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herausgegeben von
Prof. Dr. Dr. Gerhard Roth und Uwe Opolka

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The Cognitive Neuroscience of Individual Differences – New Perspectives

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Cognitive neuroscience (CN) studies human cognition with methods derived from psychology and brain science. CN has until now been mainly concerned with unraveling the basic mechanisms of cognition in respect to memory, language and attention. With methods like functional magnetic resonance (fMRI), positron emission tomography (PET) and event related potentials (ERP, MEG) significant advances have been made towards identifying the brain areas critical for performing basic mental operations, and a beginning has been made towards understanding in what pattern and sequence these areas are activated when demanding mental tasks are performed. Individuals differ in both level and organization of cognitive performance, and this variation relates to broad underlying biological factors of age, gender and genetic composition, as well as factors uniquely associated with the individual.

We need to know more about what characterizes brain activation in optimal task performance as contrasted with inefficient task performance. Brain imaging studies (PET, fMRI) have studied task performance at different levels of mastery, and in some cases it appears that persons who perform a task better show lower levels of brain activation in critical areas, whereas in other cases more intensive activation is associated with better performance. A high activation level may indicate an unsuccessful effort to solve a problem or an efficient approach to the task. Furthermore, when individuals from different age groups are compared with respect to tasks that are sensitive to aging, it appears that there are not only differences in activation levels, but also in which areas are activated. Structural (anatomical) MRI has developed significantly in recent years with procedures for quantitative measurement of selected regional brain volumes. Such data are basic to the evaluation of changes in activation patterns, and a beginning has been made in relating relevant anatomical variation to cognitive performance.

Recent developments in electrophysiological (ERP) research have attempted to relate brain function data to behaviour and their common relation to aging. Efforts have been made to coordinate work in several European laboratories towards this goal. ERP studies exploring the border area between non-optimal normal aging and early stages of pathology, have been extensively reviewed by John Polich. Researchers from Finland have studied cerebral reorganization processes in recovery from brain lesions with magneto-encephalographic methods. Researchers from Sweden have related brain activation pattern reflected in blood flow to sex differences and cognitive strategies. Finally, rapid advances are being made in studies of genes affecting the variation in specific cognitive abilities (attention) and risk of developing deficits. A common denominator for these different approaches is the general goal of progressing from an understanding of basic mechanisms to an understanding of how differences in the functioning of these mechanisms relate to individual differences in cognitive function.

This issue in mind we organized an international symposium “The Cognitive Neuroscience of Individual Differences – New Perspectives” at Delmenhorst, Germany, between 7 and 10 November, 2002. This symposium brought together a small group of researchers from different fields and using different methods under the unified perspective to focus on the study of brain functions underlying individual variations in psychological performance. We were pleased that all of the keynote speakers accepted our invitation to participate at the meeting and to present a state of the art paper on their respective field of research. The basic idea in inviting speakers was to ensure that both basic and experimental research as well as clinical disciplines engaged the issue were presented at the conference. According to this idea the presentations covered the whole spectrum from molecular biology and ERP and functional imaging work to experimental and cognitive neuropsychology and methodological approaches. With respect to the degree of development and standardization of methods in different fields presentations included both studies aiming at collecting comprehensive data bases for the purpose of relating psychological test results to neurophysiological activation, and studies in fields where methods are less standardized and where the preferred research strategy is to compare brain activation for the same subjects performing the same task under different conditions. Thus, the symposium brought together a novel constellation of researchers and encouraged the interaction and formulation of new research questions.

We were pleased that the Rector, Prof. Dr. Dr. Gerhard Roth, as well as the Scientific Board of the Hanse Institute for Advanced Study (Hanse-Wissenschaftskolleg, HWK) accepted our proposal and that we were allowed to use the stimulating and enjoyable atmosphere at the Hanse Institute as the venue for the conference. Besides the organisational efforts and the "contribution in kind" by providing rooms, logistics, etc., the HWK contributed a minor part of budget. The Volkswagen Foundation (VolkswagenStiftung) in Hanover supported the conference with a substantial amount, followed by the Universities of Oslo, Bremen and Oldenburg (the two latter ones using means of the Collaborative Research Center "Neurocognition" – SFB "Neurokognition" No. 517).

We are very grateful to the staff of the Hanse Institute – particularly to Beatrice Riewe and Wolfgang Stenzel – for the perfect organization of the meeting. They also created an enjoyable and stimulating atmosphere for critical and fruitful discussions. Moreover, we are deeply indepted to Uwe Opolka, scientific staff member at the Hanse Institute for Advanced Studies and series co-editor of the Hanse Studies, for manuscript reading and all formatting and editing work. The articles presented in this book are based directly on the papers given at the conference last November at the Hanse Institute for Advanced Study.

