bilateral activation with a clear dominance of the left side occurred in the posterior part of the medial temporal gyrus. The cuneus and the precuneus region also demonstrated marked activation. Our preliminary results indicate that verbal memory function can be clearly distiguished from other language operations on the basis of data from fMRI investigations. There is evidence of medial temporal activation associated with verbal memory retrieval.

3.2.16 Insight out: on the functional relationship between intracranial and scalp recorded visual ERPs

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In cooperation with the Department of Epileptology at the University of Bonn we recorded intracranial event-related potentials (ERPs) in patients with temporal lobe epilepsy while they performed visual oddball tasks. This research aims at further specifying the functional characteristics of the MTL P300, a P300-like component evoked in the hippocampus formation. Previous studies in animals showed that the hippocampus serves as a spatial mapping system that binds together related sub-events or stimulus features to form coherent representations of the whole event. In the present study patients were required to perform visual classification tasks in which targets were defined either by object features or spatial locations. Target objects, but not target locations, elicited an MTL P300. Given the lower hit rate for target locations it is conceivable that this differential MTL P300 pattern reflects differences in task difficulty. Alternatively, as targets appeared in variable locations in the object feature task but not in the spatial location task it is conceivable that the MTL P300 is driven by a continuous updating of memory for target locations. Both explanations were tested in a second experiment in which target objects were presented in either fixed or variable spatial locations. Despite the lower hit rate in the variable location condition, target objects in both conditions evoked a pronounced MTL P300. Taken together, MTL P300s were obtained in all conditions except the spatial target conditions of Experiment 1 in which the target was defined solely by spatial location and object features were variable. Consistent with models of hippocampal functions these results suggest the MTL P300 is only elicited in situations in which unique object features can be bound with spatial information.

Are smilies special ? Brain regions activated by natural and schematic faces

3.2.17

Mecklinger, A.[1], Bentin, S.[2], Bosch, V.[1] & von Cramon, D.Y.[1]

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Recent neuroimaging studies of face processing suggest that faces are unique objects that are processed by special neuronal mechanisms in the ventral part of the temporal lobes. There is preliminary evidence that the neuronal mechanisms engaged in face processing can even be activated by impoverished visual input that is sufficient to elicit a face concept. The present study used fMRI to test this hypothesis. fMRI measures were recorded during five stimulation blocks. In the first block, the stimuli were pairs of "X"s separated horizontally by 10 cm. In the second, an ellipse encircled the same stimuli and, with the addition of a "nose" and a "mouth", formed a schematic face. The stimuli in the third block were identical to those in the first. In the fourth and fifth blocks the stimuli were natural eyes and faces, respectively. Within each block subjects were required to count rare target stimuli and fMRI activation was contrasted between stimulation periods and luminance-matched rest periods. Bilateral fMRI activation of face-areas (fusiform gyrus between the collateral sulcus and the lateral occipitotemporal sulcus) was found in all five test blocks, with the activation of face areas only differing in degree rather than kind across the five blocks. The activation in the first and third blocks, which used identical stimuli, was highly similar with the exception that in the first block there was additional cerebellar activation (anterior lobe), presumably reflecting either visuo-constructive or attentional processes modulated by the cerebellum. Together, these data suggest that viewing schematic faces and parts thereof is associated with highly similar brain activation to that arising when viewing natural faces and their component parts.

Studying cognitive functions in patients with circumscribed brain lesions enlarges the scope of research into brain-cognition relationships. Clinical neuropsychology projects are realized in cooperation with the Day-Care Clinic of Cognitive Neurology at the University of Leipzig. In 1998 147 neurological patients took part in the individually tailored assessment or therapy programme of the clinic. Again we found a majority of them (87%, unchanged compared to 1997) willing to give us their informed consent to take part in one or several studies presented in this chapter. 55% of the patients who were tested in the MPI, took part in studies other than the anatomical MR-scanning. 75 patients participated in studies after having been discharged from the Day-Care Clinic, 54 of whom were discharged even before January 1998.

The clinical neuropsychology projects focus on

- investigation of cognitive functions in patients with circumscribed lesions, with particular emphasis on:
  a) language processing
  b) executive functions
  c) memory
  d) visuospatial attention
- understanding of cognitive deficits in defined patient groups, especially patients with
  a) Parkinson's disease
  b) Transient global ischemia
- adaptation of experiences with functional MRI to the examination of neurological patients.

In the field of *language processing* we were able to develop assessment tools in order to examine auditory processes in the ear, brain stem, thalamus and auditory cortex (3.3.1) and to collect data in a normal population of different age groups. We examined the relationship between auditory discrimination abilities and language impairment in children (3.3.2). An auditory sequential priming paradigm was used in order to analyze semantic processing in aphasic patients (3.3.3), and the analysis of ERP components during stimulus presentations with semantic and syntactic violations was used to examine the relationship between verbal memory span and sentence comprehension in an aphasic patient (3.3.4). Further experiments indicated that left frontal lesions may have a critical effect on ability to discriminate between different levels of text processing (3.3.5).

In order to understand better different aspects of *executive function*, paradigms which had been introduced in previous years were further elaborated. The paradigm of Bublak et al. (Annual Report 1997, p. 70) was further developed in order to examine the relationship between planning requirements and working memory resources in brain injured patients (3.3.6). Similarly the task switching paradigm (Mecklinger et al., Annual Report 1997, p. 72) was re-employed and revealed differences in vulnerability to interference in right and left hemisphere brain damaged patients (3.3.7).

In the field of *memory processing* the memory retrieval paradigm (Thöne et al., Annual Report 1997, p. 73) was used successfully to identify memory impaired patients in whom supposedly automatic retrieval processes were no longer available (3.3.8).

A new paradigm was introduced in order to examine *visuospatial attention* in patients with circumscribed brain lesions (3.3.9). We were able to detect different processes being affected depending on the location of the lesion (unilateral posterior infarct, right frontal lesions, closed head injury).

In *Parkinson's disease* patients, we examined working memory processes (3.3.10), implicit learning (3.3.11), movement preparation and deep brain stimulation (3.3.12) and the contribution of nigrostriatal dysfunction to cognitive and motor deficits by use of [^{123}I]ß-CIT SPECT (3.3.13). In patients with *transient global ischemia*, whom P300 scalp topography was shown to deliver a useful contribution to investigations of neuropathology (3.3.14).

Finally we were able to adapt *fMRI* experience to the examination of patients. We analyzed the contribution of the cerebellum to cognitive processing (3.3.15) and used fMRI to show processes of reorganization of speech function in patients with chronic aphasia (3.3.16).

3.3.1 The perception of prephonematic acoustic signals alters with age

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As part of a study examining at the hearing capabilities of brain damaged subjects, most of whom were stroke patients, we tested some integrational psychoacoustical paradigms with subjects of varying ages.

One hundred subjects with normal hearing were divided into five age-groups (each spanning one decade), with each group consisting of ten women and ten men. The audiogram was measured using a yes/no (heard/not-heard) criterion. For all other experiments a three-interval forced-choice method was used. From three acoustic signals offered, subjects were required to identify one as differing from two constant reference signals.

Audiogram: An audiogram acquired during a quiet period served as a basis for all other psycho-acoustic tests. The frequency-specific threshold values provided references for all discrimination tests, which were typically performed at 30 dB HL (hearing level). Thresholds varied as a function of frequency for all age groups and increased as a function of age (Figure 1).

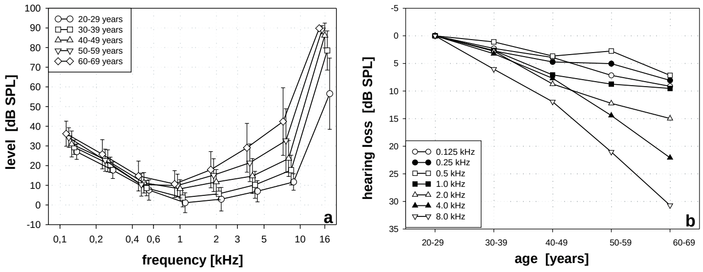

Figure 1. Changes of hearing sensitivity with increasing age. (a) Hearing threshold tested for eight frequencies between 0.125 and 16 kHz. (b) Hearing loss relative to the threshold values obtained for 20-29 year old subjects.

Frequency discrimination: Two subtests were developed to evaluate the limits of frequency discrimination: (1) binaural frequency discrimination and (2) successive frequency discrimination. Figure 2 shows the frequency difference limens (DLs), with the age of the subjects as a parameter. Under all conditions frequency discrimination worsened with increasing frequency. No significant age effects were observed.

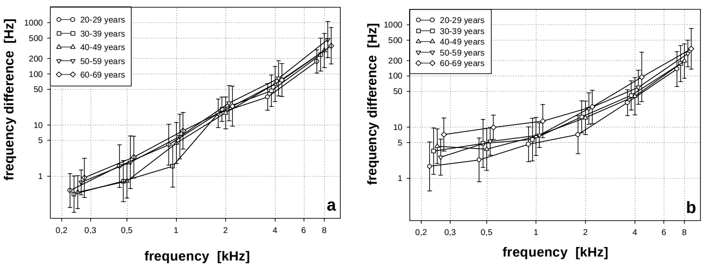

Figure 2. Frequency discrimination limens determined with two different paradigms (a) binaural signal presentation, (b) successive signal presentation.

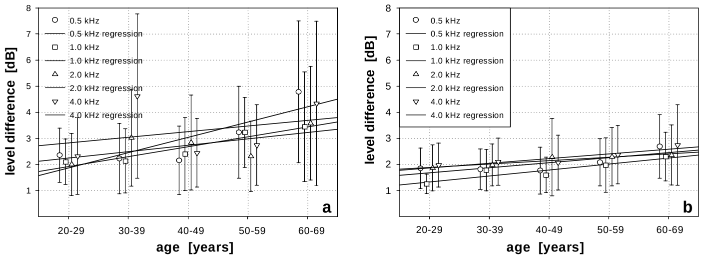

Figure 3. Intensity discrimination limens determined with two different paradigms (a) binaural signal presentation, (b) successive signal presentation.

Intensity discrimination: Binaural and successive signal presentations were also used to investigate intensity discrimination. In Figure 3 the intensity discrimination limens for these conditions are plotted against the age of the subjects. Neither test frequency nor age has a significant influence on the limens. A pairwise comparison at the different frequencies reveals higher thresholds under the binaural test conditions than under successive presentation.

Temporal processing: The duration difference limens measured for binaural stimulus presentations showed a strong dependency on test frequency, while no such influence was detected under successive stimulus conditions.

The results show that with the age-dependent peripheral hearing loss balanced by stimulating at constant hearing levels, age has a significant impact only on the duration DLs. Frequency shows its known effect on the frequency DLs, which is easily traced back to the tonotopic mapping found in the cochlea and all investigated auditory nuclei. The improvement of the DLs observed for low frequencies under binaural stimulus presentation could indicate that decision is supported by the detection of *binaural beats*. These results will be used as normative data for evaluation of categorial processing of acoustic information in stroke patients who often suffer from circumscribed unilateral lesions of the forebrain.

3.3.2 Auditory discrimination abilities of language impaired children

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The term "specific language impairment (SLI)" refers to children who have failed to develop the language capabilities expected for their age but are developing normally in all other domains. The definition of SLI (Tallal et al., 1993; Johnson et al., 1981) implies a language delay of at least one year, but an average performance IQ (i.e., 85 and above). According to Tallal (1993), the cause for SLI is a deficit in processing of rapid temporal sequences, which in turn leads to deficits in phonological processing. This hypothesis was confirmed in a discrimination task (Tallal & Piercy, 1973). Children without a language impairment could discriminate two tones with an interstimulus interval (ISI) of 40 ms. In contrast SLI-children needed an ISI of 428 ms to reach the same performance.

The present study was designed to address the question of whether the discrimination deficit occurs only for children with SLI, as defined above. As a first step, we sought to establish how many children attending a special school for language impairment (Sprachheilschule), fulfil the strict criteria defined by Tallal and colleagues. Moreover, we aimed to determine the relationship between the performance in the auditory discrimination task and a variety of cognitive parameters.

Subjects in our study were 42 children (age 8-10 years) at the Käthe-Kollwitz-Schule in Leipzig. Twelve of the 42 children fulfilled the criteria for SLI, based on the IQ (HAWIK-R). The control subjects were matched on age, gender and performance IQ but they demonstrated a higher verbal IQ. For the discrimination task, two complex tones (100 Hz and 305 Hz) and 10 different ISI's, ranging from 30 to 428 ms (eight trials for each ISI) were used.

The results showed that the control subjects performed significantly better than the experimental group ($F(1,11)=8.17$, $p<0.01$) (see Figure 4). This effect did not depend on ISI ($F(9,99)=1.05$, $p<0.40$). However, the experimental group was better than the SLI-group in the study conducted by Tallal, et al. (1993). Surprisingly, all 12 children in the experimental group were able to discriminate the tones even at the shortest interval of 30 ms.

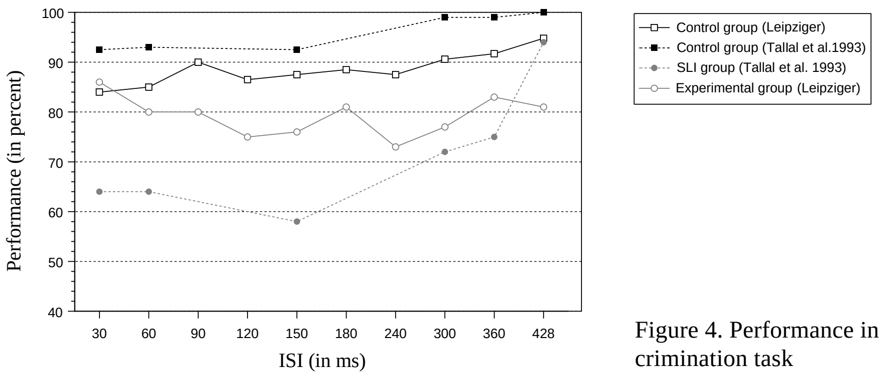

Figure 4. Performance in the discrimination task

After factoring out group differences, the discrimination ability was significantly correlated with the oral language abilities (Heidelberger Sprachentwicklungstest; $r=0.4$, $p<0.05$), the reading ability (Züricher Lesetest; $r=0.61$, $p<0.001$) and the phonological ability (Spoonerism task; $r=0.67$, $p<0.0004$).

To summarize, none of our children showed the described deficit in processing of rapid temporal sequences. In particular, the ISI did not systematically influence discrimination ability. Nevertheless, correlations with language related test scores show that the auditory discrimination task taps processes involved in language.

Auditory sequential priming in aphasic patients

3.3.3

Kotz, S.A., Lorenz, A. & von Cramon, D.Y.

Some priming research has focused on whether types of semantic information (*associative vs. non-associative*) and type of presentation (*word pair or word list*) can influence automatic or controlled processes. Kotz (1998) reported auditory and visual word list priming effects for associative relations in reaction time measures (RTs) and an event-related potential (ERP) priming effect for associative *(cat-dog*) and non-associative *(horse-dog*) relations.

The current experiment set out to test whether these priming mechanism(s) operate as a function of lesion site. We investigated auditory sequential word lists with reaction times and error rates. Two patients with anterior lesions, two patients with basal ganglia lesions, four patients with anterior temporal and four patients with posterior temporal lesions listened to words and pseudowords. The SOA was 1800 ms. Subjects performed a lexical decision task on each word.

Overall, reaction times were significantly longer in all patient groups than in age-matched control groups, but error rates were comparable. Patients with anterior and posterior temporal lesions displayed a comparable associative, but no semantic priming effect. Patients with basal ganglia lesions displayed a hyperpriming associative effect, but no priming effect in the semantic condition. Patients with a lesion in the anterior temporal lobe showed no priming effect in the associative and the semantic condition. These preliminary results indicate that sequential priming effects can be qualified as a function of type of semantic information and lesion sites in aphasic patients.

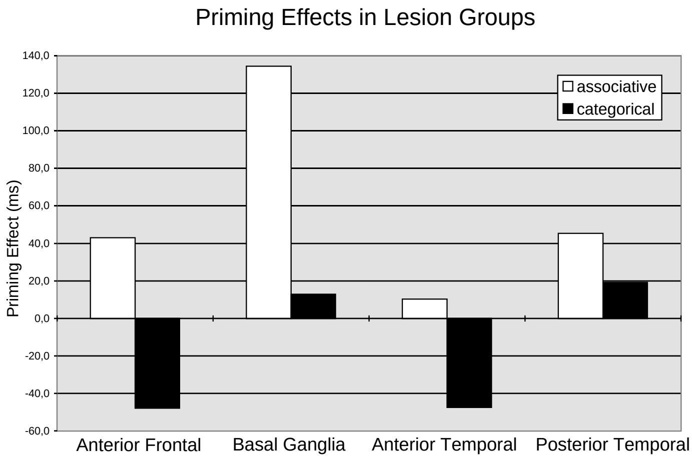

Figure 5. The size of the associative (white) and categorical (black) priming effects (in ms) are displayed for each patient group.

3.3.4 Verbal memory span and sentence comprehension

Kotz, S.A. & von Cramon, D.Y.

Even though there is ample evidence from the sentence-comprehension literature for specialized working memory systems in normal and patient populations, one open question is whether a specific resource deficit can be independent of a computational deficit. We present data from an aphasic patient with verbal working memory deficits.

Patient H.G., a 45 year old male, suffered an ischemic stroke in 1996. T2-weighted images in the axial plane taken about half a year after the stroke revealed increases in signal intensity in the following areas: (1) the left Heschl gyrus, (2) the posterior part of the superior temporal gyrus, (3) the supramarginal gyrus, and (4) the occipital gyri. The frontal lesion involves the middle portion of the praecentral gyrus and the posterior part of the frontal gyrus (F2p). The inferior frontal gyrus (F3) is spared.

A test battery on the 'phonological loop' revealed no STM (short term memory) deficit in H.G. Verbal working memory tests however, indicated a severe verbal working memory deficit. We then tested sentence-comprehension incorporating syntactic complexities (word category violations, subject/object relative clauses, subordinate clause violations) and a combination of syntactic complexity with increasing propositional content in both sentence picture-matching tasks and auditory/visual comprehension tasks. H.G. did not show a significant deficit in sentence comprehension at either the "interpretive" or the "postinterpretive" level of processing. Thus, if working memory impairments influence exclusively the "postinterpretive" processing, H.G.'s data provide evidence against this hypothesis.

To test the effects of a possible computational deficit, H.G. participated in a combined syntactic and semantic judgment paradigm utilizing event-related potentials (ERPs; cf. Friederici, Hahne, & von Cramon, 1998). Performance data were in the normal range, but the on-line computation of syntactic structure and semantic integration was influenced by the input parameters. The evaluation of syntactic violations (word category errors), semantic violations (selectional restriction errors), and correct sentences in connected speech did not elicit any of the expected ERP components in H.G. A similar picture emerged in the visual modality with a fast presentation rate (SOA: 500 ms). In a long SOA (1100 ms) visual manipulation, the N400 (onset: 350 ms) was elicited following semantic violations and a delayed P600 (onset: 1,000 ms) was elicited following syntactic violations. These results, although by no means exhaustive in the discussion of resource-capacity models, give evidence that reduced verbal working memory capacities might go hand in hand with a computational deficit.

3.3.5 Multilevel text representations in brain-damaged patients

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supported by SMWK

In text comprehension theories (van Dijk & Kintsch, 1983; Kintsch 1988, 1992) three levels of text memory are distinguished: the linguistic surface structure corresponding to the wording of the text, the propositional textbase including inferences, and the situation model representing an integration of text information with prior knowledge. In this project, we are interested in whether brain damaged patients are also able to build such a multilevel text representation. On the basis of the literature, we expect that aphasic patients will have difficulties with the surface structure, but not with the textbase and the situation model. For patients with lesions in language related cortical areas, our predictions follow Beeman (1993) who suggests that left-hemispheric lesions lead to overactivation of relevant information and problems with the separation of text information and inferred information. In contrast, patients with right-hemispheric lesions are expected to show difficulties with the activation of information necessary for building an elaborated textbase.

To empirically differentiate the levels of representation, we adopt a word recognition paradigm (cf. Welsh et al., 1991) in which subjects have to decide for a number of test words whether the word was mentioned in a text previously read. Besides old words from the text and unrelated new words, three different categories of related words are used: synonyms (or paraphrases) - which are in the propositional textbase; inference words - which tap an elaborated textbase; and contextually appropriate words - which are part of the situation model. With normal subjects, Guthke and Beyer (1995) confirmed that false alarm rates for synonyms were highest, followed by those for inferences and for context appropriate words.

We tested 39 brain-injured patients of various etiologies. The performance data of the entire group of participants showed the same test word effect as previously reported for control subjects. As expected, for the six aphasics the hit rates and false alarms rates for synonyms were equal (75%). The variable that best differentiated the behavior in this task was the presence of cortical lesions involving fronto-temporal areas of the cortex. For fifteen subjects with unilateral left-sided lesions, the false alarm rates for elaborative inferences were almost as high as those for paraphrases. For nine patients with an additional right-sided lesion, the effect was reversed. The remaining 15 participants mirrored the pattern of normal participants. The resulting interaction Group x Wordtype ($F(4,144)=3.3$, $p<0.02$) is shown below:

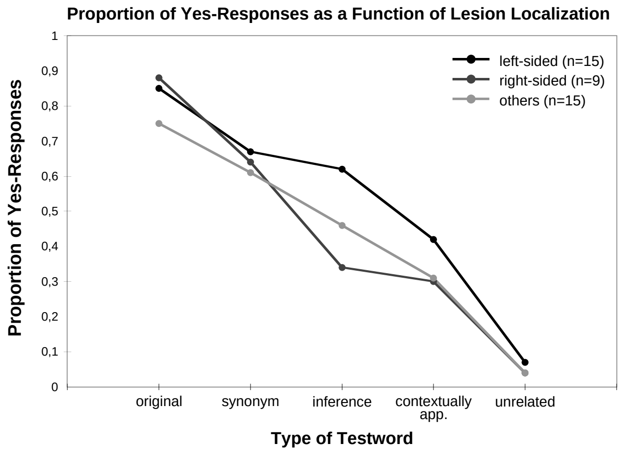

Figure 6.

These results are consistent with the hypothesis that left-hemispheric lesions leave the activation of appropriate associations intact, but interfere with inhibitory processes needed for a distinction between explicit and inferred information. In contrast, this distinction succeeds for patients with right-sided lesions due to their failure to activate the relevant knowledge needed for drawing inferences.

3.3.6 Differential demands on working memory in planning a simple action sequence: evidence from normal subjects and traumatic brain injured patients

Bublak, P., Schubert, T. & von Cramon, D.Y.

The ability to plan a sequence of actions is important for the efficient control of behavior. A plan is a list of "activity cues" (Jeannerod, 1997), that are maintained in working memory and used for guiding successive motor activities (Fuster, 1985). The process of planning can be described as the establishment of a correspondence between two sequencing-rules. The first rule matches the order in which the activity cues are encoded and initially maintained within the working memory list. The second rule determines execution by deciding the order in which the cues are selected. Planning requires the coordination of working memory processes. Operations for maintaining activity cues according to the first sequencing-rule have to be synchronized with processing operations to select specific activity cues according to the second sequencing-rule. We tested the hypotheses that (1) coordination requires increasingly more resources when the degree of rule compatibility decreases and (2) subjects with severe closed head-injury (CHI) perform significantly worse when coordination demand is high.