Worpswede, April 2003

Ivar Reinvang
Mark W. Greenlee
Manfred Herrmann

I.

Individual Differences in Brain Morphology and Neurogenetics

The Effect of Attention on Information Transfer Across the Corpus Callosum

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Einar Heiervang[1] *and Lars Morten Rimol*[1]

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Abstract

We present data from magnetic resonance imaging (MRI) and dichotic listening performance with the aim of elucidating the role of attention in information transfer across the corpus callosum (CC). We measured the corpus callosum area, split into seven regions. The MR data were correlated with dichotic listening (DL) performance under three different attentional instructions. We will put forward a hypothesis in the present paper that one of the functions of attention is to facilitate interhemispheric information transfer and connectivity, and that selective attention to the left or right in auditory space may facilitate interhemispheric communication. We will present data from 50 subjects aged 11 to 12 years who underwent both an MRI investigation and performed the dichotic listening test [8].

Introduction

The corpus callosum is the largest fiber tract in the brain. It crosses the longitudinal fissure, connecting the two cerebral hemispheres. The corpus callosum extends about 6.5 cm in the anterior-posterior direction, and it is about 1 cm in thickness in the adult brain. While it plays a critical role in perception and cognition, the exact function of the corpus callosum is still largely unknown. Anatomically, the corpus callosum consists of several areas, the most distinct in the sagittal plane being the splenium, the trunk, the genu and the rostrum. Visual information between the hemispheres passes through the splenium, while motor and somatosensory information is confined to the genu and the trunk parts of the callosum [cf. 13]. The temporal lobes are connected via both the corpus callosum and the anterior commissure. The anterior parts of the superior temporal gyrus send fibers via the anterior commissure, while the posterior parts of the superior temporal gyrus (which make up most of the auditory cortex) send fibers through the posterior parts of the trunk, just anterior to the splenium [14]. The division of the corpus callosum into functional segments is still a question for research. Some authors have developed a more sophisticated way of segmenting the corpus callosum [e.g. 5].

Studies in humans with magnetic resonance imaging (MRI) techniques have revealed differences in corpus callosum size between males and females, and between young and old individuals [see e.g. 4]. Cowell et al. [4] found that area and axis length of the callosum generally increase up to the age of 20, and then starts declining. Interestingly, the onset of decline in area occurs earlier in males than in females, depending on the specific sector studied.

Another thing which also seems to interact is handedness, with larger callosal size in consistent non-right-handers [e.g. 6, 19]. Moreover, some studies have indicated that language lateralization is related to callosal size, with larger callosal size in left hemisphere language individuals [e.g. 18]. These latter studies have typically used dichotic listening to assess language function in the two hemispheres. Another measure that has been shown to differ between left- and right-handers is scalp-recorded event-related potentials (ERPs). John Polich and his colleagues have studied the effects of handedness and gender on the latency and amplitude of the P300 ERP component. It was found that left-handers have shorter P300 latency and larger amplitude at anterior/frontal and central electrode placements in an oddball paradigm [7]. Considering that left-handers have been found to have overall larger CC area size than right-handers [19], it may be suggested that the P300 component is related to CC size and interhemisperic transmission efficacy.

Dichotic listening

Dichotic listening (DL) is a non-invasive technique used to study lateralized information processing in the two hemispheres of the brain [8]. In a more general sense, dichotic listening is a measure of temporal lobe function, attention and stimulus processing speed, in addition to being a measure of hemisphere language asymmetry [8]. *Figure 1* shows the typical right ear advantage associated with verbal stimuli, in this case consonant-vowel (CV) syllables.

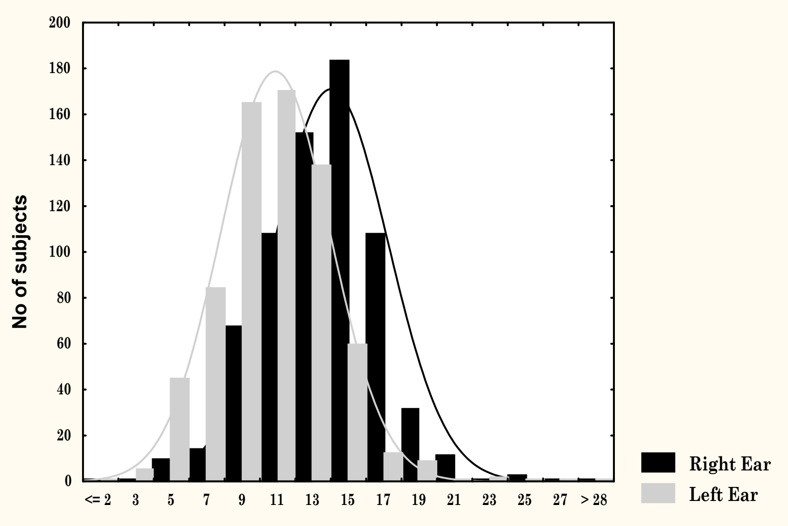

Figure 1: Graphical illustration of the right ear advantage (REA) in dichotic listening. Data based on 1,172 subjects.

The neural mechanisms underlying DL can be explored through simultaneous recordings of regional distribution of blood flow in the brain when subjects are performing the DL task. This was done with the ^{15}O-PET technique [10]. The subjects listened to either CV-syllables, musical instruments or simple tones (baseline) in three different scans. PET subtraction images were obtained by subtracting activity during the tones condition from activity during the CV-syllables and musical instruments conditions. *Figure 2* shows significant activations (p < .001, corrected for multiple comparisons) in the superior temporal gyrus. Interestingly, there was a left-sided asymmetry for CV-syllables, and a right-sided asymmetry for musical instrument stimuli.

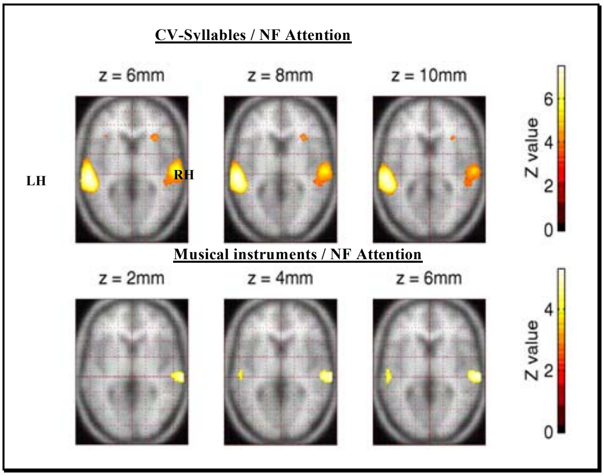

Figure 2: ^{15}O-PET activation images after presentation of CV-syllabels (upper row in both panels), and musical instruments (lower row in both panels). The upper panel show significant clusters of activation plotted onto lateral views of a brain template. The lower panel show the same data but plotted on axial slices (data from [10]).

Test-retest reliability coefficients vary between .61 and .86 for repeated presentations of the same CV-syllables within two weeks. This is in agreement with most other studies of dichotic listening reliability for verbal stimuli.

Methods

The dichotic stimuli consisted of the stop consonants paired with the vowel /a/ to form six consonant-vowel syllables (*ba, da, ga, ka, pa, ta*). The syllables were paired with each other in all possible combinations, thus giving 36 different syllable pairs. The homonymic pairs (*ba-ba*, etc.) were included as a perceptual control, but were not included in the statistical analyses. The 36 dichotic pairs were recorded three times on tape with three different randomizations. There were 36 trials for each attentional instruction. Thus, a maximum correct score was 30 (excluding the 6 homonyms). The syllables were read by a male voice, with intonation and intensity held constant. The syllables were digitized prior to computerized editing and temporal alignment of stimulus onset, and were played from a standard CD player.

Upon arrival at the laboratory all subjects were instructed about the purpose of the study. They also filled out the handedness questionnaire, and were screened for hearing acuity according to a standard audiometry screening protocol (Tegner & Co). Subjects with normal hearing were seated in a sound attenuated chamber in the laboratory. The ear plugs were attached, and the subjects were given the specific instructions regarding direction of attention.

In the standard or *non-forced (NF)* attention condition, the subjects were told that they would be presented with a list of CV-syllables. Their task was to answer with the syllable they heard on each trial. Thus, one response for each trial was emphasized. If they were able to identify both syllables on a trial, they were nevertheless told to report only the one they «heard best». Thus, in trials where subjects gave two correct responses, only the first response was used in the analysis, since the first response is highly correlated to the overall ear advantage.