A paradigm was used in which four digits were serially presented (first sequencing-rule). Subjects had to maintain the list of digits in working memory and use it to guide a sequence of motor responses during recall. The order in which the digits had to be recalled represented the second sequencing-rule. There were three conditions giving rise to different degrees of temporal compatibility between the two rules. In "coordination 0", the rules were completely compatible and digits had to be recalled in the same order as presented. In two other conditions, the rules were incompatible. In "coordination 1", two digits, and in "coordination 2" all four digits had to be transposed for recall. Mean response times and error rates increased with decreasing degree of compatibility. Compared to healthy subjects, these effects were more pronounced in patients suffering from severe closed head-injury even when the level of task difficulty was adjusted (conditions blocked for patients, randomized for controls). While patients did not take longer than controls to make the first response (initiation time), they needed more time for executing the sequence in condition "coordination 2" (Figures 7 and 8).

According to these results, coordination demand increases and more working memory resources are required for planning when activity cues have to be selected in a different order from that in which they are maintained in working memory. Task performance deteriorates in CHI-subjects when planning requires more resources than available.

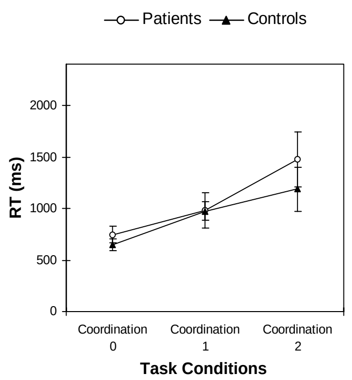

Figure 7. Mean initiation time (+1 s.e.) as a function of group and task condition. Conditions presented in blocks for patients, randomised for controls (RT: response time).

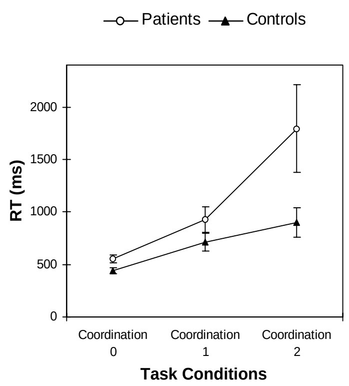

Figure 8. Mean execution time (+1 s.e.) as a function of group and task condition. Conditions presented in blocks for patients, randomised for controls (RT: response time).

3.3.7 Endogenous and exogenous interference in task shifting following right- and left-sided brain injury

Mecklinger, A.[1], Springer, A.[1], von Cramon, D.Y.[1,2] & Matthes-von-Cramon, G.[2]

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Neuropsychological theories hypothesize an executive control system that ensures goal-directed behavior by monitoring many perceptual-motor operations. We continued our examination of executive mechanisms involved in task switching in brain damaged patients. In a first study, 18 patients with mixed etiologies had to switch rapidly back and forth between two visual classification tasks (AA-BB design) and the analyses focused on switch costs, i.e., performance differences between switch and no switch trials, and on interference effects, i.e., processing costs imposed by the presence of interfering stimulus attributes. When the patients were grouped according to the side of the brain lesion the following results were obtained. First, patients with left brain damage (LBD) showed higher switch costs than patients with right brain damage (RBD). These group differences were attributable to disproportionally high switch costs in LBD patients with language or speech disorders. This result suggests that the efficiency of suppressing internal interference from a recently activated task set depends on the availability of verbal representations of the upcoming task. The switch costs were not selectively increased in patients with frontal lobe damage relative to patients without frontal lobe damage. The second key result was that patients with RBD showed higher interference from external task sets. This effect was not affected by language or speech disorders and might reflect a more general deficit in sustained attention after RBD (see Mecklinger et al., in press).

Starting in summer 1998, we aimed to extend these results by (i) adding five more patients to the clinical group (ii) including an age-matched control group and (iii) adding an experimental condition with four consecutive tasks (AAAA-BBBB design). In addition, in order to switch costs and interference effects, an analysis of inhibition processes was performed by examining switch costs in trials that require the processing of previously inhibited stimulus attributes. In showing that switch costs were higher in the patients with LBD than in patients with RBD and the control group in both testing conditions we confirmed and extended our initial results. Evidence for a contribution of inhibition processes to switch costs was obtained only for the LBD patients with language and speech disorders. The switch costs in patients with LBD without language or speech disorders did not differ from the switch costs in normal controls. RBD patients showed higher vulnerability to interference from externally presented but irrelevant task sets than the other groups under investigation. The overall results argue for a fractionation of executive functions to protect against external and internal sources of interference during task switching, with the latter function depending on the availability of verbal representations of the task components.

3.3.8 Investigations of memory retrieval processes with brain injured patients

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In order to investigate retrieval from long-term memory in brain injured patients we used a modified memory scanning paradigm (Conway & Engle, 1994), which allowed us to differentiate between short-term (STM) and long-term memory (LTM) processes. 13 patients with organic memory deficits (aged 21-56 years), and 13 healthy matched controls learned three different sets of letters (2, 4, 6 letters) to criterion. In order to control learning processes, patients' responses during learning were recorded via a touch screen. In the actual experiment, a cue for the set and a letter were presented on the screen. The patient had to decide whether the given letter was a member of the indicated set or not. When cue and letter appeared simultaneously, retrieving the set from long-term memory and memory scanning were both assumed to contribute to the reaction time. By introducing a sufficiently long delay between cue and letter, however, the processes could be differentiated.

According to the literature, retrieval from long-term memory is assumed to be set-size-independent, indicating automatic indexing of a list as a whole (Zysset & Pollmann, in press). We were interested in establishing the extent to which retrieval processes assumed as automatic are affected by brain injury.

Although patients' reaction times were generally slowed, even after controlling for perceptual encoding processes and motor response differences, activating information from LTM was a set-size independent process in patients as well as in controls (cf. figure 9). Cluster analysis, however, revealed a group of patients in whom the retrieval process was <u>not</u> set-size independent. We assume that in these subjects automatic retrieval processes were no longer available. This is in line with the fact that these patients turned out to be those with more severe memory deficits. We come to the conclusion that automatic retrieval processes are very robust against brain injury and are affected only in severely impaired patients.

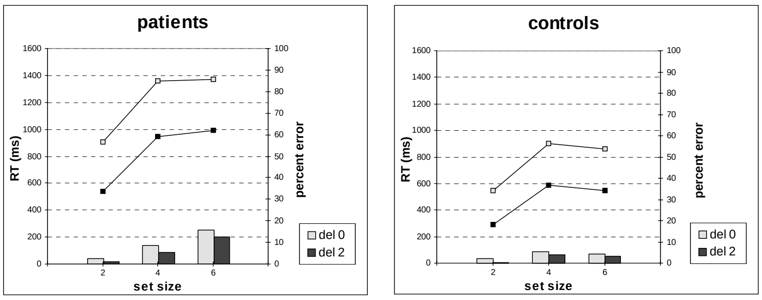

Figure 9. Mean reaction times and error rates of all patients and controls as a function of delay and set size.

An examination of the learning profiles (cf figure 10) indicated differences in the process of information acquisition between patients and controls, with the learning process of patients being characterized by smaller item chunks, while healthy controls were able to associate as many as 6 items in one chain. Loose associations between individual items of a set, however, may result in less reliable retrieval processes. Relations between acquisition and retrieval of information will be further analyzed in a subsequent experiment.

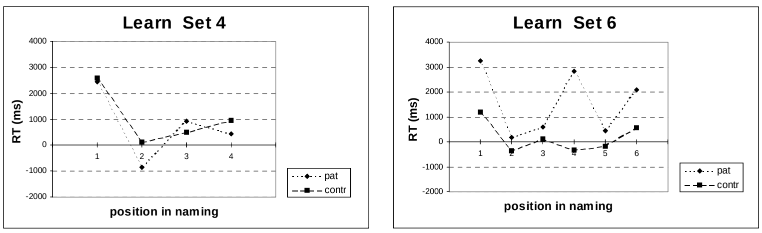

Figure 10. Mean production time for the learned sets as a function of set size and position of naming. Mean RTs of a visual search task are printed as a zero-line. The RT of the visual search task was subtracted from the time it took patients to touch the items of an indicated set during the learning phase. 0 ms means that the retrieval time equals visual search time.

3.3.9 Attentional process diagnostic in patients with focal brain lesions with the reaction time model STRAVIS (STRAtegies of VIsual Search)

Müller-Plath, G., Pollmann, S. & von Cramon, D. Y.

Deficits in visuospatial attention are commonly observed after different kinds of brain lesions. However, the nature of these attentional deficits is not well understood. We investigated whether the reaction time model for visual search (STRAVIS) is a suitable tool to specify failures of distinct subprocesses of attention, and whether such specific impairments can be related to distinct sites of brain lesions.

In our reaction time model STRAVIS, reaction times in visual search tasks are modelled as sums of the durations of successive search steps. The patients performed visual search tasks having differing levels of difficulty. With a numerical fit of the model STRAVIS to the reaction times, the following parameters were estimated: size of the focus of attention, dwell time of attention on each group of items, movement time of attention, and a 'basic time' for processes that are constant over all search tasks (e.g. initial perception, motor response). We compared the parameters of patients with different kinds of brain lesions with those of healthy controls.

Patients with hemianopia after unilateral posterior infarction showed a slowed movement of attention and a smaller attentional focus mainly in the contralesional, but to a smaller degree also in the ipsilesional hemifield. In the majority of patients with right hemisphere lesions, the size of the attentional focus was reduced. In particular, most of these patients were unable to perform pop out searches. Patients with cognitive slowing after closed head injury served as a clinical control. Although their reaction times were similar to those of the other patients, the model revealed that their attentional focus was unaffected. Their slowed reaction times were due only to prolonged fixation and movement times.

In the light of the fact that the model produced quite specific patterns of parameters for the different lesion groups, which are compatible with those in the literature, the reaction time model seems a suitable instrument for a process-oriented diagnostic of visuospatial attention.

3.3.10 Patients with Parkinson's disease show specific coordination deficits in working memory

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supported by BMBF / IZKF Leipzig

Patients with Parkinson's disease (PD) typically have deficits in cognitive functions that are mediated by the basal ganglia, namely procedural learning of skills and habits. Because of the intimate connections between prefrontal cortex and striatum, PD patients also show impairments of prefrontal functions like working memory (WM) and executive control. In our study we tested PD patients in a WM task that requires coordination of WM operations with different degrees of difficulty.

19 non-demented PD patients (age 55.8 [31-73] years, UPDRS_on 47.4 [20-76]) as well as age and education-matched normal controls were tested with a memory coordination paradigm that requires short-term maintenance and different degrees of manipulation of a digit list for guiding a sequence of simple actions (Bublak et al., Annual Report 1997, p. 70).

Increasing manipulation demand resulted in significant ($p<0.001$) increases of errors and reaction times (RTs). In all three test conditions (no, easy, difficult manipulation; blocked design) PD patients made significantly ($p<0.01$) more errors and showed slower RTs. There was a significant manipulation x group interaction ($F_{2,68}=6.99$, $p=0.002$) for the initiation time, i.e. the first RT after the delay. PD patients required more time to initiate the response sequence in the difficult manipulation condition.

(a) errors (b) execution times (c) initiation times

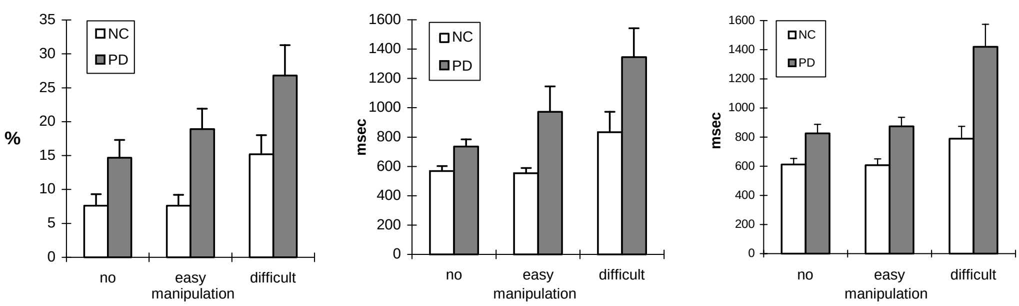

Figure 11. Comparison of PD patients with matched controls in the memory coordination paradigm (mean ± SEM[1]).

[1] 1 standard error of mean

Our results confirm previous findings of impaired WM-related executive functions in PD. Compared to controls, PD patients had more problems initiating a response sequence when the required coordination of WM operations was difficult. This result is in agreement with the assumption that in PD patients the main difficulty is the initiation and not the execution of actions. However, this result pattern is different from the problems reported in patients suffering from TBI (3.3.5).

3.3.11 Implicit learning in Parkinson's disease: differentiation between stimulus and motor sequence learning

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supported by BMBF / IZKF Leipzig

Neuropsychological research has shown that patients with Parkinson's disease (PD) are often impaired in procedural learning tasks. Implicit, i.e. non-intentionally acquired learning, has often been studied with the help of the Serial Reaction Time task (SRT) e.g. Nissen & Bullemer (1987). In this task, a repeated sequence of stimuli appearing at different locations on a computer monitor has to be responded to by a sequence of corresponding keys. In PD patients, reduced implicit learning in the SRT has been reported by several authors, e.g. Ferraro et al. (1993). However, in the SRT, the acquisition of a sequence of stimuli at different spatial locations and a sequence of motor responses are confounded. Previous research has shown that young healthy volunteers do learn both types of sequences (Goschke, 1998). We tried to examine whether the performance deficit in PD is due to impaired learning of either the stimulus or the movement sequence or both.

We examined seven patients with PD (Hoehn & Yahr stage >2, age 54.1±9.5), eight amnesic patients from the Day-Care Clinic, University of Leipzig, (MD) and fourteen matched controls. We employed the Serial Search Task (SST), a modification of the SRT developed by Goschke (1998), which allows a disentanglement of motor-based and stimulus-based implicit learning of an 8-item sequence by changing the stimulus-response mapping on a trial-to-trial basis. Each subject performed 7 learning blocks consisting of 10 repetitions of this sequence, followed by 80 random trials and a final sequence block.

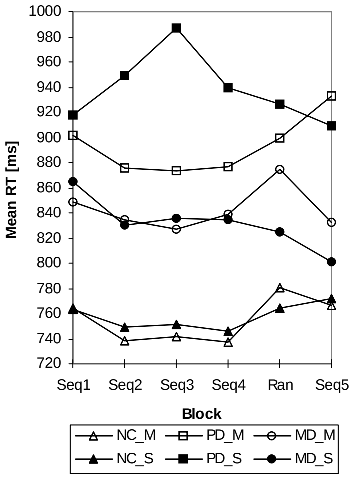

Figure 12. Reaction times during SST (Ran/Seq = random vs. sequence block, M/S = motor vs. stimulus condition)

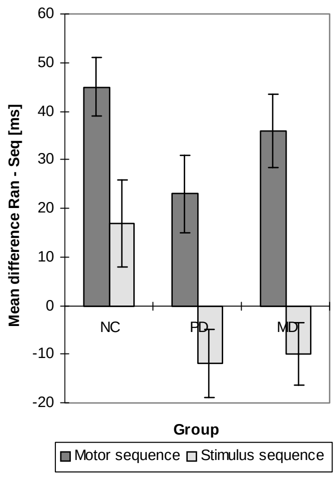

Figure 13. Difference between random block and the fourth sequence block (group means and standard errors)

Comparing differences of mean RTs between the last sequence block and the random block in each condition, we found that patients with PD (p=.05) and amnesics (p=.05) learned the motor sequence better than the stimulus sequence (see Figures 12 and 13). Normal controls showed no significant differences, although there was a trend towards better learning of the motor sequence.

Our results are in line with an earlier study testing Broca's aphasics with the same paradigm (Goschke et al., Annual Report 1997, p. 80). We propose two possibly interacting explanations: (a) there is no *general* sequence learning deficit in PD, but performance depends on the sequence type and (b) the stimulus sequence condition poses higher cognitive demands than the motor sequence condition, which leads to age-related performance deficits compared to young adults. In further experiments, we will investigate the effects of disease severity, striatal integrity and age on implicit sequence learning.

3.3.12 Movement preparation and deep brain stimulation: a study of patients with Parkinson's disease

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The aim of this study was to investigate pathways of information processing related to the preparation of simple movements. According to Alexander et al. (1986) during movement preparation information is passed through the basal ganglia-thalamo-cortical pathways. However, there is little existing knowledge concerning the functional role of basal ganglia-thalamo-cortical pathways for movement preparation. Some studies assume a special involvement of these pathways in the mechanism of movement selection (Pullman et al. 1988; Berns & Sejnowski, 1996). Other authors assume a more general involvement of these pathways in the mechanism of response initiation and the regulation of the general activation level (Wascher et al., 1997).

We assessed these assumptions with patients suffering from a basal ganglia dysfunction (Parkinson's disease - PD) who are treated with DBS (deep brain stimulation) of the basal ganglia. DBS is a recently introduced method of PD treatment where an electrode is implanted in the Globus Pallidus internus (GPi) (or other structures of the basal ganglia-thalamo-cortical pathways). A permanent high frequency stimulation of the GPi results in an improvement of information flow through the impaired basal ganglia-thalamo-cortical pathways in PD (Siegfried & Lippitz, 1994).

By manipulating DBS the GPi can be switched on and off. We compared the influence of DBS on reaction times (RTs) in choice and simple reaction tasks to investigate the role of basal ganglia in human movement preparation. The idea was as follows: if basal ganglia are involved critically in movement selection DBS should influence RTs in choice reaction tasks. DBS should not influence RTs in simple reaction tasks since these do not include a response selection stage. However, if basal ganglia are involved in response initiation DBS should influence RTs in choice reaction tasks and in simple reaction tasks equally.

The results for 5 PD-patients treated with DBS revealed that manipulation of DBS influenced the RTs in all three tasks: visual simple reaction task ($F(1,4)=5.86$, $p=0.07$), visual choice reaction task ($F(1,4)=10.18$, $p<0.05$), auditory choice reaction task ($F(1,4)=8.03$, $p<0.05$). However, DBS did not lead to an equal improvement of all RTs.

The improvement of RTs by DBS was more marked on the slower branch compared to the faster branch of the RT distribution. State of medication (level of l-dopa treatment) effected RTs only in the auditory choice reaction task ($F(1,4)=6.03$, $p=0.07$). These results are evidence for an involvement of the basal ganglia-thalamo-cortical pathways in the stage of movement initiation. There is no evidence for a selective involvement of basal ganglia-thalamo-cortical pathways in the response selection stage.

3.3.13 Striatal [^{123}I]β-CIT SPECT and prefrontal memory functions in Parkinson's disease

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Motor deficits in Parkinson's disease (PD) are mainly caused by degeneration of nigrostriatal dopamine neurones and resulting disturbances within basal ganglia pathways. The striatal deficit can be visualized by single-photon emission computed tomography (SPECT) using [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)tropan ([^{123}I]β-CIT) as a marker for the presynaptic dopamine transporter. With refined equipment this method provides similar diagnostic information to that obtained from positron emission tomography (PET) with [^{18}F]fluorodopa (Ishikawa et al., 1996). Severity and laterality of motor symptoms in PD (Seibyl et al., 1995; Marek et al., 1996) as well as disease progression (Marek et al., 1998) have been shown to correlate with [^{123}I]β-CIT uptake in the putamen. This method has, however, not previously been used to investigate the relationship between striatal dysfunction and cognitive deficits.

Twenty non-demented patients with idiopathic Parkinson's disease underwent single photon emission computed tomography (SPECT) with [^{123}I]β-CIT and neuropsychological testing with a battery focusing on prefrontal memory functions (verbal working memory and strategic memory) to further investigate the contribution of nigrostriatal dysfunction to cognitive and motor deficits.

As compared to matched controls PD patients showed significant ($p<0.05$) deficits in verbal working memory (digit ordering task, reading span) but not in short-term memory tasks (digit span). Recall of stories (logical memory) but not of figures (visual memory) was impaired. There were problem solving and set shifting deficits (card sorting task) but normal intelligence measures. Simple reaction times (RT) were slowed without effects on alertness.

A pattern of significant ($p<0.05$) correlations was observed between [^{123}I]β-CIT uptake in the putamen and motor deficits (UPDRS) as well as between both striatal compartments (head of the caudate nucleus and putamen) and cognitive tasks that involve executive processes (digit ordering, logical memory, card sorting) (Figure 14). The observed

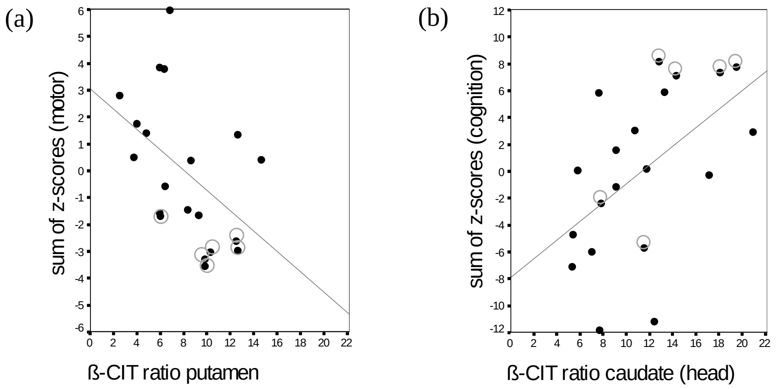

Figure 14. Scatterplots of correlations between motor deficits (z-sumscore) and putaminal [^{123}I]β-CIT ratios (a) and prefrontal cognitive deficits (z-sumscore) and caudate ratios (b). Case labeling (circle) for early patients (H&Y < 2).

Deficit	Predictor	r^2	β	p
cognition [sum of z-scores]	age	0.39	-0.62	0.003
	caudate [β-CIT ratio]	0.28	0.52	0.02
	putamen [β-CIT ratio]	0.23	0.48	0.03
motor [sum of z-scores]	putamen [β-CIT ratio]	0.35	-0.51	0.02
	caudate [β-CIT ratio]	0.33	-0.50	0.02
	reading span	0.28	-0.53	0.03

z-sumscore cognition = z-DOT[digit ordering task] + z-reading span + z-MCST_categories [Modiefied Card Sorting Test] + z-MCST_errors + z-MCST_perseverations + z-LM[Wechsler Memory Scale, revised; logical memory]_immediate + z-LM_delayed;
z-sumscore motor = z-H&Y[Hoehn&Yahr staging] + z-UPDRS[Unified Parkinson's Disease Rating Scale] _total + z-duration.

Table 1. Regression analyses (stepwise exclusion) for predicting cognitive and motor deficits

correlations together with the results of regression analyses (Table 1) confirm our prediction that both degree of nigrostriatal degeneration and age are predictors for impairments of prefrontal cognitive functions in PD.

Our results support the view that the striatum is part of a neuronal network that mediates prefrontal memory functions. Cognitive deficits related to caudate dysfunction may occur already in early stages of PD. Further clinical studies with combined neuroimaging, neuropharmacological and neuropsychological techniques are necessary to disentangle the contribution of disturbed basal ganglia outflow and cortical dopamine loss to prefrontal memory deficits in PD.