In the *forced-right (FR)* attention condition, the subjects were told to pay close attention to the right ear syllables and only report what they heard in the right ear. Otherwise the procedure was identical as for the NF condition. In the *forced-left (FL)* attention condition, the subjects were told to pay close attention to the left ear syllables, and only report what they heard in the left ear. Otherwise the procedure was identical to that of the NF condition.

The right ear advantage (REA)

The typical finding in dichotic listening is a right-ear advantage (REA) meaning superior identification of right ear stimuli compared to left ear stimuli [see 7 for further explanations]. The classic structural model [12] argues that the REA is caused by several interacting factors. (1) The auditory input to the contralateral hemisphere is more strongly represented in the brain. (2) The left hemisphere is in most individuals specialized for language processing. (3) Auditory information that is sent along the ipsilateral pathways is suppressed by the contralateral information. (4) Information that reaches the ipsilateral right hemisphere has to be transferred across the corpus callosum to the left hemisphere language processing areas.

Attentional modulation of the REA

The REA is a fairly stable and robust empirical finding, but can typically be modified by instructing the subject to attend to either the right or left side in auditory space [9, 2]. Thus, in the FR condition, the REA is typically increased, while it is decreased, or sometimes even switched to a left ear advantage (LEA) in the FL condition.

The "left ear score"

Of perhaps more relevance for the present results is the prediction from the structural model that the left ear score should be positively correlated with efficiency of callosal transfer [cf. 3]. This means that size of callosal area should correlate with left ear performance, particularly for the posterior sectors of the corpus callosum. The reason is, as explained above, that the left ear score has to be transferred across the corpus callosum from the right to left hemisphere in order to be processed. A recent study by Pollmann et al. [15] on patients with circumscribed lesions in the posterior 20 % of the CC were not able to report any correct items presented in the left ear during a DL task, which indicates that the right hemisphere may not process CV-syllable stimuli presented in a dichotic conflict situation [see also 3].

MR scanning

MR scanning was performed on a Siemens Impact 1.0 T MR scanner using whole head, ear-to-ear, multispectral 3D gradient echo acquisitions [see 11].

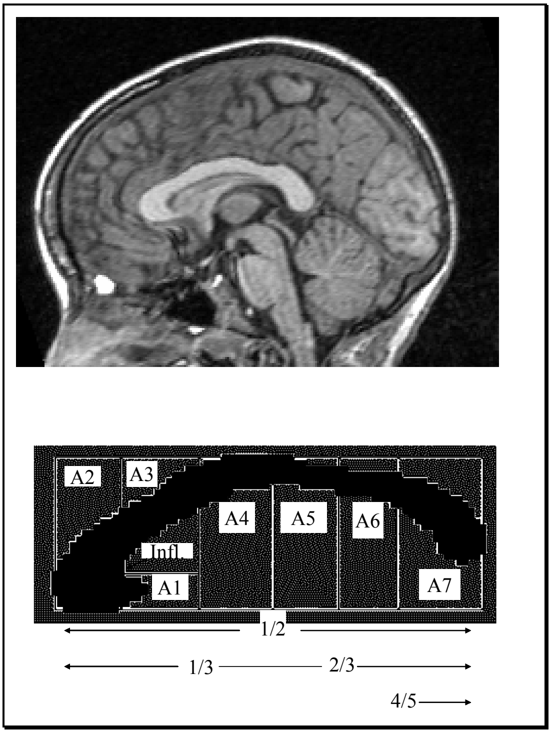

Figure 3: Upper part shows T1 MR image through the sagittal midline, outlining the hemisphere with the corpus callosum beneath. Lower part shows the division of the corpus callosum in 7 areas. Note that the denotation A1, A2 etc. corresponds to the denotation R1, R2 etc. in the text and in other figures (from [18]).

From each multispectral data set, the T1-weighted 3D FLASH channel was selected for the CC analysis because of superior signal-to-noise ratio and grey matter/white matter contrast. Total MR acquisition time did not exceed 30 minutes. In each subject, the morphometric analysis was based on the CC outline in a midsagittal slice from the 3D FLASH image volume. Each 3D data set was subject to AC-PC (anterior commisure – posterior commisure) alignment using the AFNI software package. This was applied to eliminate variability in CC shape and cross-sectional area because of individual differences in head position in the scanner and the orientation of the scan plane used to generate the midsagittal image. After determining the midsagittal slice, the outline of the CC was manually traced using the specially designed program in the XITE package for outlining regions of interest. The total area (in mm^2) of the CC region was calculated from the number of pixels inside the closed contour multiplied by the pixel size. The total midsagittal callosal area was subdivided into seven subregions after having manually chosen the inflexion point at the anterior point of the inner convexity. This subdivision was identical to that of Witelson [19]. The maximal CC length was measured parallel to the AC-PC line to allow for inter-individual comparisons. The CC was then divided into halves, thirds and the posterior fifth with the following regions: R1 (rostrum), R2 (genu), R3 (rostral body), R4 (anterior midbody), R5 (posterior midbody), R6 (isthmus), R7 (splenium), as shown in *Figure 3*.

Overall brain size was controlled for by indexing the midsagittal cortical brain area, as has been done in previous studies. The midsagittal area was delimited by tracing the superior border of the CC from the genu to the splenium and then following the cerebrum posteriorly along the inferior border of the occipital lobe and continuing anteriorly over the convexity of the brain. Finally we traced posteriorly along the inferior border of the frontal lobe until the genu of the CC was reached again.

Results

Figures 4 to *6* show the correlations between CC area and DL performance, where DL performance was indexed from a laterality index score: (RE-LE/RE+LE)*100.

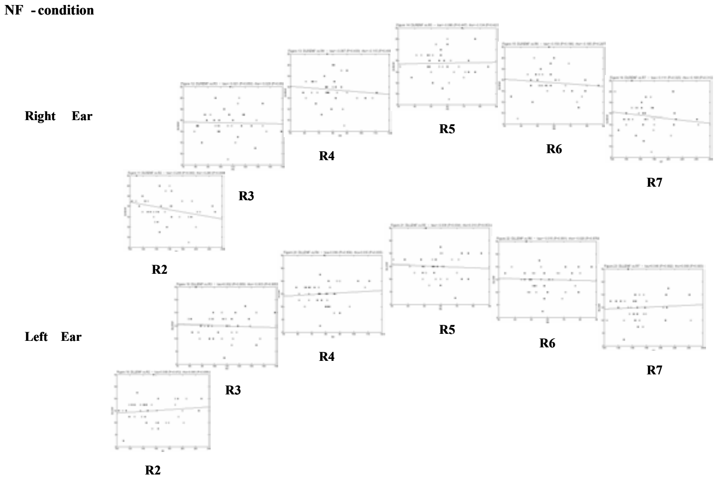

Figure 4: Scatterplots and corresponding regression lines for the correlations between CC area, region by region and DL performance during the non-forced (NF) attention condition.

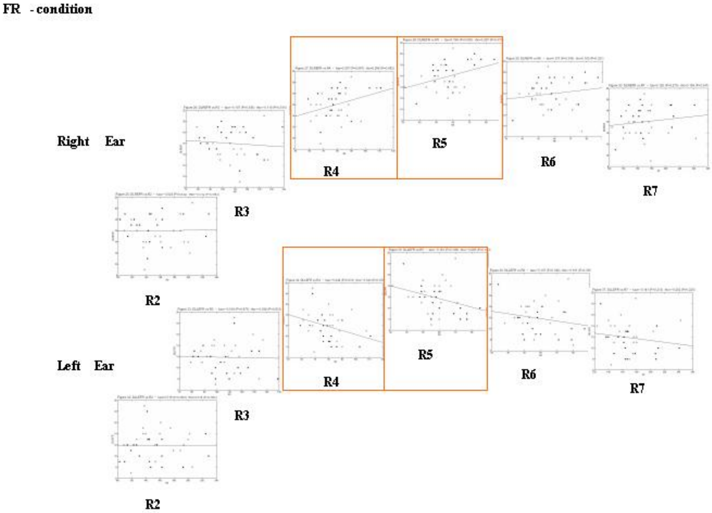

Figure 5: Scatterplots and corresponding regression lines for the correlations between CC area, region by region and DL performance during the forced-right (FR) attention condition