3.3.14 P300 scalp topography in patients with transient global ischemia

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[1]Max-Planck-Insitute of Cognitive Neuroscience, [2]Day-Care Clinic of Cognitive Neurology, University of Leipzig

In 1996 and 1997 we examined visual recognition memory in patients with transient global ischemia (TGI) and in age-matched controls by means of event-related potential (ERP) recordings (Mecklinger et al., Annual Report 1997, p. 72). We found that TGI leads to a selective deficit in explicit memory functions, usually ascribed to the medial basal temporal lobes but spares implicit memory functions such as cognitive skill learning (Mecklinger et al., 1998). To further examine the neuropathology after TGI we examined various aspects of the P300 component elicited in a visual classification task. ERPs were recorded from at least 19 electrodes in 9 TGI patients, 7 patients with traumatic brain injuries (TBI) and associated hypoxic disorders, and clinical and normal control groups, each consisting of 8 participants. P300 amplitude and latency were comparable in all 5 experimental groups. However, there was a marked difference in P300 scalp topography, with TGI and TBI patients with associated hypoxic disorders showing a selective reduction of the P300 over parietal and occipital brain regions as compared to clinical and normal controls (cf. Figure 15). Since all groups under investigation were matched for age, this topographical pattern of the P300 component cannot be ascribed to differential age-related P300 modulations. The results are more consistent with the view that the cortical arterial boundary zones are selectively vulnerable to hypoxic injury. This neuropathological process along the border zones of the large arteries might specifically affect the parieto-occipitally located brain areas involved in P300 generation. In a next step we will examine the suitability of P300 scalp topography as a predictive measure for brain diseases after hypoxic disorders.

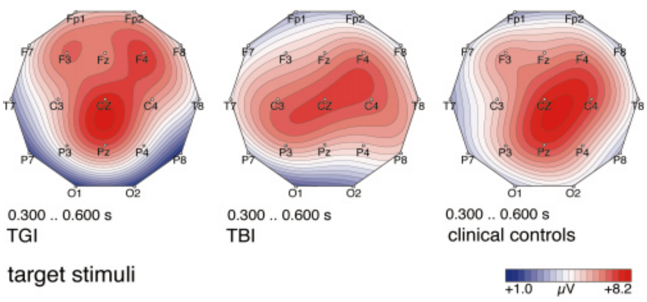


Figure 15. Spherical spline maps illustrating the scalp topography of the P300 component for the patient groups (TGI: transient global ischemia, TBI: traumatic brain injury with associted hypoxic disorder, CLIN CTRL: clinical control group).

3.3.15 Cerebellar contributions to cognitive processing

Hund-Georgiadis, M. & von Cramon, D.Y.

The cerebellum has traditionally been viewed as a neuronal device dedicated to motor control. Although recent evidence (Schmahmann, 1995, 1997) shows that it is involved in non-motor operations as well, an important question is whether this involvement is independent of motor control and motor guidance. A number of recent reports suggest that the cerebellum is also involved in cognitive functions and particularly in language processing. Functional imaging has not yet addressed this problem explicitly. In a first approach

Allen et al. (1997) showed by means of functional magnetic resonance imaging (fMRI) that attention and motor performance independently activate distinct cerebellar regions.

Our fMRI study was designed to define the role of the cerebellum in visual as compared to auditory sustained attention based on an oddball paradigm in contrast to a motor control task. 13 healthy subjects (mean age 25 years 8 month), underwent functional magnetic resonance tomography. Each subject performed a set of tasks in the scanner. In a visual oddball task, the subject was asked to respond selectively to round objects, while a set of different shapes were presented on the screen. In the auditory attention task, subjects were asked to react to high tones, while listening to a set of different tones. In a shifting attention task (SAT), the visual oddball paradigm was used in a modified version: the subject had to respond either to the form of the object or to the color of the object. The shift in attention occurred randomly, about every 4 to 8 seconds. A motor tapping task (MOTT) completed the session.
All investigations were performed using a Bruker 3 T/100 Medspec, whole-body MRT scanner (technical parameters: TR 1.5 s, TE 30 ms, Matrix = 128x128, FOV = 19.2 cm, slice thickness = 5 mm).

In all subjects, the cerebellum was active during the visual attention task and showed clear lateralization effects with a dominating left hemisphere. Most cerebellar activation was seen in the SAT. However, no relevant cerebellar activation was observed during the auditory attention tasks. The contributions of distinct ROIs to the overall cerebellar activation were further evaluated. The cerebellar motor ROI showed very little activation during the SAT, whereas it was involved maximally during the MOTT. SAT, however engaged maximally the cerebellar attention hotspot, which was significantly less active during the MOTT ($p<0.001$). These findings support a broader concept of cerebellar function, in which the cerebellum is involved in diverse cognitive and noncognitive neurobehavioral systems, including the attention and motor systems, in order to anticipate imminent information acquisition, analysis, or action.

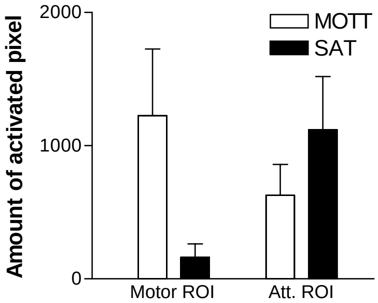


Figure 16. Involvement of distinct cerebellar ROIs during shifting attention (SAT) and motor control tasks (MOTT). According to previous research (Allen et al. 1997) the cerebellar motor hotspot included the anterior vermis, the right central lobule and the right anterior quadrangular lobule, the attention ROI, however, included the left posterior quadrangular lobule and the left superior semilunar lobule.

3.3.16 Reorganization of speech function in chronic aphasia studied by fMR

Hund-Georgiadis, M., von Cramon, D.Y.& Lex, U.

Numerous approaches have been adopted to study the functional patterns underlying recovery of language function in patients with aphasia (Weiller et al., 1995; Mimura et al., 1998). So far, it is mainly the PET and fMRI-techniques which have been used to generate functional maps of speech (re)organization during language tasks in aphasic patients. These maps can be considered as 'snapshots' taken at a certain time post stroke-onset. However, such 'snapshots' reveal little about the dynamics of reorganization and tell nothing about the relationship between clinical improvement from aphasia and accompanying changes in functional patterns. The current fMRI-study was designed to study language (re)organization in aphasia following different types of infarction in the territory of the left middle cerebral artery. 24 patients from the Day-Care Clinic for Cognitive Neurology (University of Leipzig) were examined 3 to 36 months post stroke-onset in the MR scanner. The patients' functional data were compared to those of 18 age-matched, right-handed control subjects.

During the fMRI-experiment two different word classification tasks were applied. A lexical (verb or noun) and semantic (abstract/concrete) encoding paradigm was compared with a baseline condition (fixation of a dark screen with five white Xs). Functional MRI-recording was performed using Echo Planar Imaging (seven axial slices, 7 mm slice thickness, TR=30 ms., TR=2 s, matrix 128x64). fMRI data were analyzed with the BRIAN-Software (Kruggel & Lohmann, 1995).

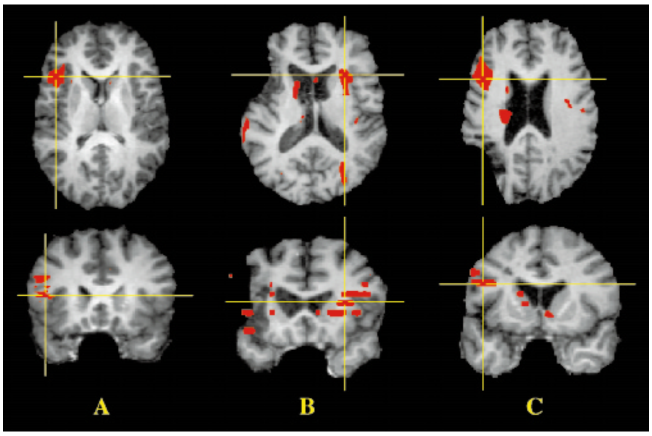


Figure 17. Semantic encoding task: A: group data of 18 right handed controls, B: typical distribution of activation patterns in a patient with a lesion in the anterior branches of the left middle cerebral artery, C: functional data of a patient with a lesion in the posterior branches of the left cerebral artery.

Activation of the left inferior frontal gyrus (Broca area) was found in all right-handed control subjects during semantic and lexical encoding. Half of the controls showed additional activation in homotopic right hemispheric cortices. Typical patterns of activation were seen in the patient group. All patients showed significantly more marked brain activation than the controls. Patients with lesions in the parietal branches of the left middle cerebral artery showed the same distribution of functional patterns as described in the control group. However, patients with lesions in the anterior and middle branches of the left middle cerebral artery showed increased activation in the right inferior frontal gyrus, which extended to the anterior insula and to subcortical striatal and thalamic areas. No correlation was found between the distribution of functional activation and behavioral data. Furthermore, the fMRI activation patterns in individual patients did not reflect the severity of aphasia as judged by AAT.

Use of telemedicine in clinical neuropsychology

3.3.17

Kopp, U.[1], Thöne, A.I.T.[1], Rüdiger, G.[2], Irmscher, K.[3], Krämer, M.[3], Richter, J.[4] & von Cramon, D.Y.[1,2]

[1]Day-Care Clinic of Cognitive Neurology, University of Leipzig, [2]Max-Planck-Institute of Cognitive Neuroscience, [3]University of Leipzig, Institute of Informatic, [4]RBM Electronik Automation, Leipzig

supported by SMWK

Deficits in prospective memory performance have a major impact on the everyday lives of patients. They arise primarily from memory deficits for future intentions, but may also be due to a lack of self-initiated retrieval processes, i.e. a failure of executive function. The use of external aids has often failed due to several difficulties inherent in the patients' functional deficits e.g. patients forget to write down appointments, they do not remember to look in their diaries at the right time, etc. Modern electronic timers or organizers on the other hand are often too complicated to deal with, and patients are unable to learn to use them.

The aim of this project is the construction and evaluation of an external aid which improves the patients' quality of life by providing active support in situations where normal function is impaired by disturbances of memory or executive functions.

After having found cooperation partners (RBM Elektronik Automation; Institute of Informatics, University of Leipzig) who will undertake the hardware and software development of a device tailor-made to the requirements of brain injured persons, our primary concern in 1998 was a first conceptual specification of the external aid. An appropriate device will incorporate enough hardware and software flexibility to be open to new developments on the computer market. At present we are considering two different solutions: the first possibility is more economical from a viewpoint of software-construction but less flexible with respect to individual layouts, and the second is highly novel and adaptable but carries with it some developmental risks. From a psychological viewpoint we have started to work out the design of the human-machine-interface on the basis of theories and results from cognitive psychology, neuropsychology and engineering psychology. On the basis of task-analysis (interviews with patients, behavioral observations) the functional specification is now completed. A non-formal description differentiates between timed and non-timed tasks. For both types of task various kinds of information are needed which are provided by an orientation module. Basic manipulations are the integration of new information, its alteration and deletion, and its repeated presentation throughout the day. In the near future, a further specification will be prepared for the communication component (syntactic level, interaction level) and the physical component (spatial layout level, device level). We aim to produce a prototype device during the course of the next year.

Having previously investigated the feasibility of event-related fMRI, especially under conditions of rapid trial succession, we have begun to use this technique for the analysis of cognitive processes and their relation to brain function. Most of work performed has been centered around executive and memory processes.

In one study, we investigated self-determined generation of actions, and the manipulation of information in working memory (3.4.1). A common neural correlate in the dorsolateral prefrontal cortex was found to be involved in both kinds of executive processes.

Further experiments analyzed the neural architecture underlying task switching (3.4.2). These experiments showed that the cost involved in switching between tasks goes along with increased activation within the network activated by the tasks, and not with activation of an additional area exclusively involved in switching. Ongoing work extends this research to switching between visual dimensions and to subprocesses involved in task switching.

By analyzing the timecourse of the BOLD-response in various brain regions, we were able to differentiate memory search processes from retrieval from long-term memory (3.4.3). The data gave no indication of any area being exclusively involved in retrieval, but of differential involvement of the activated areas in retrieval, maintenance, and search.

Delayed matching experiments were used to analyze the cortical networks underlying stimulus processing and maintenance of information during the delay and response preparation (3.4.4). Fast fMRI enabled us to trace the timecourse of the BOLD-response with precision. We found stimulus, delay, and response-related timecourses in close proximity to one another within regions of prefrontal, premotor and parietal cortex. Thus all aspects of the task activated a widespread network of cortical areas, albeit to differing extents.

From a methodological perspective, most of these studies relied on event-related analysis, which was usually achieved in designs with rapid succession of trials. Analysis of the activational timecourse was often vital to the investigation of the participation of brain areas in cognitive function. Recently, we have been able to use an imaging sequence with very short repetition times, allowing a temporal resolution of 300 ms (3.6.1). Fast fMRI-sequences offer the advantage of combining a spatial resolution in the millimetre range with a reasonably high temporal resolution. Currently, the analysis of the temporal dynamics of well localized brain activation is used by this group as a central tool to investigate the relationships between cognitive processes and brain function.

Most members of this group are also involved in patient work (CNPS-projects [3.3]). One project was explicitly started as a patient study, with later fMRI-applications (3.4.5). A mathematical reaction time model of visual search processes was developed, with the aim of improving the diagnosis of attentional deficits in brain damaged patients. Once the model had been empirically tested in normal subjects, experiments with different types of patient were carried out. Modelling of the data indicated distinct patterns of attentional deficits in the different groups of patients.

3.4.1 Generation of self-determined actions and manipulation of information in working memory: a common neural substrate in the dorsolateral prefrontal cortex

Schubert, T. & von Cramon, D.Y.

The dorsolateral prefrontal cortex (DLPFC) is assumed to be involved in the generation of internally triggered behavior, called self-determined actions (Frith et al., 1991). However, this assumption is questioned by studies relating DLPFC activation in the self-determined action task to task-specific working memory (WM) load (Petrides et al., 1995). We assume that the generation of self-determined actions requires higher order executive processes which control the maintenance and manipulation of information held in WM and used for the generation of self-determined actions. To examine this assumption we compared regional blood flow during a self-determined action task with that during a WM task using fMRI. Parametric trial designs allowed the manipulation of difficulty of WM control processes in both tasks. It was then possible to address the question of whether difficulty-related activity changes are localized in similar regions in these separate tasks.

We hypothesized that if generation of self-determined actions and WM load affect similar regions in the DLPFC it should be possible to predict the localization of difficulty-related regions in one task by the localization of difficulty-related regions of the other task.

The generation of self-determined actions was investigated by asking subjects to generate random finger sequences (Baddeley, 1996). In this task difficulty of the generation was manipulated by increasing movement frequency. We used two conditions - 1 movement per 2 seconds versus 2 movements per second. As a task which involves WM processes we used the n-back paradigm. In that task load was increased with 3 load-steps (0 back - 2 back). The results showed: (1) In both tasks, the left DLPFC (Fig.1), a region in the vicinity of left and right frontal eyefields, the supplementary motor area, and the left and right intraparietal sulci are activated. Additional comparisons of the Talairach-coordinates of peak activity in these regions revealed no differences between tasks. (2) A separate analysis of the percent signal change revealed that increased generation difficulty and WM load led to increased regional blood flow in both tasks in all of the named regions. (3) For the random generation task difficulty-sensitive DLPFC regions could be predicted if we transferred the localization of WM load-sensitive regions from the n-back to the random generation task.

Thus, the generation of self-determined actions and the manipulation and maintenance of items in working memory activated identical regions in the DLPFC. Moreover, frequency related signal intensity changes in the generation of self-determined actions and WM-load related signal intensity changes in the n-back task affected identical regions in the DLPFC. These results indicate a common region in the DLPFC involved in executive control of WM processes in both tasks.

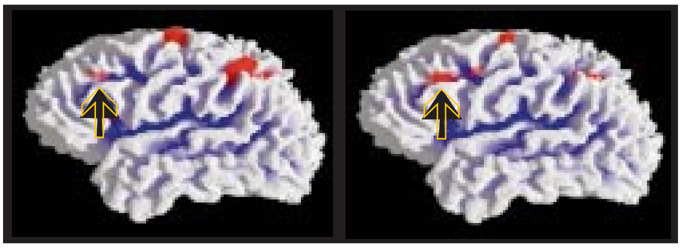


Figure 1. Localization of activation along the banks of the left interior frontal sulcus related to the generation of self-determined actions (left panel) and working memory load (right panel).

3.4.2

Examination of BOLD-responses elicited by task-repetition and task-switch trials: an event-related fMRI study

Dove, A., Pollmann, S., Wiggins, C.J. & von Cramon, D.Y.

The task switching paradigm is one of several approaches for the examination of executive processes. Subjects are required to switch between two or more pre-specified tasks. This allows the investigation of a certain aspect of executive processes: the process of configuration for a new task (Monsell, 1996). Only a few neuroimaging studies have been published to date which have identified brain areas involved in task switching. We used event-related fMRI to localize these areas, since this approach allows intermixing of switch and task-repetition trials, and performed an analysis of the BOLD-response timecourses.

16 right-handed subjects were examined. In the basic task subjects pressed the left button of a response box when a green plus was presented. A green minus required a press of the right button. In unpredictable switch trials the stimulus color changed to red, indicating that a response reversal was required (red plus: right; red minus: left). 20 single unpredictable switch trials were presented embedded in 125 basic task trials.

A two-shot EPI sequence was run. After preprocessing, data were averaged over subjects. A t-test was conducted to compare activation in the unpredictable switch condition with that in the task repetition condition (basic task trials presented after basic task trials). Areas which showed activations were chosen as regions of interest (ROI). Time courses were generated using a cluster of the most activated pixels in each ROI.

Significant differences in reaction time (RT) were observed between conditions (Figure 3). We identified regions in the lateral prefrontal and premotor cortex, the anterior insula / frontal operculum, the left intraparietal sulcus, the precuneus and the SMA/pre-SMA as belonging to the network involved in task switching (Figure 2). ROI analyses (Figure 4) showed that these areas were already activated in the task repetition condition.

The brain areas identified as belonging to the task switching network are regions which have been reported in several studies in which manual responses were governed by visual stimuli. In line with Klingberg's (1998) conclusions regarding the related dual task paradigm, our results show that no additional areas are required to control the task switch, but that the areas that are generally associated with the task are more strongly activated during the task switch.

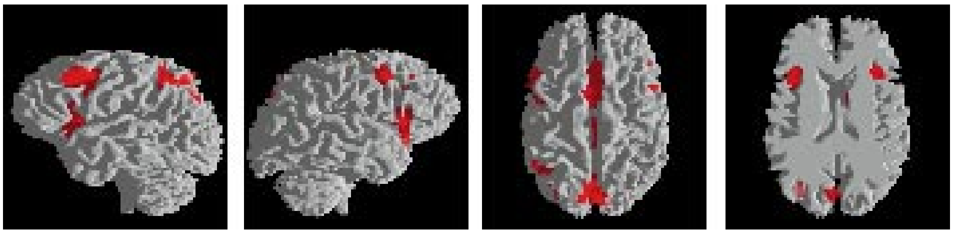


Figure 2. Areas activated in the switch vs task repetition condition. Activations are overlaid on the white matter segmentation of a single subject.

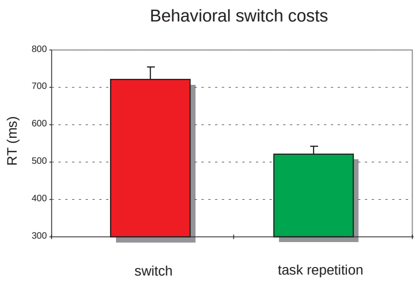


Figure 3. Reaction times in the switch and task repetition condition.

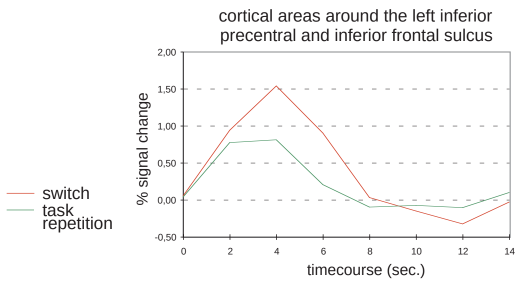


Figure 4. Averaged event-related BOLD signal changes for the switch condition and the task repetition condition.

3.4.3 Dissociation of memory scanning from retrieval and rehearsal processes: an event-related fMRI study

Zysset, S., Pollmann, S., von Cramon, D.Y. & Wiggins, C.J.

Subprocesses underlying memory retrieval can be experimentally dissociated in time. We analyzed the temporal delay of BOLD-responses in several memory related brain areas in order to investigate the neuronal correlates of retrieval processes. By varying the temporal onset of a subprocess within a flow of processes, it is possible to induce variations in the timecourse of the hemodynamic signal in areas involved in these delayed subprocesses.

In our experiment, we used a Sternberg memory-scanning task (Sternberg, 1966), where verbal information kept in short-term memory is manipulated by working memory. The task was modified so that memory contents have to be activated from long-term memory prior to being processed by working memory. In this task, subjects learn sets of letters with differing numbers of members. Once they have memorized the sets, subjects perform a speeded verification task. A digit, corresponding to one of the memory sets, and a probe item (letter) are presented. Subjects have to decide whether or not the probe item belongs to the indicated set.

By specifying the set first and delaying the presentation of the probe item, the scanning process can be separated from the retrieval process. The time course of the hemodynamic response in brain areas involved only in retrieving the information from long-term memory should not vary if the presentation of the probe item is delayed. Areas in which the hemodynamic response follows the delay of the probe item are those involved either in scanning, response selection or response execution.

By taking advantage of the temporal resolution of fMRI we were able to dissociate areas involved in memory scanning from areas involved in rehearsing and retrieving information. Figure 5 shows an examples of the activation patterns and timecourses.

We showed that the antero-superior insula along with the posterior parietal cortex (BA 7, 39, 40) are involved in memory scanning processes. We argue that the antero-superior insula playes an active part in scanning the sets, whereas the parietal cortex contributes to phonological storage and scanning processes. Event-related activation in the precuneus indicates that the subjects had a visual representation of the learned sets while completing the task. The left anterior prefrontal cortex appears to be involved in retrieving the set and keeping it active in short-term memory, but does not take an active part in scanning the set. The right prefrontal cortex does not seem to support task specific processes such as memory retrieval or scanning, but is involved in general processes such as monitoring and verification.

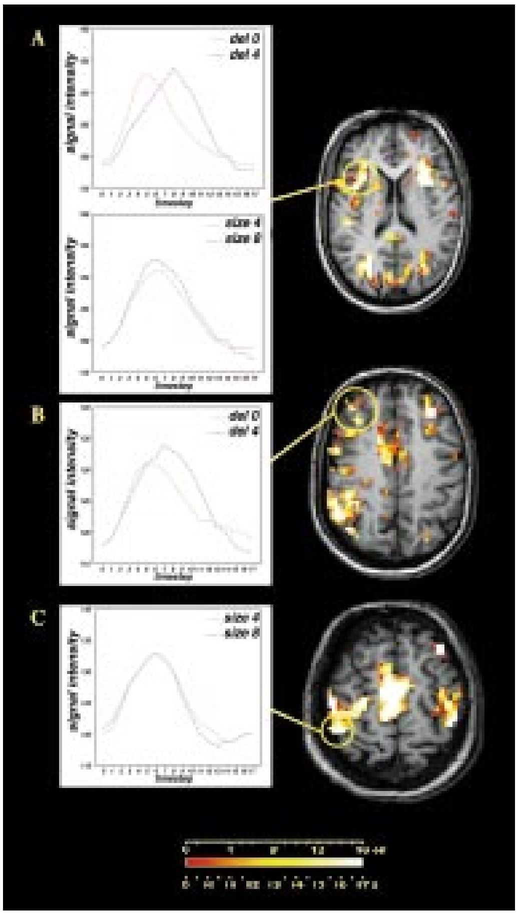


Figure 5. Insets show the time-courses of the measured fMRI signal as a function (A) of delay and set size for the left insula, (B) of delay for the left middle prefrontal cortex and (C) of set size for the left motor cortex. The activation maps are of one representative individual subject showing the corresponding activated areas.