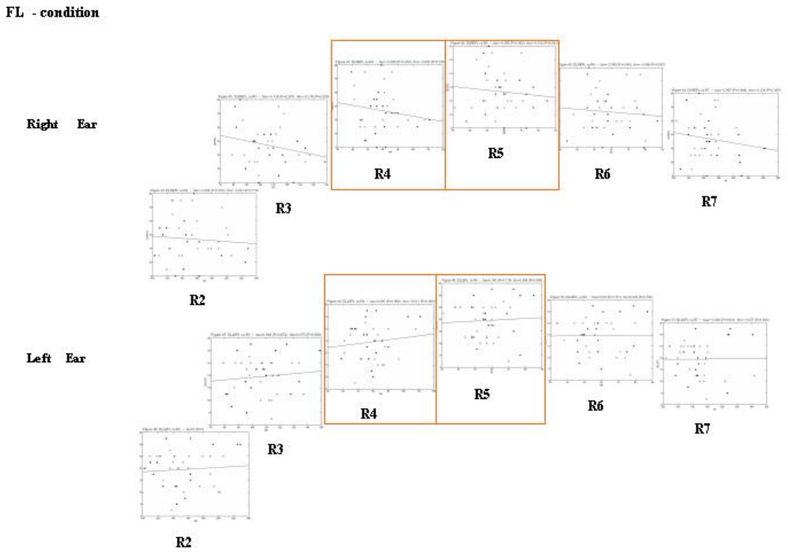

Figure 6: Scatterplots and corresponding regression lines for the correlations between CC area, region by region and DL performance during the forced-left (FL) attention condition.

In the NF attention condition, there were no significant correlations between DL and CC area size for any of the 7 CC regions (see *Figure 4*). In the FR attention condition, there were significant ($p < .05$) positive correlations for the right ear stimulus in CC regions R4 and R5 (see upper panel in *Figure 5*), and significant ($p < .05$) negative correlations in the same CC regions for the left ear stimulus (see lower panel in *Figure 5*). In the FL attention condition, the positive correlations in regions R4 and R5 in the FR condition for the right ear stimulus, switched to significant negative correlations (see upper panel *Figure 6*), while the negative correlations in the FR condition for the left ear switched to significant positive correlations in the FL condition (see lower panel in *Figure 6*).

Thus, it seems that attention affected transfer of the DL signal across the CC as a consequence of which ear that was attended to, and that this transfer correlated with the size of the anterior and posterior midbody areas.

Discussion and conclusions

It should be noted that the CC areas that showed significant correlations with shifting of attention from one ear to the other (regions R4 and R5) were anterior to the classic pathways for transfer across the callosum of the auditory fibers. According to Pandya and Seltzer [14], the auditory projections cross in the area just anterior to the splenium in the isthmus. The present results thus indicate that attention affects traffic in other fibers than the primary auditory fibers. Aboitiz [1] have suggested that there are abundant "thin" fibers surrounding the large diameter fibers that are sensory modality non-specific. We would like to suggest that these small diameter unmyelinated fibers are recruited in situations of attentional gating. This new model for information transfer across the CC takes into account attention as a modulating factor which may increase interhemispheric information processing efficacy. We will call this model a "two-channel" threshold model of callosal transfer.

The starting point for our argument is the findings in a study by Reinvang et al. [17] on the relationship between callosal sector size and left ear performance in multiple sclerosis (MS) patients. The corpus callosum often shows atrophic changes in MS patients, and measures of the corpus callosum are also often included in the diagnosis of this disease. The results showed a significant REA in both the MS patients and a healthy control group during the NF condition. Interestingly, when subjects were instructed to focus their attention to the left ear (FL condition) the correlations between left ear performance and callosal size were clearly significant, particularly for the three most posterior sectors (including the auditory sector anterior to the splenium).

It thus seems as if an "attention-gating" factor is needed in order to enhance callosal transfer of the left ear score. This may indicate the existence of a "two-channel" threshold model of callosal transfer with a sensory modality specific channel involving the large diameter myelinated fibers, and a diffuse sensory non-specific channel involving the small diameter non-myelinated fibers which are responsible for transfer of cognitive information. The model may act in a "thresholded" way in the sense that in most normal instances the recruitment of the cognitive channel is not necessary. The sensory channel is enough for efficient transfer. However, in situations of increasing cognitive load (as in the "cocktail party" situation), or when the callosum is degenerated (as in the case of the MS patients), attention may be recruited to facilitate, or amplify the sensory transfer. The point is that attention may be recruited only when the sensory transfer falls below a threshold value which defines the interaction between different ways of information transfer across the callosum.

In conclusion we suggest that:

- Attention facilitates information transfer across the corpus callosum, thus increasing hemisphere connectivity and overall processing capacity.
- A two-stage model of callosal function is suggested where the small diameter, diffusely spread, fibers may be related to "cognitive gating" which may facilitate or inhibit transfer of information.

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Inhibitory Control: Cognitive Subfunctions, Individual Differences and Variations in Dopaminergic Genes

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Abstract

The term "inhibitory control" as used in this report describes the cognitive operation when an automatic, over-learned, pre-potent response has to be inhibited. The first part of the reported study is whether inhibitory control is an unitary cognitive function. For this reason two different marker tasks of inhibitory control were administered to 135 subjects and the individual performances in both tests correlated. The second part of the study is about normal individual differences in the efficiency of inhibitory control and common variations in dopaminergic genes. The performance of normal subjects in a test for inhibitory control – the colour-word Stroop-test – was used as the behavioural phenotype and correlated with the individual's genotype in dopaminergic genes.