3.4.4 Involvement of human cortical areas in delayed matching, assessed with fast fMRI

Pollmann, S., Wiggins, C.J. & von Cramon, D.Y.

Electrophysiological studies using the delayed matching paradigm (DMS) in monkeys have found different classes of neuronal responses. Neurons were found to respond most vigorously either during stimulus presentation or during the delay between cue and match stimuli. In addition, neurons with delay activity may increase firing over the delay, suggestive of a role in response preparation, or decrease firing, which may be indicative of a decaying stimulus memory. Those neurons which respond primarily during stimulus presentation may fire equally strongly during sample and match presentation, indicating sensory processing, or they may show enhanced firing during the match period, suggesting participation in the matching process or response-related processes.

In this study, a fast EPI sequence was applied to investigate the temporal dynamics of the BOLD-response measured in different brain structures during the course of a DMS-experiment. We applied a fast EPI sequence (TR=300 ms) to investigate the time course of the BOLD-response in DMS-trials with geometrical shapes. Activated areas included lateral prefrontal cortex, premotor and parietal cortex bilaterally, and parts of the motor cortex and the supplementary motor area. Region-of-interest (ROI) analyses were carried out in lateral prefrontal, premotor, and posterior parietal cortices. Using multiple regression, we applied regressors capturing stimulus, delay, and response related activity. Peak activations under these regressors were often found in close proximity in the ROI. Analyzing these peak activations we found BOLD-timecourses indicating preferential activation during stimulus presentation, delay, and response execution in all three ROI. In line with analogous findings from the animal literature, our results show that networks of prefrontal, premotor and parietal neurons are involved in all stages of the task. We are currently analyzing the anatomical specificity of these networks.

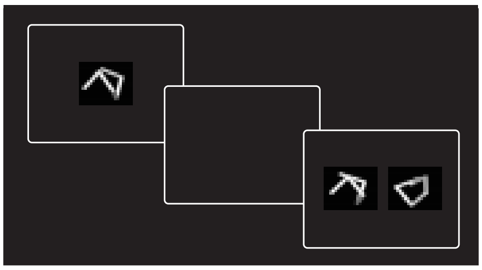


Figure 6.

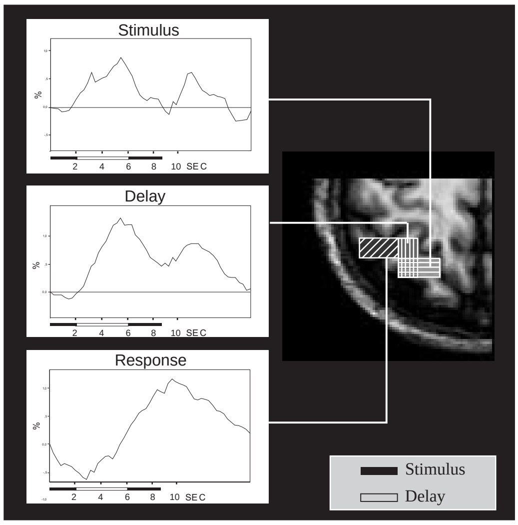


Figure 7.

3.4.5 Determining visual search strategies with reaction time models

Müller-Plath, G., Pollmann, S. & von Cramon, D.Y.

Visual search paradigms are central to the investigation of visual attention. In a typical experiment, a subject has to search for a target object among a given number of distractor objects. From the reaction times in different task conditions, conclusions are drawn concerning the operation of visual attention in the respective conditions.

In our approach, reaction times were modelled as sums of the durations of successive search steps. Model parameters were task characteristics (similarity, number and arrangement of target and distractors) and processing characteristics of the subject (size of the attentional focus, attention dwell and shift times). Based on current ideas about the nature and interaction of parallel and serial subprocesses in search tasks (e.g. Guided Search), several model variants were formulated. They were fitted numerically to empirical reaction times from 3 experiments with graded target-distractor-similarities. From the parameter estimations, the individual search strategies were computed (sequence and duration of search steps in each task condition). The model fit and the plausibility of the estimated values and strategies were compared between the model variants.

The best fitting model (more than 98% reduction of variance) proposed that

- items are processed in groups with group size depending on similarity of target and distractors
- movement of attention is discrete and not continuous
- an explicit attention shift to the target is not always necessary before the answer

Figure 8 illustrates the sequence of search steps as proposed by the best model. Table 1 shows the mean estimated parameter values for the 15 search experiments (3 tasks, 5 subjects each).

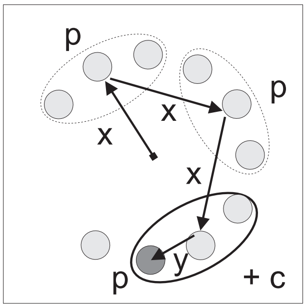
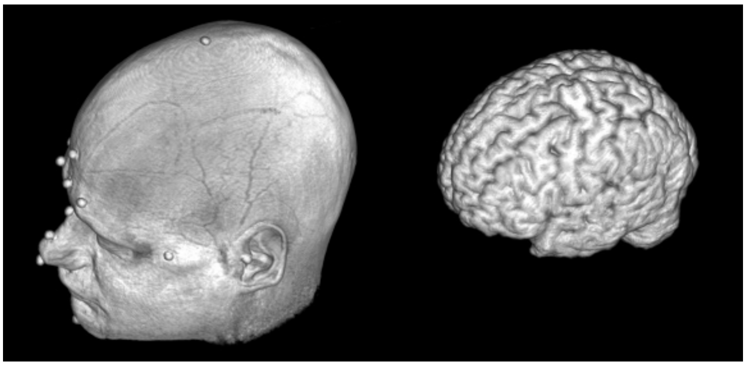


Figure 8. The best model: sequence of search steps

Target-distractor-similarity	1	2	3	4	5
Focus size (no. of items)	2.3	4.2	4.8	6.8	>10
Attention dwell time *p* (ms)	152	94	75	41	22
Attention shift time *x* (ms)	40				
Last attention shift time *y* (ms)	31 (5 experiments)				
	0 (10 experiments)				
Constant time *c* (ms)	333				

Table 1. Averaged parameter estimations across n=15 experiments)

Responses to functional stimulation of the human brain can be recorded using methods such as fMRI, EEG, MEG, SPECT and PET, which characterize different aspects of the underlying cognitive processes. Because these different methods yield complementary information about the anatomical, metabolic and neurophysiological state of the brain, integrated data evaluation is highly desirable and will lead to results not attainable with a single modality.



The Signal and Image Processing Group (SIP) works towards the following aims:

- development and installation of new algorithms for processing of functional data
- combination of results from different modalities
- attainment of a precise anatomical description and quantification of functional activity
- development of structural and functional models of the brain

These long-term aims were addressed in 1998 by the following projects:

- analysis of the individual neocortical structure of the human brain (3.5.1)
- analysis of functional MR images (3.5.2, 3.5.3, 3.5.4, 3.5.5)
- segmentation of pathological MR images (3.5.6, 3.5.7, 3.5.8)
- spatio-temporal analysis of EEG/MEG data (3.5.9, 3.5.10)

In addition two Ph.D. projects are underway (3.5.11), the first covering inverse problems of mechanical finite element models of the brain, and the second a new way of filtering EEG/MEG datasets using perturbation theory (3.5.10).

3.5.1 Automatic labelling of the human cortical surface using sulcal basins

Lohmann, G. &
von Cramon, D.Y.

Human brain mapping aims at establishing correspondences between brain function and brain anatomy. One of the most intriguing problems in this field is the high interpersonal variability of human neuroanatomy that makes studies across many subjects very difficult. Sulcal patterns often serve as landmarks that help to identify corresponding brain loci. In this project, we developed a method that automatically detects and attributes neuroanatomical names to cortical folds in T1-weighted magnetic resonance data of human brains.

We claim that cortical folds can be subdivided into a number of substructures which we call *sulcal basins.* Sulcal basins are concavities in the white matter surface bounded by convex ridges that separate one basin from the next so that adjacent basins meet at the top of the ridge. The concept of sulcal basins permits a more precise definition of brain loci than the traditional concept of sulci.

The automatic identification of sulcal basins proceeds in two steps. In the first step, we segment sulcal basins from MR images using a sequence of morphological operators and pattern recognition techniques. In the second step, we attach anatomical labels to the segmented basins using a model matching approach. The model was obtained by hand-labelling sulcal basins segmented from twelve data sets. It describes average locations of 38 model basins and their spatial relationships. Figure 2 displays the centers of gravity of these loci against sulci of one individual data set. Spatial relationships are represented by arcs.

We have applied this method to 37 T1-weighted MRI data sets. So far, we have only processed the lateral surface of left hemispheres. On average, 1.5 basins received false identifications, so that about 90 percent of the lateral surface was labelled correctly. Figure 3 shows the result of an automatic labelling.

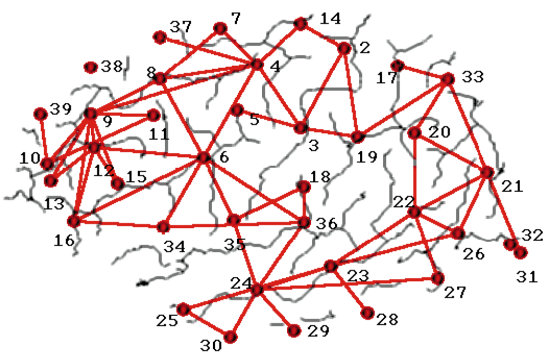


Figure 2. The sulcal basin model. It contains 38 model basins and their spatial relationships.

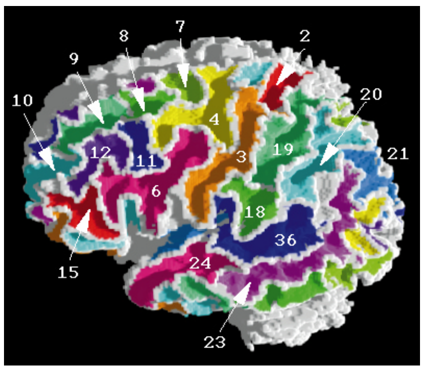


Figure 3. Automatically identified sulcal basins.

The most important aspect of our future work will be to provide a neuro-psychological validation for our concept of sulcal basins. We plan to correlate sulcal basin labellings with functional activations measured by fMRI studies. We expect to find that functional activations fall into equivalent basins across subjects. Some preliminary experiments show that this is indeed the case.

Statistical analysis of fMRI time-series

3.5.2

Pélégrini, M. & Kruggel, F.

The BRIAN package includes a statistical module (*vfstat*) for analyzing fMRI time-series and detecting significantly activated areas. The statistical tests currently available (Kruggel et al., Annual Report 1997, p. 117) yield statistical parametric maps (SPM) whose distribution depends on the test performed (e.g., SPM$\{t\}$ for Student's tests, SPM$\{F\}$ for multiple regression). These maps are then converted to an SPM$\{Z\}$ (normal distribution), which allows the subsequent use of thresholding procedures based on the spatial extent of activated clusters. The transforms converting initial probability distributions to a Z distribution were studied and their precision improved for the available tests: Student's tests, Kolmogorov-Smirnov test, Pearson's correlation, ANOVA and multiple regression.

A Fourier-based method for estimating the hemodynamic response function of the brain was proposed last year for periodic experimental designs (Kruggel et al., Annual Report 1997, pp. 118-119). This approach, generalized to designs with variable inter-trial interval, was included in *vfstat* as an independent option:

- for a given time-series, the voxel-wise parameters (lag, dispersion, gain) of the hemodynamic response (modelled as a Gaussian, a Poisson or a Gamma kernel) can now be estimated and their spatial distribution stored in images,
- estimated hemodynamic responses can be accounted for while performing a univariate multiple regression analysis.

All previously available tests in *vfstat* were univariate (they processed one pixel at a time). We also included a multivariate method (processing all the pixels at the same time): the conditioned fixed-effect model (developed at INSERM U494, Paris), which can be used for processing two-level blocked-trial experiments. This method first determines the part of the signal acquired during activation states which is not spatially correlated with the brain signal measured during control states (conditioning step). The resulting signal is then modeled as the sum of a deterministic activation signal and of an error (fixed-effect model). The deterministic signal is finally estimated using a principal component analysis and the first orthogonal image is stored as an SPM$\{Z\}$.

fMRI time-series can be analyzed using a large range of methods. However, there is a lack of consensus in the literature as to how the statistical power of these methods may be determined. Our current work therefore focuses on their evaluation, in terms of specificity and sensitivity.

3.5.3 Analysis of fMRI time-series with multiple regression and hemodynamic modeling: an event-related memory experiment

Pélégrini, M., Zysset, S., Kruggel, F. & von Cramon, D.Y.

Univariate multiple regression analysis is a standard statistical procedure which allows analysis of fMRI experiments involving several cognitive or experimental conditions. This method aims at detecting brain areas specifically activated depending on the effect of a particular condition on the measured signal. However, this requires modelling the hemodynamic response (HR) function of the vascular system of the brain, which is a critical issue when event-related trials are considered.

Considering neuronal-vascular coupling as a functional convolution, a data-driven method for estimating a space-variant HR had already been proposed to deal with periodic experimental designs (Kruggel et al., Annual Report 1997, pp. 118-119). We generalized this approach to designs with variable inter-trial intervals (ITI). The hemodynamic response was incorporated into the regression model by modulating theoretical waveforms by the Gaussian kernel estimated in each voxel.

We considered an event-related memory task experiment, using a modified version of the Sternberg paradigm with fixed sets (size: 4, 6 or 8 letters) and variable delay (0, 2 or 4 seconds) between cue and probe presentation. To determine whether it was possible to distinguish between delay-independent activated areas (whose time course was not correlated with the cue presentation) and delay-dependent activated areas (whose time course was correlated with the probe presentation), two theoretical waveforms were used: the first was a periodic box-car function synchronized with the cue presentation and the second was a box-car function with variable ITI synchronized with the probe presentation. fMRI time-series were analyzed using univariate multiple regression without hemodynamic modelling (M1); with hemodynamic modelling assuming a constant Gaussian HR with parameters previously proposed in the literature (M2); and with hemodynamic modelling assuming a spatially-variant Gaussian HR estimated for each regressor independently (M3).

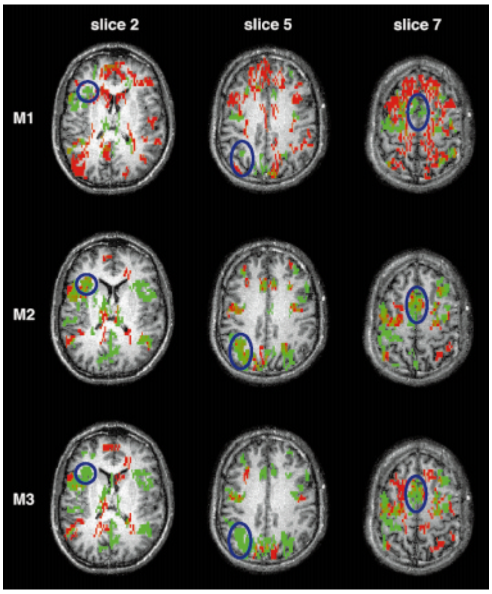


Figure 4. Relative contribution of positive regression coefficients obtained for one subject. Left AI (slice 2), left PPC (slice 5) and SMA (slice 7) are circled. The regression coefficients were coded in red for the first regressor and in green for the second regressor.

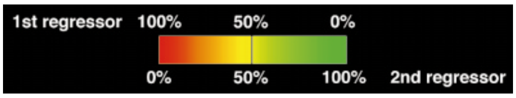


Figure 4 shows the results obtained for a particular subject. Regression coefficients corresponding to the first regressor were mapped to red, the second regressor to green. Only the second regressor is expected to have a significant influence in regions AI, PPC and SMA, where voxels should be pure green. The results obtained with regression analysis (M1) alone confirmed the necessity of modelling the hemodynamic response. Regression analysis with a constant Gaussian HR (M2) failed to distinguish between the influences of both regressors, leading to many "brown" voxels. On the other hand, regression with a space-variant data-driven HR (M3) better separated the responses to each visual stimulus, yielding more pure green sites (i.e., delay-dependent activated areas) than M2 in left AI, PPC and SMA. Results favor a spatially-variant model such as M3, which automatically adapts to the signal in each voxel.

Characterization of the hemodynamic response in event-related functional MRI experiments

3.5.4

Kruggel, F. &
von Cramon, D.Y.

The previous project introduced the use of spatially-variant models for the hemodynamic response. Today, most studies of cognitive processes using functional MRI (fMRI) experiments adopt a single-trial design, which is expected to result in modification of the hemodynamic response (HR) from trial to trial. In this project we focus on the 'on' time course of the HR: its temporal characteristics during a single trial and trialwise changes induced by the stimulation context. We adapt a Gaussian model function to the hemodynamic response and generate parameter sets for each trial and each pre-defined region-of-interest (ROI). These parameter sets incorporate the *gain* (the "height" of the HR), the *dispersion* (proportional to the duration of the HR), the *lag* (the time delay from stimulation onset to the HR peak), and the *norm* of a HR (proportional to the amount of activation). In a fMRI study in language processing, single sentences were presented aurally, and subjects were asked to classify a sentence for grammatical correctness. The presentation of a single sentence needed approx. 3 s, followed by a pause of 21 s. At 912 timesteps during the 76 trials, functional images were recorded. Functionally active regions were detected and ROIs were defined by selecting the 6 most highly activated voxels around local maxima in the z-score map.

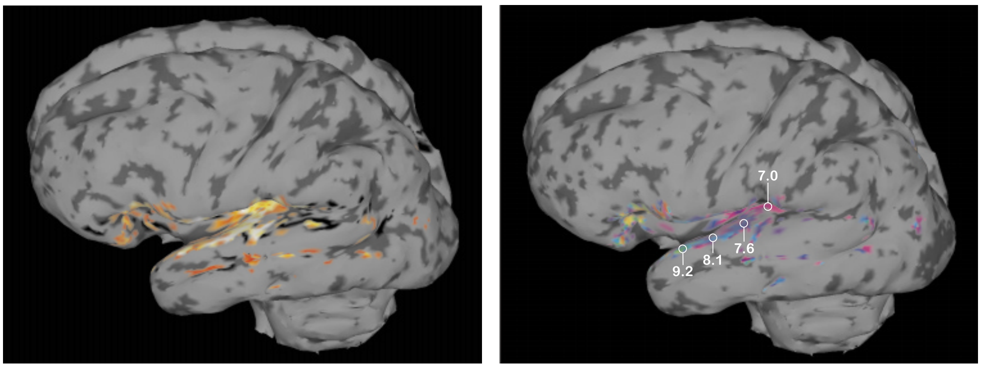


Figure 5. Surface view of the left temporal lobe: z-scores (left) and resp. lag times (right, in s) are mapped on the flattened brain surface. Four regions with averaged timings mark a temporal signal trajectory along the superior temporal gyrus.

For 42 ROIs, we adapted our HR model in each of the 76 trials, thus yielding 42x76 estimates for the gain, norm, lag and dispersion. We summarize our findings as follows:

- On the basis of an EPI protocol using a repetition time of 2 s, lag time differences of approx. 250 ms could be resolved in a series of 76 single trials.
- We were able to show that primary cortical areas are activated before secondary areas, which are in turn activated before veins.
- A temporal sequence of activated regions was found to originate from Heschl's gyrus and to spread along the superior temporal gyrus anteriorily and laterally (see Figure 5).
- It was possible to connect behavioural data (i.e., reaction times, responses) with the estimated parameters of the proposed model in a meaningful way (see Figure 6).
- A longer sentence presentation length was reflected by a higher norm and a longer lag of the HR.

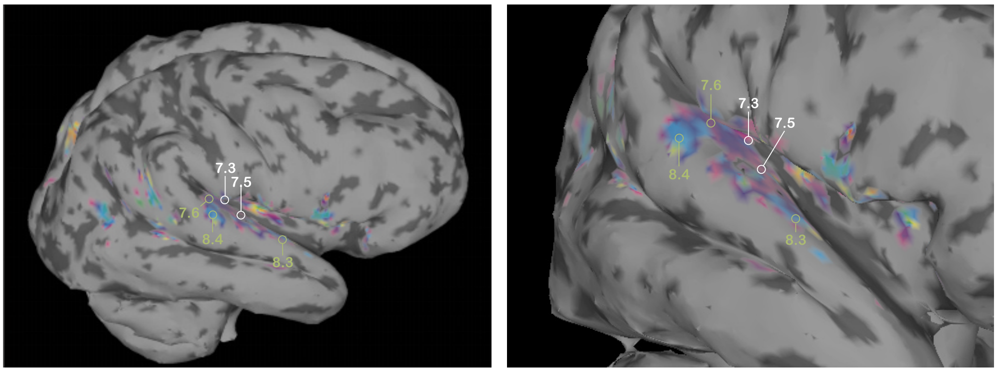


Figure 6. Surface view of the right temporal lobe, showing average lag times for ROIs. Early responses were located in Heschl's gyrus, which only showed a dependence on the sentence length (numbers in white). Late responses, which were located more laterally and anteriorily, showed a dependency on the correctness manipulation (numbers in green).

3.5.5 Probabilistic modelling of fMR images

Svensén, M. & Kruggel, F.

The previous approach requires pre-defined regions of interest. In this project, we were interested in extending our temporal model of the hemodynamic response (HR) into a spatio-temporal model. Each pixel is assumed to belong to one of k classes, which correspond to parametric models of the HR. We model the image as a Markov random field and implicitly assume that the spatial distribution of the classes will be locally smooth, so that neighbouring pixels typically belong to the same class. Thus, images will consist of one or more spatially homogeneous regions, each region consisting of pixels with similar characteristics in their HR. Again, we choose the Gaussian model function which allows us to give parameters a physiological interpretation. As an additional benefit, we can use knowledge about the HR and the experimental design to define a prior distribution for the parameters. Since fMRI data are very noisy, the use of such prior information significantly increases our chances of achieving a reasonable fit.

An EM-like joint segmentation-estimation procedure is employed, which alternates between segmenting the image into regions and estimating the parameters of the HR model functions associated with the different classes. Figure 7 shows results obtained by applying this model to fMRI data, from an experiment designed for investigating sentence comprehension.

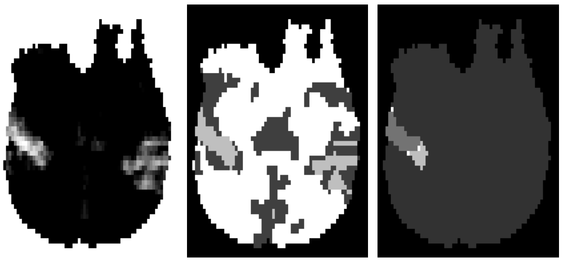


Figure 7. Correlation-based z-score map overlaid on the brain mask (left), a segmentation from our method (middle), with light and dark grey areas corresponding respectively to the solid and dashed HR model functions shown in the left plot in Figure 6; white areas belong to the constant background function. The right image shows a segmentation of a selected region, based on single trial data. The light and dark grey areas correspond respectively to the solid and dashed HR model functions shown in the right plot in Figure 8.

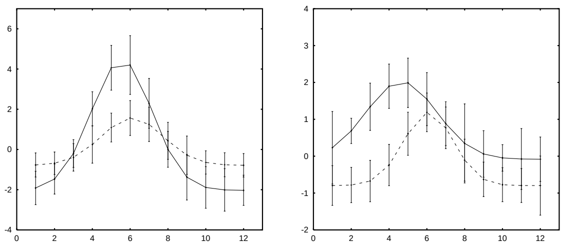


Figure 8. The left and right plot show the HR model functions corresponding to the segmentations shown in the middle and right images in Figure 7, respectively.

The right image in Figure 7 was obtained by applying the proposed method to data from a single trial, restricting attention to a defined region comprising the superior temporal gyrus and Heschl's gyrus, which are known to demonstrate a strong response. The corresponding HR functions are shown on the right in Figure 6. Results suggest that (1) regions of activated pixels may not be spatially homogeneous, but rather have sub-regions with different characteristics in their HR, and (2) during a set of *n* trials, less distinct spatial activation patterns are observed. Averaging over trials may hide this. The proposed method can serve as a sophisticated tool for analysis of fMRI data, which is complementary to existing techniques.

3.5.6 Neurobiology and prognosis of mild cognitive disturbances in elderly people

Gertz, H.-J.[1], Angerhöfer, S.[1] & Kruggel, F.[2]

[1]Clinic for Psychiatry, University of Leipzig, [2]Max-Planck-Institute of Cognitive Neuroscience

This clinical project is performed in cooperation between the Interdisciplinary Center for Clinical Research, Leipzig, and our institute. The prevalence of dementia and mild cognitive disturbances (MCD) in a population of elderly people is relatively high, and recent studies suggest that the incidence rises with age. MCD are measurable cognitive deficits which are not severe enough to warrant the diagnosis of dementia. Some cases become demented within a couple of years (crossover type) while other retain their abilities (stable type). The most common cause of dementia in elderly people is

Alzheimer's disease, followed by vascular dementia and their mixed variant. Recent publications suggest that biological parameters which characterize MCD and dementia in longitudinal studies are potential predictors of the alternate types of MCD.

The aim of this project is the characterization of MCD on the basis of a representative group by considering their clinical presentations. We recorded measures of brain atrophy and focal lesions (cerebral infarcts, white matter lesions) from MRI scans, neurophysiological parameters from digital EEG, genetic and cellular markers (ApoE-characterization, lymphocyte stimulation) from blood samples, and long-term blood pressure recordings. Included in the study were persons drawn from the LEILA study (Leipziger Langzeitstudie zur Ermittlung der Inzidenz dementieller Erkrankungen), who were between 75 and 85 years of age and rated 19-30 points in their MMS. Careful clinical and paraclinical examination ruled out secondary causes of cognitive disturbances. For a standardized clinical examination we used the "Structured Interview for the Diagnosis of Dementia" based on the criteria of DSM-IIIR and ICD-10.

To date, we have examined 45 subjects using the Siemens MRI scanner at the University Clinic, Leipzig, using a high-resolution T_1-weighted sequence for anatomical scanning and 18 T_2-weighted axial slices to detect white matter lesions. Datasets were transferred to the MPI and analyzed using the BRIAN software. All datasets were aligned with the stereotactical coordinate system. Periventricular lesions and lesions of the deep white matter were rated according to their location and extent using a semiquantitative method developed by Fazekas et al. (1987). Cerebral infarcts were recorded likewise. For the evaluation of medio-temporal atrophies, cross-sections of the hippocampus were measured at the head and the body in 5 consecutive coronal slices with a slice-to-slice distance of 3 mm. In addition, we determined an estimate for the volume of the superior temporal gyrus. The intracranial volume, the brain volume, ventricular and CSF volume were determined automatically by image processing procedures developed at the MPI (see following section).

We expect that atrophies of medio-temporal substructures and white matter lesions are predictors for development of dementia in persons with MCD. Re-examination of all persons included in the study is planned for 1999.

3.5.7 Extraction of descriptors for brain atrophies

Hojjatoleslami, A. & Kruggel, F.

Extraction of quantitative descriptors for brain atrophies (as found with patients from the previous project) involves computing a number of measurements representing the properties of anatomical structures in the brain. Evaluating the change of measures over time and their deviation from normal categories allows the investigation of the relationship between pathological changes and changes in cognitive abilities. Descriptors can be categorized into: (1) global measures (i.e. total brain volume, white matter, ventricle, or CSF volume), and (2) local measures (i.e. cortical thickness, white matter lesions, cortical and sulcal volumes, number, location and size of small white matter lesions).

We focused on the development of a segmentation technique to separate brain, white matter, CSF and ventricles from other parts of the head. To overcome problems encountered with standard segmentation methods, a region growing technique was implemented which incorporates (1) a global discontinuity measure computed on the whole boundary of a region and (2) a criterion to detect junctions between the brain and other parts of the head. To obtain a separate segment for the brain, we first employ the method to segment bright parts of the head including eyes and scalp. The result is used as a mask to segment the brain which prevents the growing process from joining the non-brain parts of the head.

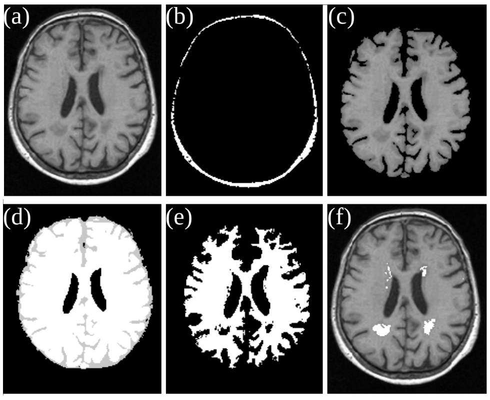


Figure 9. Different structures segmented by our region growing technique. (a) original MR image, (b) segmented scalp, (c) brain, (d) external cisterns in gray and internal cisterns in black, (e) white matter and (f) the white matter lesions overlayed on the original image.

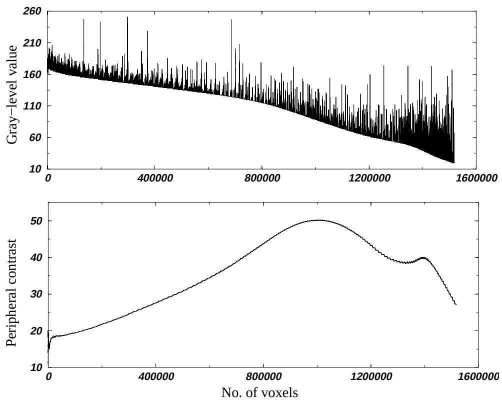


Figure 10. Mappings of gray levels and peripheral contrast during the growing process. The global peak is related to the brain boundary and the local peak at the end of the graph is related to the CSF.

The segmented CSF is then used for extracting the lateral ventricles by cutting their connection to other parts of CSF at the lamina terminalis (Figure 9d). Applying the algorithm on the segmented brain (Figure 9c) produces a local peak related to the gradient between the white matter and the gray matter (Figure 10), which corresponds to a white matter segmentation (Figure 9e). The algorithm can also be used to segment white matter lesions (Figure 9f). Brain, CSF and ventricular volumes extracted from the images are compared with clinical and behavioral data obtained in the previous project.

Design and implementation of an editor for polygonal meshes

3.5.8

Nowotka, G. & Kruggel, F.

To enhance the functionality of the IPE (Image Processing Environment) project an editor module for polygonal meshes was developed. IPE is a part of the BRIAN (Brain Image Analysis) package. Surfaces obtained from volumetric datasets are represented as polygonal meshes. These surfaces are very complex with respect to their number of primitives (typically triangles) and their topology. Within the cortical surface of the human brain, interesting details are often hidden in deep folds. It is desirable that parts of the surface can be extracted manually, e.g., those representing a specific cortical region. The surface patches are easier to handle, due to the reduced data and the higher rendering rates.

General operations for editors, such as translation, rotation, scaling and mirroring can be performed by the editor. With these operations objects can be positioned to get a better overview of the scene. The editor also allows measurement of the area of surface segments. The editor expects a single (complex) object of a surface as input. Sub-objects are primitives, i.e., vertices and polygons.

Projecting surfaces in 3D onto a 2D computer screen presents certain difficulties. It is useful to split 3D operations into several 2D operations at different viewpoints to achieve the desired effect. The translation of vertices is a good example of this method. Use of 3D display and input devices does not generally improve the situation, because of the complex topology of the commonly used surfaces.

There are two convenient ways of extracting details from a surface. The easiest is to select and delete the irrelevant parts of the surface. Vertices may be selected by pointing, by a bounding rectangle or a connected component. Another procedure for extracting details from the mesh is to define interactively a closed line on the surface and to cut out the part of the surface that is surrounded by this line. The success of cutting (obtaining a completely separated sub-surface) depends on the surface topology, i.e. a torus can not be separated into two components by cutting with a closed line around its cross section.

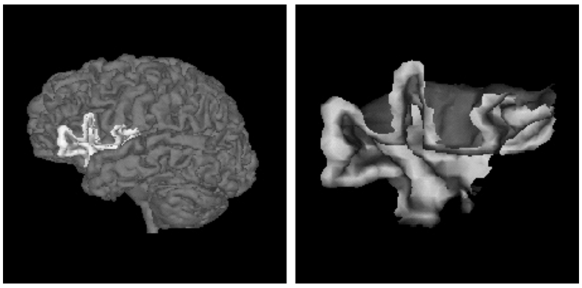


Figure 11. Brain surface (left image) in the form of a polygonal mesh. The left pars triangularis, as extracted from the surface, is shown on the right.

Another useful operation on surfaces is to cut the surface along a user-defined plane. New edges are created by dividing triangles at the plane intersection. The resulting borders at the plane are smooth.

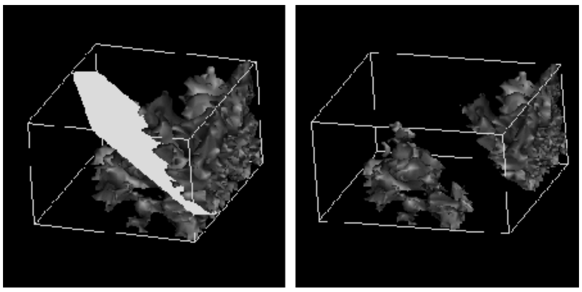


Figure 12. Surface cut by a plane.

In some situations, merging surfaces is useful. The editor allows connection of meshes along their borders. In order to achieve a reasonable result, the borders should have a similar geometry. The user must specify the path of the connecting borders. An undo-function working on several levels has been created to assist user interactions.

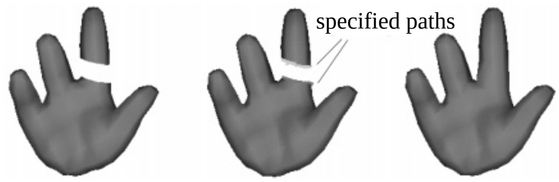


Figure 13. Connecting two meshes.

The impact of dynamical systems based modeling (DSBM): a new definition of components and improvement of source localization in EEG/MEG

3.5.9

Uhl, C. & Kruggel, F.

EEG/MEG signals represent electromagnetic potentials/fields arising on the scalp surface due to neuronal interactions in the human brain. The *high-dimensional* complex dynamical system on the neuronal level exhibits *low-dimensional* behavior on the level of measurements on the scalp surface, observed by correlation dimension studies as well as source modeling leading to low-dimensional dipole models. We have recently outlined the link between EEG/MEG signals, brain functioning and dynamical systems, and presented an algorithm (DSBM) to represent the signal and its dynamics, i.e. to dissociate the dynamically relevant subspace and the irrelevant subspace (noise) from given data sets. The interpretation of the fitted dynamical systems led to a new definition of components and we suggested that more objective criteria for analyzing EEG/MEG data may evolve from this concept (see Figure 14).

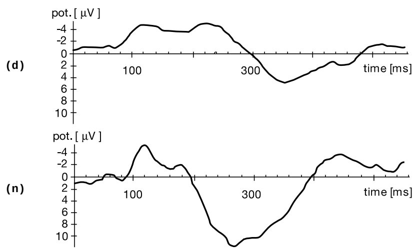


Figure 14. The amplitude of averaged signals measured at the Fz-electrode for two different stimuli: (d) deviant and (n) novel stimuli in an auditory ERP-study.

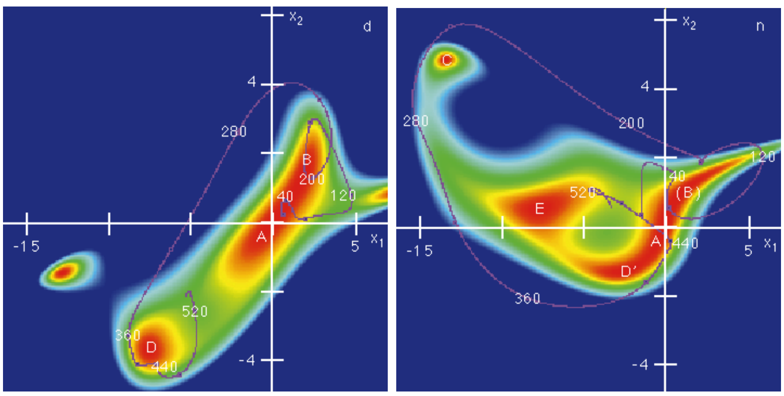


Figure 15. The spatio-temporal signal projected in phase space, which is obtained by DSBM. The signal is represented by the solid pink line, the underlying dynamics are characterized by the color-coded background.

The behavior of the dynamical system can be analyzed by means of fixed points, which are represented in Figure 15 by capital letters. The hypothesis of an equivalence between fixed points and conventional components was studied by investigating single subject data. Figure 16 shows the difference between a number of fixed points, novel-deviant as a function of time. One observes two statistically significant accumulations of fixed points: in the time interval 225-325 ms for the novel condition (p = 0.007), and in the time interval 150-175 ms for the deviant condition (p = 0.014). These findings confirmed our hypothesis, since these time intervals corresponded to expected conventional components: the novel P3 component and the component of mismatch negativity (MMN). Since conventional components are vaguely defined, the definition of components by fixed points of an estimated dynamical system may lead to more objective criterion, and represents a shift from a data-driven to a model-based approach.

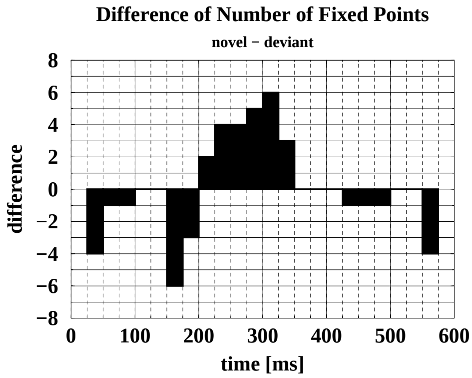


Figure 16.

DSBM was compared to conventional source modeling by simulated noisy data sets. The error of obtained dipole positions was minimal with the DSBM reconstruction for all signal types studied. For noise levels at which two underlying dipoles cannot be resolved from unfiltered data, DSBM reconstruction was successful. PCA fails if signal and noise are not orthogonal to each other, and if noisy parts contribute more than parts of the relevant signal to the data sets.

3.5.10 Analysis of spatio-temporal EEG/MEG signals: a new method for noise filtering and dimensionality reduction

Hutt, A. & Uhl, C.

Reducing the dimensionality of measured high-dimensional EEG/MEG-signals is an important issue. One suitable linear technique is Principal Component Analysis (PCA), which leads to spatial modes and to the rank of their contributions to the signal. Investigation of DSBM (introduced in the previous section) showed dramatic changes in results when increasing the influence of the dynamics component. Such changes can be examined further by perturbation theory. We start from well-known spatial modes determined by PCA and add a small perturbation to fit the signal dynamics. We calculated modes for a 3-dimensional noisy signal with a 2-dimensional deterministic part in the case of a small perturbation (Figure 17). The improvement in the dynamic representation, compared with simple PCA (left image top row), is obvious in this example.

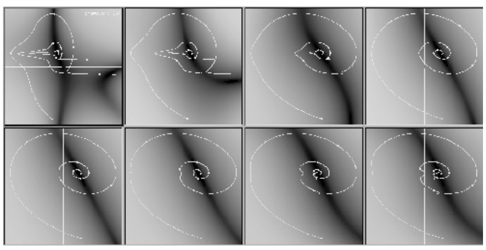


Figure 17. Projections of the signal on the hyperplane spanned by the new modes at increasing perturbation parameters. The projected signal of PCA (top row on the left) represents the dynamics less accurately than the best fit of our perturbative method (the bottom row).

As conventional linear filters do not distinguish between noisy and deterministic contributions to a signal, it is not possible to attribute certain modes to the noise space.

Since our method considers deterministic parts only, noise modes are neglected. It functions well with orthogonal and non-orthogonal uncorrelated noise. We computed a simulation of the Lorenz-attractor (Figure 18), which clearly shows the advantage of this method in comparison to PCA.

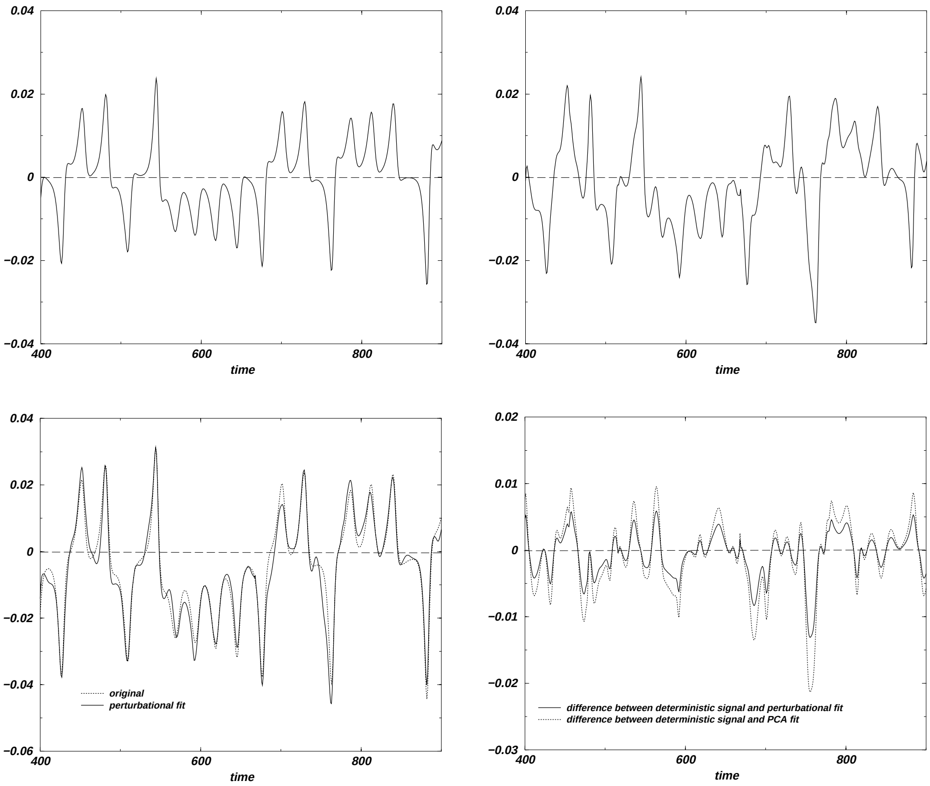


Figure 18. Simulated Lorenz-signal, without noise (top left) and with non-orthogonal noise (top right). Comparison between the deterministic signal and the perturbative fitted signal (bottom left) and between PCA and our proposed method (bottom right).

So far, filtering properties of our method have been described. Our method contains a free parameter for the number of modes to be obtained. An investigation of the influence of this parameter led to a criterion for the actual number of interacting modes. Results for simulated data are presented in Figure 19. We achieved the best dynamic fit with 2 interacting modes (conforming to the original deterministic signal), thus deriving a criterion for the dimensionality of the relevant subspace.

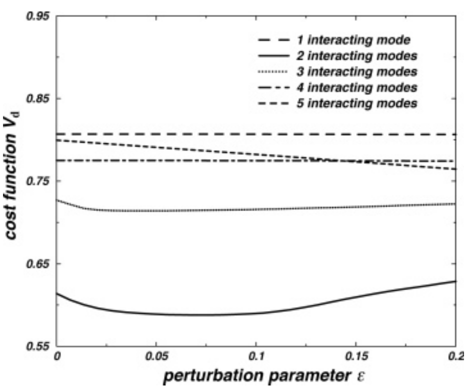


Figure 19. Dynamical cost function with respect to the number of interacting modes. We obtain the best fit with 2 interacting modes, corresponding to the dimensionality of the deterministic signal.

3.5.11 Mechanical forces induced by disease processes in the brain

Wollny, G. & Kruggel, F.

Changes induced by pathological processes (i.e., tumor growth, scarification, atrophies) may be monitored by MRI time-series. We are interested in learning more about the forces on the brain induced by these processes as well as about the mechanical properties of the brain. Mechanical modelling will allow the detection of principal directions of tumor growth and predict the brain shift in neurosurgical interventions.

The following steps are necessary: (i) normalization of scan intensity in the time series data, (ii) performance of a (rigid) transformation of the MRI brain scans, (iii) analysis of changes with time. Here, we need a non-rigid matching procedure to detect shifts of brain structures. Using a 3D finite element model of the brain, we can calculate the driving forces which induced the changes. This will allow us to draw conclusions about the mechanical properties of the brain.
Although this project was only started very recently, we can already present a method for normalizing the scan intensity to a reference image. We use the average and the dispersion of the intensity distribution as a two-dimensional vector. The distance between two images is defined as the euclidean distance between the corresponding vectors. The optimal normalization parameters are found by computing for the image to be normalized the contrast and brightness values which minimize the distance between this image and the reference. An example is shown in Figure 20.

Figure 20. Brain slice at examination time 1 (left), resp. time 2 (middle). On the right, the intensity corrected slice is shown.

This year can best be described as one of consolidation. At the start of the year the replacement magnet was taken into operation. This procedure went very smoothly and by mid-January it was possible to recommence routine studies.

The project examining the temporal accuracy of functional MR (fMR) using double voxel techniques (3.6.1) continued to yield encouraging results, and was supplemented by high speed EPI experiments. These indicate that the accuracy of fMR may exceed even the 300 ms so far achieved. The progress made with the functional GRASE (Gradient and Spin-Echo) experiment (3.6.2) is significant. It was possible both to demonstrate the application of functional GRASE in the visual cortex and to show that GRASE will be capable of outperforming EPI in some regions of the brain. The NMR group aims not only at exploring the methodological boundaries of fMR, but also at improving our knowledge of the underlying physiology. In the project examining the dependence of the BOLD contrast on oxidative metabolism (3.6.3) it could be shown that the BOLD contrast change during functional activation is reduced as a consequence of increased oxidative metabolism. One methodological project with significant promise is the development of velocity selective radio-frequency pulses (3.6.4) with which blood flowing within a given range of velocities can be magnetically tagged. These pulses have considerable potential in the development of multi-slice perfusion methodologies. On a somewhat more mundane level a new approach has been found to alleviate the problem of high RF-power deposition in multi slice T1 imaging (3.6.5). Despite many technical difficulties diffusion tensor imaging has continued to make steady progress and reliable tensor maps can now be produced (3.6.6).