Introduction

The model of attention by Posner [1] identifies and describes functionally and anatomically three attentional networks: orienting, alerting and executive control, executive attention respectively. Executive control is thought to represent the mechanism which is performed by the "Supervisory Attentional System" (SAS) as proposed by the Norman-Shallice model [2]. The SAS intervenes in various kinds of situations: when planning or decision making is necessary, when errors have to be corrected, in novel, difficult or dangerous situations, or when an automatic response has to be overcome. Behaviourally it has been shown that the performance in tasks in which executive control is needed is not necessarily highly correlated [3, 4]. Thus executive control as measured by cognitive tests is not a unitary function but diverse: e.g., mental set shifting, information monitoring and updating and inhibition of pre-potent responses.

Accordingly, the SAS operates through different independent cognitive mechanisms in different kinds of situations. One of these cognitive sub-functions is the inhibition of a pre-potent response to an irrelevant stimulus dimension. We refer to this sub-function of the Supervisory System as inhibitory control. Inhibitory control can in return be broken down into monitoring and executing components. It is operationalized by tests where a conflict between two competing stimulus dimensions or responses has to be resolved. Two different marker tasks to evaluate the efficiency of individual inhibitory control are the Colour-word Stroop-task and the Attention Network Test (ANT) [5]. The ANT has been designed to measure the individual performance of all three attentional networks of the Posner model simultaneously. In this report we focus on the behavioural results from the conflict condition which is a variation of the flanker task. Both tasks require inhibition of irrelevant information and additionally it has been shown that both conflicts activate nearby but not identical areas in the anterior cingulate gyrus (ACC) and the dorsolateral prefrontal cortex (DLPFC) [6, 7, 8]. A remaining question in this context is if the ACC resolves or just monitors the conflict.

The efficiency of inhibiting pre-potent responses as measured by cognitive tests differs between individuals. This is true for psychological disorders like ADHD [9], or schizophrenia [10]. But also in healthy individuals this ability varies and declines with age [11, 12].

Behavioural genetics tries to relate the genotype of an individual to its behavioural phenotype. There are many means of assessing a behavioural phenotype including ICD-10 diagnoses as seen in schizophrenia, personality traits as measured by questionnaires or the performance in psychometric tests. And there are two general approaches: quantitative and molecular behavioural genetic studies.

Quantitative behavioural genetic studies use the known degree of genetic similarity in families to explore and quantify the influence and interaction of genetic and environmental factors on inter-individual differences in behavioural phenotypes. Francis Galton started this research tradition influenced by Charles Darwin with his investigation about the heritability of “genius” 1869 [13] and McGuffin and colleagues [14] summarized 2001 the research on the heritability of behaviour: “nearly all behaviours that have been studied show moderate to high heritability – usually, to a somewhat greater degree than do many common physical diseases.”

In these studies it has been consistently shown that attentional performance of normal subjects in a variety of tests is influenced by genetic factors. More specific the efficiency of executive control measured by the ANT was found to be highly heritable in a twin study [15]. For the Stroop test findings mainly from schizophrenia research point to a genetic influence [e.g., 16]. An impaired ability to inhibit an automatic response is thought to be an endophenotype of schizophrenia [17]. Quantitative behaviour studies show to what degree a behaviour is heritable and are therefore the basis for further molecular genetic investigations.

Molecular behavioural genetic studies take advantage of the growing knowledge about the human genome: after finishing the human genome project more and more normal genetic variations, polymorphisms, are known these days. Using these individual differences as variables in association studies with behavioural phenotypes it is possible to determine if one particular gene, or the protein is involved in that behaviour. According to the Quantitative Trait Loci Theory variations in many genes contribute to the variability in behaviour and none of them is sufficient or necessary for the manifestation of this variability. Each genetic difference in one of the concerned genes explains a certain part of the behavioural variance. The challenge is to identify reasonable candidate genes for behaviour [18] in order to link complex behaviour to genes.