While adequate in the short term, the requirement to remain at the forefront in imaging technology means that the group will be forced to upgrade the gradient system in 1999.

3.6.1 Temporal resolution of fMR experiments

Dymond, R.C., Wiggins, C.J., Norris, D.G., Pollmann, S. & Zysset, S.

The temporal resolution of fMR investigations is limited to 3-4 s by the blurring effect of the haemodynamic response. This study attempted to establish whether temporal displacements in activation onsets which are shorter than the limits of the intrinsic resolution can be detected. In an initial study, functional MR spectroscopy (fMRS) was adopted on account of its short repetition times. Two distinct volumes were defined using a PRESS localization strategy. Magnetic field homogeneity was optimized for each voxel individually. Repetition times (between successive acquisitions from the same voxel) were either 300 ms or 600 ms.

The paradigm used for testing the double voxel technique was designed to elicit a prolonged visual response in V1 and V2 and a secondary trial-dependent signal change in the anterior supplementary motor complex (SMA and pre-SMA) relating to saccade generation. It comprised a period of background flicker stimulation with an embedded search task which commenced at 4.2, 4.8 or 5.4 s after the visual stimulus onset. The different task conditions were randomly interleaved with a full experiment comprising 40 repetitions of each task.

Examination of functional timecourses demonstrated reliable activations in both visual and SMA regions. For the visual data, activation onset times were found to remain constant and the biphasic activation curves reflected both the primary visual stimuli and the appearance of the secondary search objects (see Figure 1 below). Intersubject averaging revealed the secondary activation maxima to be delayed by 600 ms between successive search conditions. The SMA timecourses were uniphasic and demonstrated a single activation maximum. The positions of activation onset and maximum were displaced by 600 ms between successive task conditions. Although these displacements were not always clear on visual inspection of timecourses from individual subjects, a further analysis involving the fitting of a Gaussian response form to the timecourse obtained from the first trial and its subsequent correlation with the response to all trial types did render them apparent.

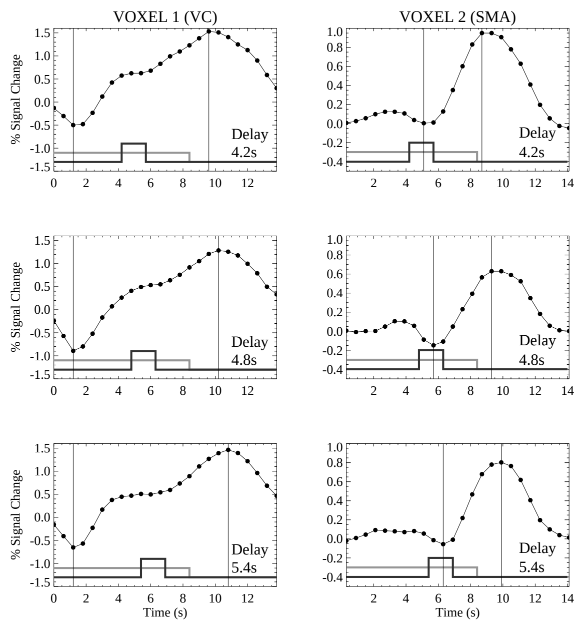


Figure 1. fMRS response curves obtained by averaging of data from 3 subjects (TR=600 ms, 120 trials for each delay condition, 3pt smoothing over timecourses)

In a follow-up study, the paradigm was used with a fast MR imaging technique (EPI). A low-resolution mode (32x32 pixels) was used to give a voxel size similar to that of the PRESS experiment. This was run with three slices and a repetition time of 300 ms. Initial analysis shows similar timecourses to the fMRS experiments. While EPI does not allow the localized shimming used in double-voxel PRESS, acquiring images allows for coverage of different brain areas and reduces the need for exact voxel positioning.

The main conclusion is that fMR techniques can detect temporal displacements in activations in the subsecond range. This finding opens up new perspectives for investigating the relationship between timecourses of cognitive processes and haemodynamic changes in localized regions of the brain.

3.6.2 An investigation of the use of GRASE for functional magnetic resonance imaging

Jovicich, J. & Norris, D.G.

The use of Gradient- and Spin-Echo (GRASE; Oshio et al., 1991) as an alternative imaging method to Echo Planar Imaging (EPI) for functional magnetic resonance imging in brain regions with short T_2^* was investigated using the institute's 3 Tesla MRI system. The choice of GRASE is motivated by its lower sensitivity to magnetic field inhomogeneities compared to EPI and its lower radio-frequency (RF) power deposition in comparison with a pure spin-echo method (Jovicich & Norris, Annual Report 1996, pp. 113-114; Jovicich & Norris, Annual Report 1997, pp. 132-133). The Blood Oxygenation Level Dependent (BOLD; Ogawa 1990) contrast capabilities of GRASE were examined by considering two strategies: a) use of the *intrinsic* BOLD contrast which is available in the GRASE sequence and b) incorporation of an *additional* BOLD contrast by using a T_2^*-preparation experiment.

A computer simulation showed that in principle the intrinsic BOLD contrast of GRASE can be used to give a similar functional sensitivity to that given by EPI. This, however, is at the cost of needing a large number of gradient-echoes per RF interval, making GRASE similar to a spin-echo EPI sequence. Therefore, the use of the intrinsic BOLD contrast of GRASE will lead to similar difficulties to those encountered with EPI.

To use GRASE in such a way that it offers advantages (better image quality) with respect to EPI, an alternative method for incorporating BOLD contrast was investigated which allows the use of a low number of gradient-echoes per RF interval. BOLD contrast was incorporated by using a T_2^*-weighted GRASE with the displaced-echo technique (Jovicich & Norris, 1998). With displaced GRASE it is possible to adjust freely the T_2^* contrast from zero upwards at the cost of a 50% SNR reduction in comparison with EPI. Functional imaging performed on 7 healthy volunteers using a conventional visual stimulation paradigm with both displaced GRASE and EPI showed strong and reproducible activation in the primary visual cortex. As expected, displaced GRASE images gave less activation than EPI due to the reduced SNR.

A computer simulation was used to estimate the functional sensitivity of displaced GRASE as compared to EPI in regions with short T_2^*. The simulation and preliminary experimental results suggest that displaced GRASE may offer better functional sensitivity than EPI in brain areas with T_2^* less than approximately 15 ms.

3.6.3 Investigating the dependence of BOLD contrast on oxidative metabolism

Schwarzbauer, C.

BOLD contrast is the result of a complex interplay between cerebral hemodynamics and oxidative metabolism. To separate these effects, we applied consecutively two different stimuli: visual stimulation (black/white checkerboard alternating with a frequency of 8 Hz) and hypercapnia (inspiration of 5% CO_2). Changes in cerebral blood flow (ΔCBF) and the effective transverse relaxation time (T_2*) were measured in an interleaved manner by combining a previously described spin labelling technique called BASE (Schwarzbauer et al., 1998) with BOLD based fMRI. In six of eight healthy volunteers T_2* was significantly longer during hypercapnia than during visual stimulation, whereas the corresponding ΔCBF values were the same at the given level of significance ($p<0.01$). This finding is explained by a significant increase in oxygen consumption during visual stimulation.

Figure 2 illustrates the relative changes in T_2* related to cerebral hemodynamics, oxygen consumption, and the resulting BOLD effect. The average changes in T_2* (n=6) caused by cerebral hemodynamics and oxidative metabolism were 10.6 ± 3.0% and -4.7 ± 1.2%, respectively, resulting in a net BOLD increase of 5.9 ± 2.3%. These results clearly demonstrate that although the hemodynamic effect is dominant, the increase in cerebral oxygen consumption induced by visual stimulation gives rise to a significant decrease in the BOLD contrast.

The calculated relative changes in the cerebral metabolic rate of oxygen ($CMRO_2$) are depicted in Fig. 3. The average value of 4.4 ± 1.1% (n=6) is in excellent agreement with previous results obtained by positron emission tomography (Fox et al., 1988).

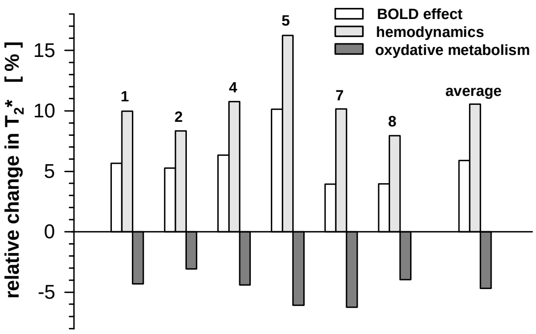


Figure 2. Relative changes in T_2* related to cerebral hemodynamics, oxidative metabolism, and the resulting BOLD effect.

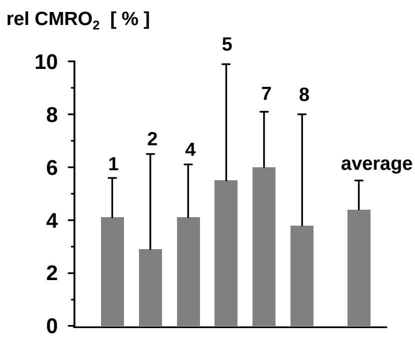


Figure 3. Calculated relative changes in cerebral oxygen consumption ($CMRO_2$).

3.6.4 Velocity selective radio frequency pulse trains

Norris, D.G. & Schwarzbauer, C.

Trains of short RF-pulses are an established method for achieving solvent suppression in NMR spectroscopy. The principle of operation of these pulse trains is that the evolution of the chemical-shift between the individual RF-pulse elements modulates the pulse angle. The pulse angle as a function of chemical shift is determined by the phase of the magnetization at the time of the RF-pulse elements, and not by its value at intermediate times.

It has long been established that position, and its time-derivatives can be phase-encoded by means of pulsed magnetic field gradients, and particularly that velocity can be phase-encoded by means of bipolar gradient pulses (or equivalently by pairs of unipolar gradient pulses separated by 180° refocusing pulses). It is thus clear that the insertion of bipolar gradient pulses between the RF-pulse elements will additionally sensitize these pulse trains to velocity. The effects of chemical shift and main field inhomogeneity can best be eliminated by inserting 180° refocusing pulses midway between RF-pulse elements. The velocity-encoding gradients are then placed about the refocusing pulse as shown in figure 4.

The efficacy of such pulses was demonstrated using a simple phantom consisting of two stationary bottles placed upon two tubes containing flowing water. The results obtained for saturation and excitation are presented in Fig. 5. In (a) and (b) the saturation of non-flowing and flowing material respectively is depicted. The saturation of the water in the stationary bottles means that only spins in the tubes can be seen in (a). For (b) the reverse is true. In (c) and (d) the corresponding excitation images are shown. In (c) only non-flowing spins are excited, in (d) only those flowing. A simple 121 or $1\bar{2}1$ RF-pulse train was used as appropriate. The effects of the laminar flow profile are visible in all these images.

Conceivable applications for these pulse trains can be found in numerous NMR investigations. In functional imaging inflow effects could be reduced, and saturation of the venous compartment could improve the localization of activation to the parenchyma. In recent years significant progress in perfusion imaging has been made using spin labelling methods. Velocity selective perturbation could improve these methods by labelling blood closer to the imaging plane without significantly perturbing slow moving or stationary spins. Cross-talk due to the flow of labelled blood between slices could be eliminated by the use of such pulse trains, making them eminently suited to multi-slice perfusion imaging.

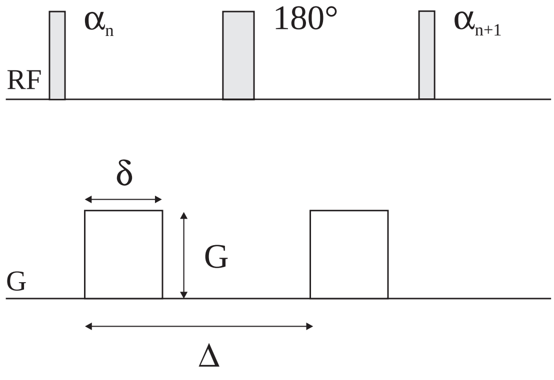


Figure 4.

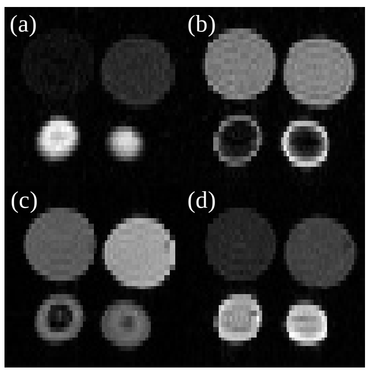


Figure 5.

3.6.5 Low power multi-slice MDEFT imaging

Norris, D.G.

T_1 imaging at high main magnetic field strengths suffers from the known disadvantages of lengthening and converging T_1s. Despite this it has been shown possible to obtain high quality T_1 images from the human head at field strengths of up to 4 T using the MDEFT technique (180°-τ-90°-τ-). At field strengths of 3 and 4 T increased power deposition can also be a limiting factor: the number of slices that can simultaneously be acquired with MDEFT using the conventional pulse sequence is largely determined by the requirement to invert the magnetization in each slice using an energy-intensive 180° pulse.

The low power multi-slice MDEFT sequence circumvents this problem by using a single non-selective inversion pulse for all slices. The central lines of *k*-space are always obtained mid-way between successive inversion pulses, and thus perfectly satisfy the MDEFT condition. This ensures that all slices exhibit the same T_1 contrast. The higher *k*-space coordinates are obtained at times further away from the midpoint between inversions. Thus after each inversion one line of data is acquired from each slice. The phase-encoding scheme and slice excitation order are so organized that the Point Spread Function (PSF) for each slice is identical. The maximum number of slices that may be acquired in this way is limited only by the number of data acquisitions that can be inserted between the inversion pulses. Within this limit the total acquisition time is independent of the number of slices acquired. As the MDEFT method only produces positive magnetization the PSF for this method is very robust. There is no discernible affect on image quality caused by the number of slices acquired. The illustration shows three slices from a 20 slice data set obtained with a data matrix of 512, a field of view of 25 cm and 5 mm slice thickness.

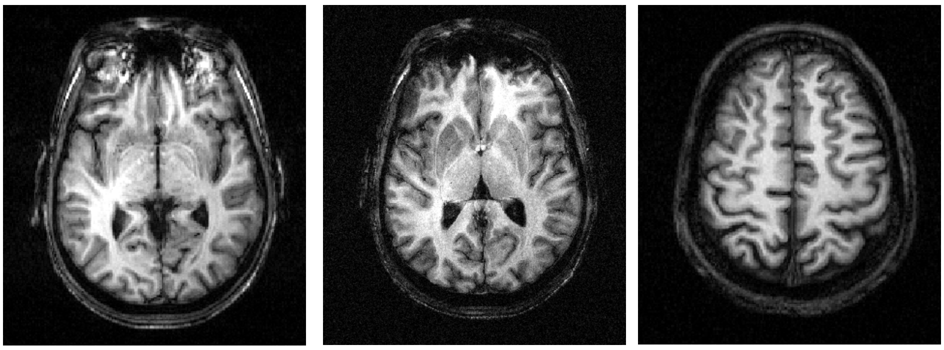


Figure 6.

3.6.6 Diffusion tensor imaging

Koch, M. & Norris, D.G.

Spatially resolved measurements of the self diffusion tensor of water in the human brain can serve as a means to:

1. image fibre orientation in human brain white matter
2. provide information about the tensor of electrical conductivity in human brain. With this information the accuracy of source localization from MEG data could be improved (3.7.8).

Magnetic Resonance Diffusion Tensor Imaging (DTI) requires a magnetization preparation including two diffusion gradient pulses, and a rapid imaging sequence. DTI sequences based on three different imaging methods (UFLARE, EPI, and GRASE) have been implemented.

To measure the full self diffusion tensor of water the direction and strength of the diffusion gradient pulses have to be varied (Basser et al., 1994). In order to find the direction with the largest diffusion coefficient the diffusion tensor is diagonalized. The eigenvector of the diffusion tensor that corresponds to the largest eigenvalue represents the estimated fibre direction.

The dominant problem is an "artefactual" anisotropy that corrupts the tensor maps. This problem could be reduced to a large extent by using a method for adjusting the preemphasis unit that is more sensitive to eddy currents than the method used previously. By means of extensive averaging, the number of pixels that exhibit artefactual anisotropy could be decreased.

The figures show examples of diffusion tensor maps acquired with UFLARE overlaid on a T1 image of the same slice. The lines show the in-plane components of the eigenvector directions corresponding to the largest eigenvalue. In white matter this is the fibre direction. Eigenvectors in pixels with low anisotropy were excluded. The largest diffusion anisotropies are found in the corpus callosum. The anisotropic appearance of CSF in the ventricles is caused by flow effects. Total imaging time was approximately 50 min.

Due to its low sensitivity to eddy currents and despite its relatively low signal-to-noise ratio UFLARE provides the best tensor maps at present. Tensor maps based on the EPI or the GRASE sequence suffer from apparently anisotropic ghosts and from image shifts or distortions due to eddy currents.

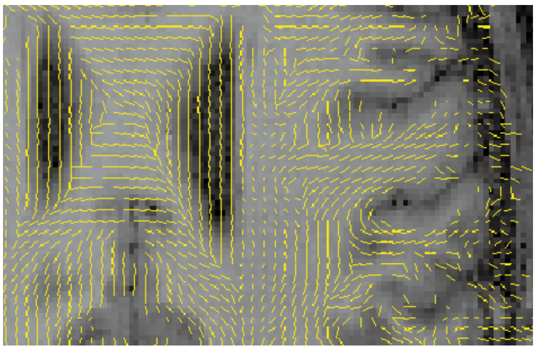


Figure 7.

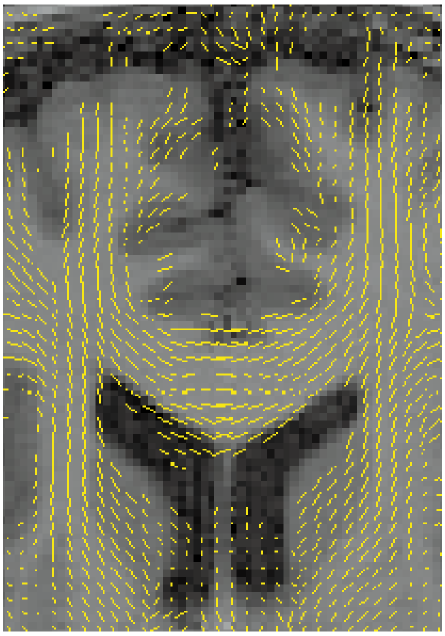


Figure 8.

This year's activity of the group was characterized by the move of the MEG system to a location outside the city of Leipzig in order to combat the environmental magnetic noise in the inner city. The system was relocated in August and after recalibration ready for use in October. Since then a number of MEG studies have been conducted in the auditory processing domain. To some extent, these have replicated previous work on the auditory M100 response (3.7.1). However, they have also opened up a new area of research by combining EEG and MEG measures to explore auditory processing in musicians and non-musicians as well as music processing in non-musicians (3.7.2, 3.7.3, 3.7.4).

Violations of structural expectancies in the music domain were found to be correlated with an early right anterior negativity and a late positivity in the electrophysiological measures, and a dominant late effect in the MEG measures. Modelling of the generators of this activity will need to take into consideration the difference between EEG and MEG effects. The findings for processing in the music domain may be contrasted with those from processing in the auditory language domain reported in 3.1.6. Violations of structural expectancies in the language domain are correlated with an early left anterior negativity followed by a late positivity in the EEG measures. MEG measures show both an early and a late effect although the early effect is not lateralized to the left. Modelling reported in 3.1.6 takes this difference into account. Since the violations investigated in the language domain related to the difference between nouns and verbs, these two major lexical categories were made the focus of an additional MEG study (3.7.5).

Advances in dipole modelling were made by using fMRI data to constrain possible sources (3.7.6) as well as by applying new mathematical approaches to the modelling of MEG data in particular (3.7.7, 3.7.8). A rule-based artefact rejection program for the preprocessing of event-related potentials was developed (3.7.9).

3.7.1 Temporal coding of frequencies in the neuromagnetic M100 to auditory stimuli – a replication

Fiebach, C.J., Herrmann, C.S., Knösche, T.R., Maess, B. & Friederici, A.D.

After the MEG laboratory had been moved to its new location in Bennewitz, a first study was carried out to replicate the recently reported effect of tonochrony (i.e. temporal coding of frequencies in the latency of the M100 [Roberts & Poeppel, 1996]). Seven participants were stimulated bilaterally with pure sinusoidal tones of 500 Hz, 750 Hz, 1000 Hz, 1500 Hz, 2000 Hz, 2500 Hz, 3000 Hz, 3500 Hz, and 4000 Hz (400 ms duration; slopes of 25 ms; 100 trials per condition) at 45 dB above their hearing threshold. Data were acquired in 4 blocks from 148 MEG channels with a sampling rate of 250 Hz and a bandpass of 0.1 Hz to 50 Hz.

The signals were averaged blockwise. For every block, fields were transformed from individual gradiometer positions to a standardized gradiometer array. Finally, averages for each participant and each frequency and grand averages were calculated. In the grand averages of the nine stimulus conditions, M100 peaks showed signal strengths of between 97 fT and 266 fT (mean 176 fT; mean signal to noise ratio 19).

In order to analyze the latency of the M100 peak as a function of frequency, an array of 28 channels with signals larger than 70 fT was selected for each hemisphere. These channels were located over temporal regions and distributed symmetrically. Analogous to the procedure described by Roberts & Poeppel (1996), the root mean squared field (rms) was determined for each participant and hemisphere separately. Figure 1 displays the averaged latencies of the M100 rms peaks and the corresponding standard errors. The graph shows that the tonochrony effect could be replicated. The relationship between M100 latencies and frequencies strongly resembles the results reported by Roberts & Poeppel (1996). However, the latency distribution reaches its minimum at a higher frequency than in the previous study, namely at 2000 Hz instead of 1000 Hz.

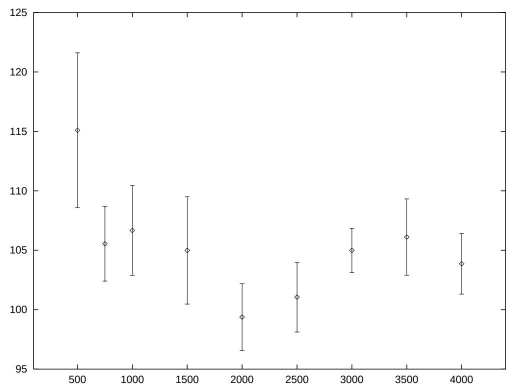


Figure 1.

3.7.2 Echoic memory functions are modified by experience: musicians have superior automatic auditory processing

Kölsch, S.[1], Schröger, E.[2] & Tervaniemi, M.[3]

[1]Max-Planck-Institute of Cognitive Neuroscience, [2]Department of Psychology, University of Leipzig, [3]Cognitive Brain Research Unit, Helsinki, Finland

Mechanisms of sensory memory, the earliest cognitive memory system, are typically assumed to be independent of experience (Cowan, 1995). The present study aimed to provide evidence for influences of experience on auditory sensory (echoic) memory mechanisms.

These mechanisms function pre-attentively, i.e. even when incoming sound is ignored (Näätänen, 1992). We investigated whether the superior auditory processing in musicians is solely due to elaborated functions on higher cognitive levels involving the attentional processing of sounds, or also to a superior processing at a pre-attentive level. The current results demonstrate that highly trained musical experts profit in their auditory discrimination abilities from elaborated neural mechanisms on a sensory memory level. This was revealed by the brain's automatic change-detection response, which is reflected electrically as the mismatch negativity (MMN) and generated by the operation of echoic memory.

Examining musical experts and musical novices, we found that MMNs of both groups did not vary when single tones were presented, even when the frequency of these tones was varied slightly. Conversely, when the same tones were embedded in chords (arranged in such a way that the standard stimulus was a perfect major chord, and the deviant stimulus a slightly impure chord), MMN was enhanced in musical experts, but almost absent in novices, independent of whether stimuli were attended to or ignored. When stimuli were ignored, deviant chords elicited a distinct MMN in experts but no MMN in novices, reflecting improved sensory memory processing in experts compared to novices (Figure 2). When chords were attended to, slightly impure chords were clearly discriminable for experts, but virtually undetectable for musical novices.

In summary, these results provide the first evidence for superior *pre*-attentive auditory processing in musicians, i.e. that the superior discrimination performance of musicians is not only due to processing at higher cognitive levels but also to pre-attentive memory-based processing. Since attentive auditory discrimination performance can be improved by training, the present data demonstrate that long-term training is able to modify even *pre*-attentive neural memory mechanisms. These mechanisms are located on the earliest physiologically measurable level of auditory comparison processes in the human brain. This study is part of diploma work conducted at the Institute of Biological Psychology, University of Leipzig.

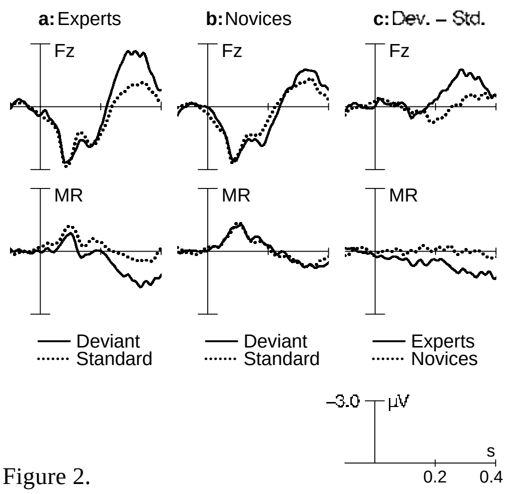


Figure 2.

3.7.3 Electrophysiological correlates of music processing: "non-musicians" are musical

Kölsch, S.[1], Gunter, Th.C.[1], Friederici, A.D.[1] & Schröger, E.[2]

[1]*Max-Planck-Institute of Cognitive Neuroscience,* [2]*Department of Psychology, University of Leipzig*

To date, there has been very little research into the event-related brain potentials (ERPs) elicited by the cognitive processing of music. With a starting point of music-psychological knowledge obtained using subjective measures, the present study focused on how the brain reflects in an electrophysiological sense musical expectancy violation and harmonic reintegration. Non-musicians listened under 'ignore' conditions to cadences, i.e. chord-sequences, either consisting of in-key chords or Neapolitan sixth chords. Since Neapolitan chords contain out-of-key notes, the sound of these chords violated the expectancy generated by the preceding tonal context.

ERPs of Neapolitan chords elicited an early negativity compared to in-key chords with an onset of around 150 ms which was right-anteriorly predominant. Moreover, a late bilateral frontal negativity peaking around 500-550 ms was also elicited by Neapolitan chords (Figure 3, chord duration 1.2 s). To the best of our knowledge, both components have not previously been described. Whereas the early right anterior negativity is likely to reflect the violation of sound expectancy, the late bilateral frontal negativity is interpreted as reflecting harmonic reintegration processes. The amplitudes of both the early and the late negativity were found to be dependent on the amount of musical expectancy induced by the preceding harmonic context. It should be emphasized that participants were "non-musicians". Thus the present study provides the first electrophysiological evidence for implicit musicality of the human brain.

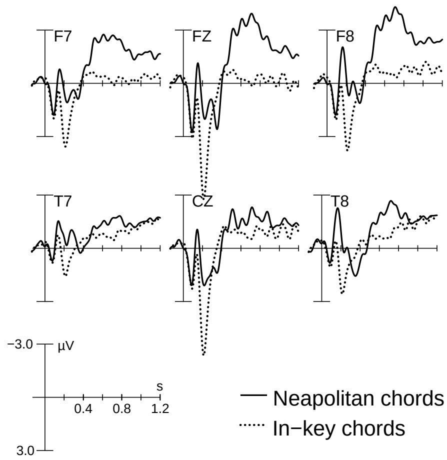


Figure 3.

3.7.4 Locating electrophysiological correlates of music processing: an MEG-study

Kölsch, S., Gunter, Th.C., Maess, B. & Friederici, A.D.

Brain magnetic responses elicited by the processing of music were examined with the same paradigm which was employed in an EEG-study (3.7.3), where the electrical responses of the brain to unexpected sounds were early right anterior and late bilateral frontal negativities. These ERP-deflections were taken to reflect the violation of sound expectancy and harmonic integration processes. As in the ERP-study, participants were "non-musicians" who listened under 'ignore' conditions to the stimuli.

Preliminary data seem to reveal an additional early process which was not visible in the ERP. Its functional significance is not yet clear, but it is assumed that several neural processes contribute to the early right anterior negativity (which is maximal around 150-250 ms). Besides temporal lobe activation, these processes may originate from insular cortex. Thus, several regions were highly (and suprisingly rapidly) activated in brains of "non-musicians" by the musical stimulation. Since experimental conditions (e.g. the degree of violation) were exactly controlled, results are expected to provide precise information about the location of neural substrates connected to the processing of music.

Single word perception as monitored by MEG: processing of morphologically ambiguous nouns and verbs

3.7.5

Maess, B., Fiebach, C.J., Friederici, A.D., Alter, K., Herrmann, C.S. & Oertel, U.

It is widely accepted that the lexical entries of nouns and verbs differ in a number of syntactic and semantic dimensions. Lesion studies suggest that the processing of nouns is supported by left temporal areas (Bierwisch & Schreuder, 1992), while the processing of verbs also involves frontal parts (Danielle et al., 1994). Earlier ERP studies (Gunter et al., in press) resulted in spatially and temporally differing N400s of verbs and nouns.

To investigate this issue, especially with respect to its temporal parameters, neuromagnetic fields were recorded while 29 paid volunteers listened to bisyllabic verbs and nouns which ended on the vowel 'schwa' (e.g., 'forsche/investigate' , 'Hase/rabbit'). In order to avoid a noun-verb ambiguity in the infinitive form of German verbs, only verbs in the first person singular were selected. For the nouns, the nominative singular form was chosen. The participants' task was to detect target stimuli from a list of function words conforming to the same acoustic restrictions (e.g. 'alle/all').

Twenty one participants (11 female; mean age 23.2) whose MEGs demonstrated SNRs of greater than 6 took part in the analysis. The target detection task was performed at 98% correctness and with a mean reaction time of 808 ms (SD: 160 ms).

In the grand averages, an N100m-like field pattern around 170 ms was observed over the auditory cortex. It was followed by a strong sustained activity, also located over temporal regions, that peaked at around 500 ms (250 fT). The ERFs between verbs and nouns were nearly identical from the word onset up to 500 ms.

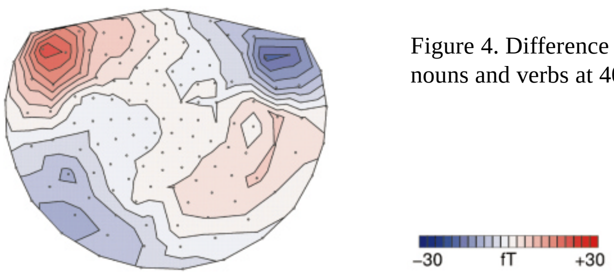


Figure 4. Difference field strength between nouns and verbs at 400..600 ms

The difference map (Fig. 4) between verbs and nouns from a window around 500 ms displays two weak peaks over fronto-lateral regions.

In contrast to the ERP study (Gunter et al., in press), in which sentences ending with a noun or a verb were compared, in this investigation a randomized list of single words was presented. As a consequence, items in the ERP study were morphologically marked while items in the present study were not. Hence, it appears that the differences between nouns and verbs are much weaker when morphologically ambiguous nouns and verbs are presented as single items.

3.7.6 Highly constrained dipole modeling of slow cortical potentials

Bosch, V., Mecklinger, A. & Knösche, T.R.

Dipole modeling allows the estimation of the neuronal brain sources of event-related scalp potentials (ERPs). Within a given head model, virtual brain sources (dipoles) are placed and iteratively manipulated until the dipoles account for a considerable amount of variance in the the ERP data. However, solutions are not unequivocally interpretable, because the number of dipoles, their locations and their orientations cannot be determined uniquely and an unlimited number of possible solutions exists.

In 1997 (Bosch et al., Annual Report p. 54) we reported an EEG-experiment in which retaining object forms in working memory was associated with left frontal negative and parieto-occipital positive slow potentials (SPs). We first assumed that this SP is generated in the ventral part of the extrastriate cortex, i.e. the fusiform gyrus (FG) because, due to the orientation of this area, dipoles project with their positive pole towards parieto-occipital electrode sites. However, an fMRI-experiment with the same stimulus materials (3.2.1) revealed no activation of the FG but rather showed activation in anterior regions of the intraparietal sulcus (IPS), in the left inferior frontal gyrus (IFG) and the left precentral gyrus. Dipoles within the posterior bank of the IPS project positively towards parieto-occipital electrode sites, and thus could also account for the observed posterior positive SP. To test this hypothesis, a highly constrained dipole model was developed.

A 3-shell head model was computed and bilateral dipoles were placed within the posterior bank of the anterior part of the IPS. A third dipole was positioned in the left IFG. To reduce the number of possible solutions all dipoles were fixed and the orientations of the IPS dipoles were forced to be symmetric whereas the orientation of the frontal dipole was free (Figure 5).

The model explained 92% of the variance of the SPs in an 800 ms time interval in the grand-average ERP data.. The orientations of the dipoles are as indicated in Figure 5. The measured and the modeled scalp distribution are illustrated in Figure 6. An additional dipole model, omitting the frontal dipole still explained 86% of the variance. However, using this latter model no circumscribed left frontal focus was obtained, indicating that though IPS activity accounted for a substantial amount of the SW pattern, an additional left frontal source provides a more complete picture of the ERP data.
We assume this dipole model to be highly accurate for two reasons. First, predictions about possible brain sources were derived independently from fMRI data. Second, degrees of freedom were minimal, i.e. the number of dipoles as well as their locations and orientations were determined a priori. As a consequence, the probability of a reasonably good but invalid solution can be considered to be small.

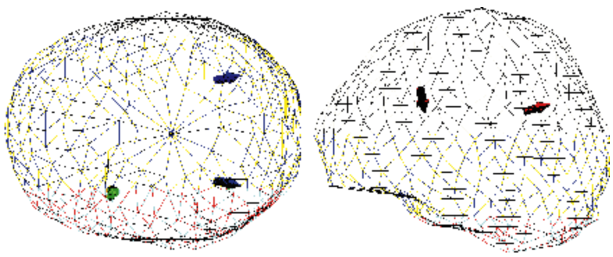


Figure 5. Location of the three dipoles within the 3-shell head-model. Two dipoles are located bilaterally within the IPS, the third within IFG. The inner shell (border between brain and skull) is displayed. Dipoles project in the positive direction.

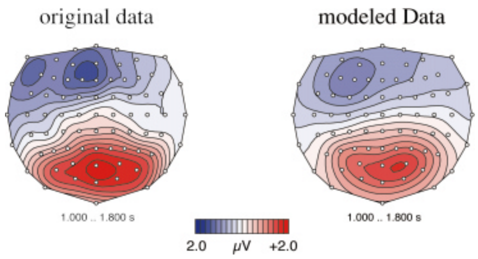


Figure 6. Topographic maps of the original and modelled data of the difference between object and perceptual task. Data are averaged across the 1000-1800 ms time interval.

Influence of white matter anisotropy on EEG/MEG

3.7.7

Wolters, C.[1+2], Hartmann, U.[3], Koch, M.[1], Burkhardt, S.[1+2], Maess, B.[1], Kruggel, F.[1] & Wagner, M.[4]

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Measured bioelectromagnetic fields outside the head do not only arise from the primary currents (dipoles) which are due to the electromotive force impressed by biological activity in conducting tissue. The electric field around the source is present in the whole head and induces so-called return currents which depend strongly on the conductivity profile inside the volume conductor and which also contribute to the measurements (see e.g. Haueisen et al, 1995).

Up to now, there has been no reliable method for determining the conductivity distribution inside the head. All of the realistically-shaped head models in common use rely on the assumption of a piecewise homogeneous conductor with isotropic (i.e. constant) conductivity values for each layer. However, a strong influence of isotropic conductivity changes of the white matter layer in such a multilayered conductor on the EEG/MEG forward solution has been reported. In addition an anisotropy (different conductivity values for each principal direction) ratio of 1:10 (normal to fibres : parallel to fibres) has been measured.

Our project aims at determining the influence of white matter anisotropy on EEG/MEG-source reconstruction. The first step will be simulations in a four layer sphere model. Anisotropy in "white matter" planes and in "fibre" cylinders will be modelled and various dipolar sources will be placed in the inner sphere. The coupling of the net-generator VGRID to our finite element (FE) tool CAUCHY has been successfully carried out. Apart from tetrahedra meshes in CAUCHY-format, created by CURRY (CUrrent Reconstruction and Imaging, Philips Hamburg), we are now able to generate cube meshes and to use BRIAN's (Kruggel & Lohmann, 1996) powerful multimodal neuroimaging facilities.

Figure 7 shows the four layer sphere model and the FE-meshes created by VGRID and CURRY. Cubic elements are numerically stable, but the approximation of smooth surfaces is more difficult. On the other hand degenerated tetrahedra elements (large ratio of internal angles), which can occur in practice, can lead to strong numerical problems.

Thus, as a precaution, we will compare the numerical results of both mesh-generators with analytical formulae in a homogeneous sphere model.

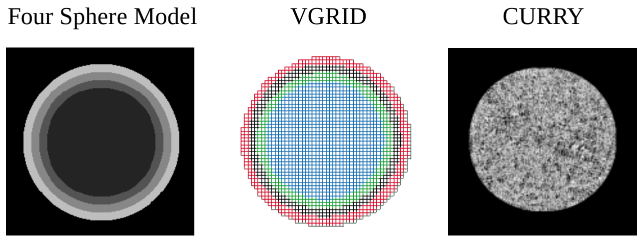

Figure 7. (left) Four layer sphere model (radii 100 mm, 90 mm, 80 mm, 70 mm and layer conductivities 0.33, 0.0042, 1.0, 0.33); (center) 3D VGRID-FE mesh consisting of cube elements (65,360 elements; 71,403 nodes; 4mm edge length; total memory allocation for a CAUCHY run: 71 MB); (right) 3D CURRY-FE mesh consisting of tetrahedra elements (541,802 elements; 90,538 nodes; 3.5mm middle edge length; total CAUCHY-memory allocation: 112 MB).

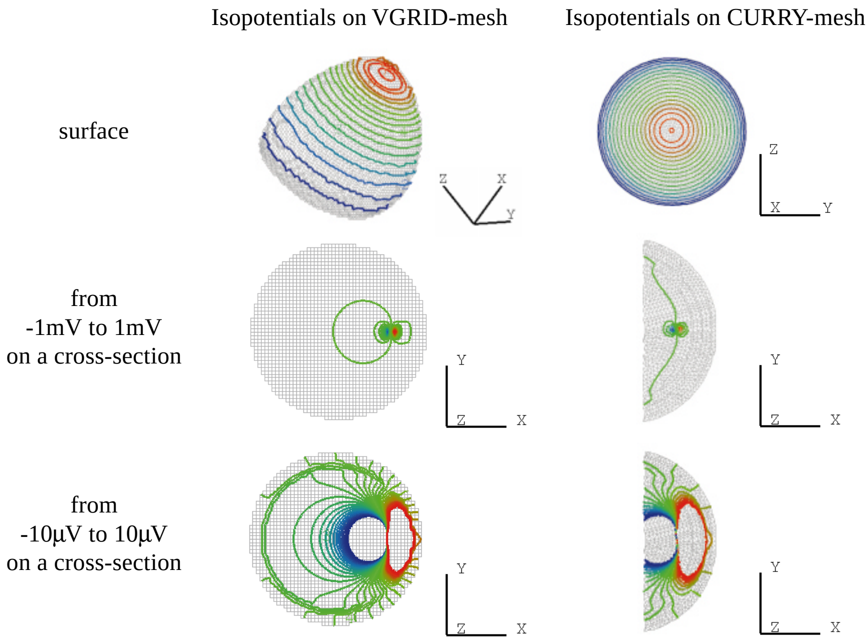

Figure8. CAUCHY forward results on the VGRID cube mesh (left) and on the CURRY tetrahedra mesh (right). Visualization of isopotential lines has been carried out with EIPP on the surface of a sphere segment (top, left) and of the whole sphere (top, right) and on a cross-section of the sphere from -1 mV to 1 mV (center) and from -10 µV to 10 µV (bottom).

Figure 8 shows first results for a source simulation (dipole location: (x,y,z)=(60,0,0) mm; orientation and strengths: (x,y,z)=(100,0,0)nAm) in the piecewise homogeneous four layer sphere model. The influence of the different meshes on the calculated potential distribution can be studied. Note the blurring effect of the "skull layer" on the isopotential lines and the strong potential gradient inside the "skull layer" (bottom).

For the application of a realistic geometry, we will make use of diffusion tensor imaging methods (Koch & Norris, 199?) to determine the conductivity tensors for every finite element inside the skull. Conductivity and water diffusion tensors are both determined by the tissue architecture and thus have the same principal directions. By means of homogenization theory (Müller, 1998/99), and especially the effective medium approach (Tuch et al., 1998), the outstanding principle conductivities can be calculated from the diffusion eigenvalues.

For our further simulations and applications we should reach a very high resolution (edge lengths of 2 mm) and the forward problem should be solved for many thousands of sources. For these great demands on mathematical and computational power, we will make use of a diverse parallelised equation solver, already implemented on an NEC Cenju-4 super-computer (64 processors of type r10000).

New regularization method for nonlinear and constrained dipole fit

3.7.8

Wolters, C.[1+2], Beckmann, R.[3], Rienäcker, A.[4] & Buchner, H.[3]

[1]Max-Planck-Institute of Cognitive Neuroscience, Leipzig, [2]Max-Planck-Institute for Mathematics in the Sciences, Leipzig, [3]Department of Neurology, RWTH Aachen, [4]BMW Rolls-Royce GmbH, Dahlewitz

The inverse problem arising from EEG and MEG is largely underdetermined. One strategy to alleviate this problem is to use only a limited number of point-like sources, the focal source model (Scherg & von Cramon, 1985). Although the singular value decomposition of the spatio-temporal data gives an estimate of the minimal number of dipoles contributing to the measurement, the exact number is unknown in advance and noise complicates the reconstruction. Classical nonlinear dipole fit algorithms do not give an estimate of the correct number because they are not stable with regard to an overestimation of this parameter. Some sources may only describe noise but may nevertheless be assigned large signal components during the inverse procedure and may be indiscernible from the true sources. We have developed a nonlinear dipole fit reconstruction algorithm with a new regularization approach for the embedded linear problem, the SA-TSVD (Simulated Annealing from combinatorial optimization theory combined with the Truncated Singular Value Decomposition from regularization theory), automatically controlled by the noise in the data and the condition of the occuring least square problems. The algorithm is more stable with regard to source components which lie in the kernel of the lead field operator, e.g. sources which nearly cancel each other with regard to their surface field distribution (EEG/MEG), deep sources (EEG/MEG) or radial sources (MEG). It thus gives an estimate of the unknown number parameter.

Simulation studies in a simulated sulcus structure (Figure 9) have been carried out and spatial resolution in the sulcus and stability of the new method were compared with the classical nonlinear dipole fit method SA-COF (Simulated Annealing combined with the Complete Orthogonal Factorization method).

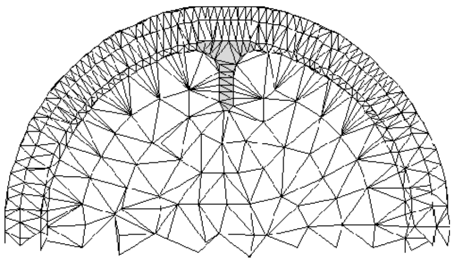

Figure 9. Cross-section through the finite element mesh of the four layer sphere model with simulated sulcus embedded in the innermost sphere.

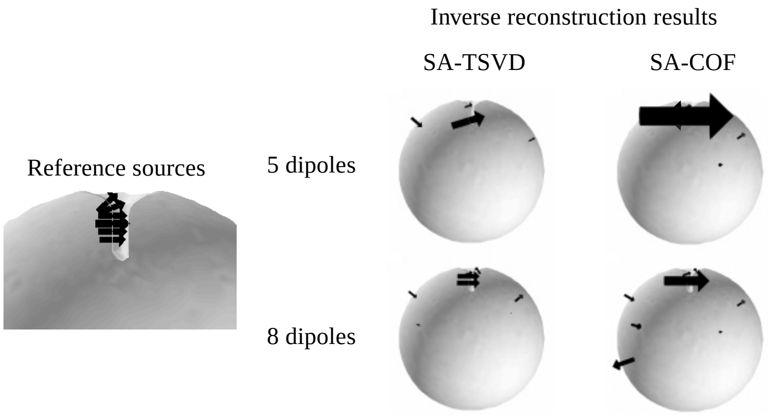

Figure 10. Reference dipole configuration (left) and the reconstruction results of the SA-TSVD and SA-COF when searching for 5 dipoles and for 8 dipoles.

If reference activity is restricted to one sulcus wall and EEG-noise complicates the reconstruction, high spatial frequency inverse source configurations such as dipoles on both sulcus walls having opposite directions can have a strong influence on the result of the SA-COF (Figure 10, 5 dipoles). The SA-TSVD is more stable (Figure 10, 5 dipoles) and has a better resolution (Figure 10, 8 dipoles).

The presented regularization concept can be of particular importance if dipole locations are already known (a-priori information, e.g. fMRI-constrained dipole fit) whose corresponding influence matrix is ill-posed, as is the case for the localization of M100-generators in the auditory cortex to stimuli of different frequencies (tonotopy).

3.7.9 Rule-based artefact rejection for pre-processing event-related potentials

Herrmann, C.S. & Arnold, T.

The following research was carried out in the framework of the BMBF project *'Artificially intelligent brain analysis'* together with Mainz University Clinic and Walter Graphtek GmbH (Herrmann, 1998).

For the purpose of averaging event-related potentials (ERPs) it is necessary to select EEG-epochs which are not contaminated by artefacts. This procedure is usually carried out manually. We have developed a rule-based approach which solves the task automatically. EEG raw data is pre-processed by the Adaptive Frequency Decomposition (Herrmann et al., 1998). Spectral features of the EEG-signal are transformed into symbolic representation by means of Fuzzy Logic, allowing a linguistic description of the EEG. The symbolic features (e.g. a medium-voltage delta-wave) are analyzed in a rule-based system (expert system). Pseudo-verbal rules, formulated by the physician, are used to detect artefacts in raw data. Artefactual epochs are automatically marked and classified. Afterwards, the user can decide whether to reject the classified epoch or to correct it by standardized correction methods.

We were able to detect eye-movement-artefacts, eye blinks, electrode-artefacts and muscle-activity by means of medical expert rules. Simple IF-THEN type rules made rule-formulation easy for the physician. In five subjects, we examined the first 60 seconds of clinical routine EEG and calculated the discrimination index according to Snodgrass (1988). The discrimination index P_r (P_r = hit rate - false alarms) yields a value of 87.8% across the subjects.

Our method of automatically detecting and excluding the most common EEG artefacts constitutes a valuable tool for ERP pre-processing. The modular, rule-based architecture offers the possibility of extending the system with definitions of further artefacts by medical experts.

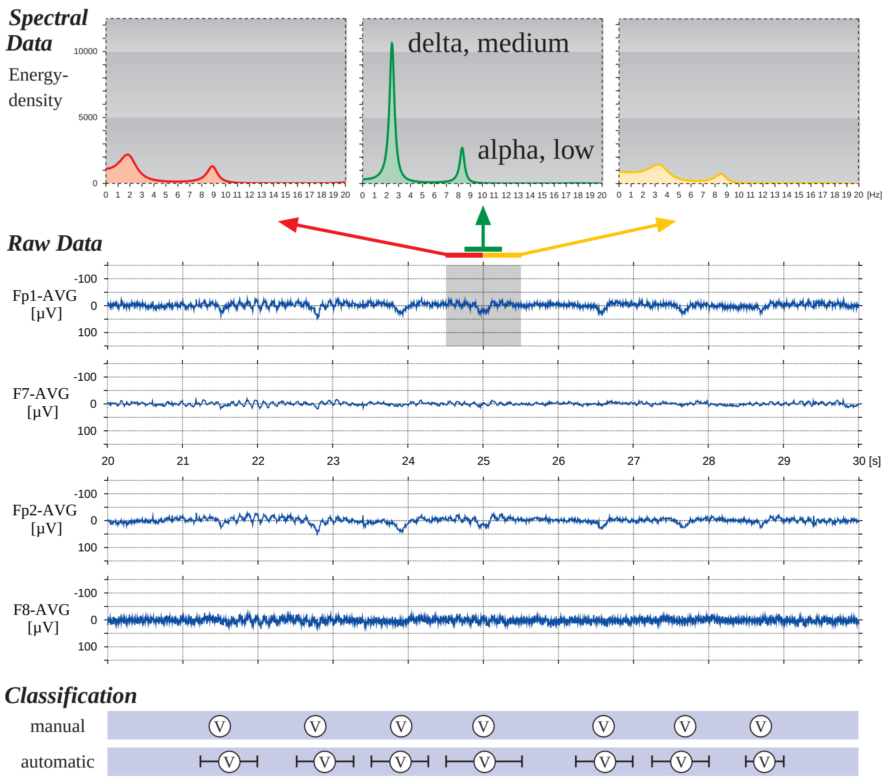

Figure 11. Ten seconds of sample EEG showing the detection of vertical eye movements that are assumed if the delta amplitude is maximal in both frontopolar electrodes (Fp1 and Fp2) and decreases to at least 66% in the frontal electrodes (Fz, F3, F4, F7, F8).

Library report

4.1

Lewin, G.

Since the completion of the new institute building, the working conditions in the library have improved considerably. This has provided our scientists with a modern and spatious facility which is equipped with all up to date resources including a barcode-based lending system, reading tables and computer terminals and a separate copier room. While the library design is geared towards an appropriate functionality, the use of materials such as light wood, chrome and glass contribute an additional aesthetic merit.

Certain recent developments relating to the increasing digitalisation of scientific information are of specific relevance to our institute. Following discussion we have opted for an initial subscription to the electronic periodicals of the Academic Press, Elsevier and Springer. These will be available on a trial basis until May 1999. Financial considerations make it important to establish which titles are of particular interest to institute scientists. A further ongoing project within the library is the identification of appropriate strategies for internet presentation of metadata.

Print media will continue to be stocked as previously and will retain their traditional importance. The range of books available has been extended considerably and back copies of periodicals have been obtained according to requirement. The entire stock of the library now comprises 7000 media units. These can be summarised as follows:

2245	monographs
170	current journal titles
3000	bound volumes of journals
10	CD-ROM data bases
4	data bases with access via Internet

From the frequency of visits from both internal and external users, it is already apparent that the quantitative and qualitative expansion as well as the improved working environment has greatly improved the service which the library provides.

4.2 Teaching

S O M M E R S E M E S T E R   1 9 9 8

Bildgebende und andere Untersuchungsverfahren in der Klinischen Neuropsychologie
Universität Leipzig
von Cramon, D.Y. mit MitarbeiterInnen der Tagesklinik für kognitive Neurologie und des Max-Planck-Institutes für neuropsychologische Forschung

Seminar 'Kognitive Neurowissenschaft'
Universität Leipzig
Hund-Georgiadis, M., Müller, U., Pollmann, S. & Schubert, T.

Seminar 'Kognitive Psychophysiologie'
Universität Leipzig
Schröger, E. & Mecklinger, A.

W I N T E R S E M E S T E R   1 9 9 8 / 9 9

Funktionelle Neuroanatomie
Universität Leipzig
von Cramon, D.Y. mit MitarbeiterInnen der Tagesklinik für kognitive Neurologie und des MPI für neuropsychologische Forschung

Neuropsychologie der Sprache
Universität Leipzig
Friederici, A.D. mit MitarbeiterInnen des MPI für neuropsychologische Forschung.

Graduiertenkolleg Intercell: Kognitive Störungen bei Parkinsonscher Erkrankung.
Universität Leipzig
Müller, U.

Seminar 'Nicht-lineare Phonologie'
Univeristät Leipzig
Alter, K.

Aktuelle Themen der Kognitionspsychologie
Universität Leipzig
Friederici, A.D., Geißler, H.G., Gunter, Th.C., Kaernbach, C., Mecklinger, A., Müller, H., Sommerfeld, E., Schröger, E.

Seminar 'Streßkonzepte'
Universität Leipzig
Mecklinger, A.

Prof. Dr. Angela D. Friederici

Deutsche Forschungsgemeinschaft
Member of the Senate

University of Leipzig
1. Director of the Zentrum für Kognitionswissenschaften (Center for Cognitive Science)
2. Speaker of the Board of Directors of the Zentrum für Höhere Studien (Center for Advanced Studies)
3. Member of the Research Group "Arbeitsgedächtnis" at the Center for Cognitive Science
4. Member of the Graduiertenkolleg "Universalität und Diversität"

University of Potsdam
Member of the "Initiativkreis Potsdamer Naturwissenschaftliche Vorträge / Potsdam Lectures"

Berlin Brandenburgische Akademie der Wissenschaften
Active Member

Editorial Activities
1. Editor-in Chief of the *"Zeitschrift für Experimentelle Psychologie"*
2. Member of the Editorial Board of the *"Journal of Psycholinguistic Research"*
3. Member of the Advisory Board of *"Neurolinguistik"*
4. Member of the Advisory Board of the *"Psychonomic Bulletin & Review"*

Prof. Dr. med. D. Yves von Cramon

University of Leipzig
Director of the Day-Care Clinic of Cognitive Neurology

Nomination Committees (University of Leipzig)
1. Neurological Rehabilitation
2. Nuclear Medicine
3. Experimental Physics
4. Neurology, Psychiatry, Psychology
5. Junior Research Group for MR-Spectroscopy

Interdisziplinäres Zentrum für Klinische Forschung (Interdisciplinary Center for Clinical Research), Leipzig

1. Member of the Board
2. Coordinator of the "Schwerpunkt Neurowissenschaften" (Center for Neuroscience)

Zentrum für Kognitionswissenschaften (Center for Cognitive Science)

Member of the Board

Other Committees (University of Leipzig)

1. Committee of Computer Resources
2. Doctorate Committee: Neurology, Neuropathology and Neurosciences

Deutsche Gesellschaft für Neurologie (DGN)

Chairman of the DGN-Committee 1.08 (Behavioral Neurology)

Other Committees

Member of the Gemeinsame Kommission Klinische Neuropsychologie (GKKN)
Scientific Board of Biomedicine, Forschungszentrum Jülich

Editorial Activities

Member of the Editorial Board of *"Cortex"*
Member of the Editorial Board of the *"Journal of Neuropsychological Rehabilitation"*
Member of the Advisory Board of the *"Nervenarzt"*
Member of the Editorial Board of the *"Zeitschrift für Neuropsychologie"*

4.4 Visitors

Prof. Dr. Dahlia Zaidel, University of California, Los Angeles, USA
01.02.-12.03.1998

Prof. Dr. Eran Zaidel, University of California, Los Angeles, USA
22.02.-21.03.1998

Dr. Padraigh O'Seahgdha, Lehigh University of Bethlehem, USA
02.-05.03.1998

Prof. Dr. John Conolly, Department of Psychology, Dalhousie University, Halifax, Nova Scotia, Canada
04.-06.05.1998

Prof. Dr. Emanuel Donchin, University of Illinois, Champaign, USA
30.05.-05.06.1998

Dr. Joseph Demestre, University of Tarragona, Spain
08.06.-28.07.1998

Dr. Mireille Besson, CNRS, University of Marseille, France
14.06.-21.06.1998

Prof. Dr. Marta Kutas, University of California, La Jolla, USA
15.06.-17.06.1998

Dr. Vera Kempe, Department of Psychology, University of Ohio, Toledo, USA
28.06.-10.07.1998

Dr. Matthias Schlesewsky, Institute for Linguistics, University of Potsdam, Germany
29.06.-29.07.1998

Prof. Dr. Herbert Schriefers, Nijmegen Institute for Cognition and Information (NICI), Nijmegen, The Netherlands
01.07.-11.07.1998

Prof. Dr. Stefano S. Cappa, University of Brescia, Italy
01.07.-31.07.1998

Prof. Dr. Shlomo Bentin, Department of Psychology and School of Education, Hebrew University, Jerusalem
15.07.-31.08.1998

Prof. Dr. David Poeppel, University of Maryland at College Park, USA
24.08.-26.08.1998

Prof. Dr. Stefano S. Cappa, University of Brescia, Italy
21.09.-26.09.1998

Dr. Lee Osterhout, Department of Psychology, University of Washington, Seattle, USA
27.09.-22.10.1998

Dr. Jens Haueisen, Biomagnetical Center, University of Jena, Germany
19.10.-13.11.1998

Guest lectures 4.5

PD Dr. Axel Buchner, University of Trier, Germany
Prozeßdissoziation: Meßmodelle und Mißverständnisse
07.01.1998

Prof. Dr. Michael Rugg, University of St. Andrews, UK
Using functional neuroimaging to study memory retrieval: what we know, and what we want to know
14.01.1998

Prof. Dr. Hans Engelkamp, University of Saarbrücken, Germany
The role of motor processes in episodic memory
15.01.1998

Prof. Dr. N.K. Logothetis, Max-Planck-Institute of Biological Cybernetics, Tübingen, Germany
Neural activity during ambiguous vision
21.01.1998

Prof. Dr. Helmut Buchner, RWTH Aachen, Germany
Quellenmodelle somato-sensorisch und visuell evozierter Potentiale
28.01.1998

Dr. Toshiya Murai, University of Kyoto, Japan
Reduplicative paramnesia: prevalence and pathogenesis
03.02.1998

Dr. Wolfram Ziegler, Städtisches Krankenhaus Bogenhausen, Munich, Germany
Zeitaspekte gestörter Sprachproduktion bei Patienten mit Hirnschädigung
04.02.1998

Prof. Dr. Thomas Brandt, University of Munich, Germany
Vestibular cortex: its locations, functions and disorders
11.02.1998

Prof. Dr. Erich Schröger, University of Leipzig, Germany
Unwillkürliche Aufmerksamkeitszuwendung: Ein neues Distraktionsparadigma
18.02.1998

Prof. Dr. Dahlia Zaidel, University of California, Los Angeles, USA
The relationship between human facial beauty and the human brain
18.02.1998

Prof. Dr. Eran Zaidel, University of California, Los Angeles, USA
The split brain calling, what is right and what is left?
25.02.1998

Dr. Padraig G. O'Seaghdha, Lehigh University, Bethlehem, PA, USA
Competition and cooperation in word and sentence regeneration
04.03.1998

Prof. Dr. Dahlia Zaidel, University of California, Los Angeles, USA
Left and right human hippocampus: size, shape, and other morphological features of neurons
10.03.1998

Dr. Martin Heil, University of Marburg, Germany
Reaktionswahl, mentale Rotation und die Theorie des zentralen Flaschenhalses
01.04.1998

Dr. Joachim Grabowski, University of Chemnitz, Germany
Ein antromorphologisches Modell der dimensionalen Raumauffassung
15.04.1998

Prof. Dr. John Connolly, Dalhousie University, Halifax, Nova Scotia, Canada
ERP and MEG studies of reading and speech processing
05.05.1998

Prof. Dr. Kenneth Hugdahl, University of Bergen, Norway
Auditory laterality: Evidence from dichotic listening
13.05.1998

Prof. Dr. Brian MacWhinney, Carnegie Mellon University, Pittburgh, PA, USA
Functional MRI and experimental studies of language organization in children with focal lesions
20.05.1998

Prof. Dr. K. Willmes-von Hinckelday, RWTH Aachen, Germany
Multivariate Permutationstests in der funktionellen Bildgebung
02.06.1998

Prof. Dr. Emanuel Donchin, University of Illinois at Urbana, Champaign, USA
Ockham's razor dulled: On the proliferation of domain specific ERP components
03.06.1998

Prof. Dr. Marta Kutas, University of California, La Jolla, USA
Semantic/conceptual knowledge, sentence processing, and ERPs
17.06.1998

Dr. Vera Kempe, State University of New York at Oswego, USA
Does Motherese facilitate the acquisition of Russian gender?
01.07.1998

Prof. Dr. Marie-Helene Giard, INSERM, Lyon, France
Dissociation of auditory ERP components by scalp current density analysis
02.07.1998

Dr. Thomas Münte, Medizinische Hochschule Hannover, Germany
Kognitive Elektrophysiologie neurologischer Erkrankungen
15.07.1998

Dr. Matthias Schlesewsky, University of Potsdam, Germany
Perspective-taking or syntactical constraints - some aspects of processing relative clauses
22.07.1998

Prof. Dr. Shlomo Bentin, Hebrew University of Jerusalem, Israel
Electrophysiological indices of structural and semantical processing of faces I
23.07.1998

4.6 Congresses, workshops and colloquia

Workshops

GNP Workshop *'Diagnostik und Therapie von Störungen der Exekutivfunktion'*
Matthes-von Cramon, G.
Leipzig, Germany, March 1998.

GNP Workshop *'Verhaltenstherapeutische Interventionen in der Neuropsychologie am Beispiel der Behandlung von Patienten mit zerebraler Hypoxie'*
Matthes-von Cramon, G. & Gemkow-Mecklinger, H.
Leipzig, Germany, March 1998.

GNP Workshop *'Alltagsorientierte Gedächtnisdiagnostik und Therapie'*
Thöne, A.I.T., Guthke, T. & Ferstl, E.C.
Leipzig, Germany, May 1998.

GNP Workshop *'Neuropsychopharmaka'*
Müller, U.
Frankfurt, Germany, May 1998.

Workshop *'Processing of grammatical gender'*
Jacobsen, Th. &Friederici, A.D.
Leipzig, Germany, July 1998.

GNP Workshop *'Neuropsychologie der Sprache'*
Kotz, S.A., Ferstl, E.C. & Guthke, T.
Leipzig, Germany, September 1998.

GNP Workshop *'Funktionelle Bildgebung in der Neuropsychologie'*
Hund-Georgiadis, M.
Leipzig, Germany, November 1998.

Degrees 5.1

Dr. S. Pollmann	Privatdozent (Psychologie), PD Dr. Free University of Berlin
Ricarda Schubotz	Doktor der Philosophie, Dr. phil. University of Potsdam
Volker Bosch	Doktor der Naturwissenschaften, Dr. rer. nat. University of Leipzig

Awards 5.2

C.H. Wolters	Award of the Friedrich Springorum medal of the Technical University Aachen

PUBLISHED BOOKS AND BOOKCHAPTERS 6.1

BOOKS

Besson, M. & Friederici, A.D. (Eds.) (1998).
Language and Music Processing. Special Issue, *Music Perception,* Berkeley, CA: University of California Press.

Friederici, A.D. (Ed.) (1998).
Language comprehension: A biological perspective. Berlin/Heidelberg/New York: Springer.

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Sprachrezeption. Enzyklopädie der Psychologie. vol. C/III/2, Göttingen: Hogrefe.

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Rule learning: Rule extraction and representation. Berlin/New York: Walter De Gruyter.

Lohmann, G. (Ed.) (1998).
Volumetric image analysis. Chichester, UK: Wiley & Sons; Stuttgart: Teubner.

Uhl, C. (Ed.) (1998).
Analysis of neurophysiological brain functioning. Heidelberg: Springer.

BOOKCHAPTERS

Alter, K., Matiasek, J., Steinhauer, K., Pirker, H. & Friederici, A.D. (1998).
Exploiting syntactic dependencies for German prosody: Evidence from speech production and perception. In B. Schröder, W. Lenders, W. Hess & T. Portele (Eds.), *Computers, Linguistics, and Phonetics between Language and Speech* (pp. 141-152), Frankfurt: Peter Lang.

Bosch, V. (in press)
Das Halten von Information im Arbeitsgedächtnis: Dissoziationen langsamer corticaler Potentiale. In Max Planck Institute of Cognitive Neuroscience (Ed.), *MPI Series in Cognitive Neuroscience,* vol. 3., Leipzig.

Clahsen, H. & Friederici, A.D. (in press).
Sprachverlust. In G. Holthaus & M. Metzeltin (Eds.), *Lexikon der Romanistischen Linguistik*, Tübingen: Niemeyer.

Cramon, D.Y. von & Müller, U. (1998).
The septal region and memory. In F. Cohadon, V.V. Dolenc, J. Lobo Antunes, H. Nornes, J.D. Pickard, A.J. Strong, N. de Tribolet & C.A.F. Tulleken (Eds.), *Advances and Technical Standards in Neurosurgery*, vol. 24 (pp. 3-40), Wien: Springer.

Cramon, D.Y. von & Markowitsch, H.J. (in press).
Memory dysfunctions due to septal lesions. In R. Numan (Ed.), *Behavioral Neuroscience of the Septal Region,* Berlin: Springer.

Eulitz, C., Maess, B., Pantev, C., Friederici, A.D., Feige, B. & Elbert, T. (in press).
Oscillatory neuromagnetic activity induced by verbal and non-verbal stimuli presented in visual and auditory modalities. In C. Woods et al. (Eds.), *Advances in Biomagnetism'96*, Amsterdam: Elsevier.

Ferstl, E.C. & Flores d'Arcais, G.B. (1998).
The reading of words and sentences. In A.D. Friederici (Ed.), *Language Comprehension: A Biological Perspective* (pp. 177-212), Berlin: Springer.

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Das Lesen von Wörtern und Sätzen. In A.D. Friederici (Ed.), *Sprachrezeption, Enzyklopädie der Psychologie*, vol. C/III/2, Hogrefe: Göttingen.

Ferstl, E.C. & Guthke, T. (in press).
Diskursanalyse als Hilfsmittel zur klinischen Evaluation von nicht-aphasischen Sprachstörungen. In I.M. Ohlendorf, W. Widdig & J.-P. Malin (Eds.), *Bonn-Bochumer Beiträge zur Neuropsychologie und Neurolinguistik BBB. Texttraining innerhalb der Aphasietherapie: Interdisziplinäre Ansätze*, vol. 5, Freiburg: HochschulVerlag.

Ferstl, E.C. & Kintsch, W. (1999).
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Diagnosis and reanalysis: Two processing aspects the brain may differentiate. In J.Fodor & F. Ferreira (Eds.), *Reanalysis in Sentence Processing* (pp. 177-200), Dordrecht: Kluwer.

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Learning syntax: From syntactic preferences to syntactic rules? In N. Dittmar & Z. Penner (Eds.), *Issues in the Theory of Language Acquisition. Essays in Honor of Jürgen Weissenborn* (pp. 135-142), Bern: Peter Lang.

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Developmental patterns of brain activity for semantic and syntactic processes. In B. Höhle & J. Weissenborn (Eds.), *Approaches to Bootstrapping in Early Language Development*, Amsterdam/Philadelphia: John Benjamins.

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Event-related neuromagnetic responses to semantic and syntactic parameters during auditory sentence perception. In T.F. Münte, H.J. Heinze & G.R. Mangun (Eds.), *Mapping Cognition in Time and Space: Combining EEG, MEG with Functional Imaging,* Boston: Birkhäuser.

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Analyzing spatio-temporal patterns of complex systems. In H. Kantz, J. Kurths & G. Meyer-Kress (Eds.), *Nonlinear Analysis of Physiological Data* (pp. 101-114), New York: Springer.

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Charakteristika syntaktischer und semantischer Sprachverarbeitungsprozesse bei der auditiven Sprachverarbeitung: Evidenz aus ereigniskorrelierten Potentialen. In Max Planck Institute of Cognitive Neuroscience (Ed.), *MPI Series in Cognitive Neuroscience,* vol. 1., Leipzig.

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Neuropsychologische Grundlagen der Sprachverarbeitung: Ereigniskorrelierte Potentiale beim Satzverstehen. In G. Diller, V. Gall, C. von Ilberg & J. Kiefer (Eds.), *Hören - Verstehen - Kommunizieren,* CIC Rhein - Main.

Hahne, A. & Friederici, A.D. (in press).
Rule-application during language comprehension in the adult and the child. In A.D. Friederici & R. Menzel (Eds.), *Learning: Rule extraction and Representation,* Berlin: Walter de Gruyter.

Herrmann, C.S. (in press).
AI and cognitive science: Feedback leads to a new neural concept. In St. Hölldobler (Ed.), *Intellectics and Computational Logic: Papers in Honor of Wolfgang Bibel,* Dordrecht: Kluwer.

Jescheniak, J.D. (in press).
Accessing words in speaking: Models, simulations, and data. In Chr. von Stutterheim & R. Meyer-Klabunde (Eds.), *Processes in Language Production,* Opladen: Westdeutscher Verlag.

Knösche, T.R. (1998).
Disentangling ERP components using spatial and temporal constraints - Dipole analysis. In C. Uhl (Ed.), *Model-based Analysis of Neurophysiological Brain Functioning* (pp. 150-175), Heidelberg: Springer.

Knösche, T.R. (1998).
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