Much evidence from various sources suggests that dopamine has a strong neuromodulatory effect on executive functions like inhibitory control. The prefrontal cortex including the anterior cingulate gyrus has a dense dopaminergic innervation. From neuroimaging studies the relevance of these brain areas for executive control is known. Additionally patients with frontal lobe lesions often have difficulties in inhibition of their behaviour. Furthermore there exists much support for the dopamine hypothesis of schizophrenia and also ADHD is successfully treated by the dopamine agonist Ritalin®. Both disorders share as a diagnostic criterion attentional difficulties. In animal studies the important role of dopamine in prefrontal cortex and its strong influence on behaviour has also been confirmed repeatedly.

Candidate genes for molecular behaviour genetic studies of executive control are therefore genes that play a role in dopaminergic neuromodulation and metabolism. In recent years a lot of studies were published relating dopaminergic genes to a broad variety of psychological phenotypes. Most of the results are very heterogeneous. Relatively consistently associations with ADHD, novelty seeking and schizophrenia have been reported.

Aims of this study

(1) Employ the colour-word Stroop-test and the ANT to evaluate the efficiency of normal subjects in inhibitory control. Testing the hypothesis that both marker tasks for executive control requires the same cognitive sub-functions of inhibition provided by the "Supervisory System".

(2) Testing the hypothesis that variations in efficiency measured by the Stroop-test correlates with genotypic variation in a set of candidate genes which are involved in the dopaminergic neurotransmitter system.

(3) Testing a third – more explorative – hypothesis that the normal variability in dopaminergic genes is associated with individual differences in overall reaction time in the Stroop-test: Quantitative behavioural genetic studies showed consistently a strong heritability for reaction time (RT) in various tasks. Due to the widespread dopaminergic innervation in the human brain it is reasonable to test dopamine genes also as candidate genes for this phenotype.

The association of the efficiency in the three attentional networks measured by the ANT with normal variances in candidate genes is reported elsewhere [19].

Methods

Subjects: In the behavioural part of the study 135 subjects (age: 17 to 57, mean 30.2 years, 58 % female) from the New York City area participated. The subjects were recruited by posters in the Cornell Medical College/Presbyterian Hospital. A signed informed consent approved by the New York Presbyterian Hospital/Weill Medical College of Cornell University was obtained from each participant prior to the experiment. 96 subjects were randomly assigned to the genetics analysis. Ethnical heterogeneity was high and no genetic tests were performed to assess population stratification.

Behavioural Methods: The ANT is a combination of the cued reaction time [20] and the flanker task [21]. It has been designed to measure the individual performance of all three attentional networks in a single session [5]. The participant's task is to identify the direction of the centrally presented arrow by pressing a corresponding key. In this report we focus on the measurement of the individual efficiency in executive control. The conflict occurs in the incongruent condition by the interference between the target arrow and the flanking arrows which point in the opposite direction (*Figure 1*). The efficiency of executive control is evaluated by subtracting the median reaction time in the congruent from that in the incongruent condition.

In the colour-word Stroop-test [22] the conflict is introduced by the fact that in some of the trials the colour-words are printed in an ink different from the word meaning (incongruent condition). The participant's task is to name the colour of the ink and to inhibit the automatic reading of the word. The individual efficiency of inhibitory control is calculated by subtracting the median RT in the congruent condition where ink and word meaning are identical from the median RT in the incongruent condition.

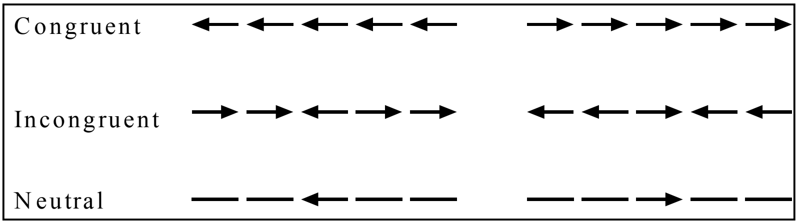

Figure 1: The different stimulus conditions of the Attention Network Test (ANT). The central arrow is the target.

Genetic sample collection and genotyping: Buccal swabs were obtained via buccal cell brush from consenting subjects and prepared as directed by the manufacturer. We used the MasterAMP TM Buccal Swab DNA Extraction Kit (Epicentre Technologies, Madison, WI). Yields range from 0.5 to 3 µg of DNA from each buccal sample. Yields were determined spectrophotometrically by absorbance at 260 nm. Taq polymerase, PCR buffer and dNTPs were obtained from QIAGEN and used at recommended concentrations for a 20 ul PCR reaction. PCR reactions and restriction digests (PCR-RFLP) are optimised for each marker and performed on the PTC-100 Programmable Thermal Controller (MJ Research) outfitted with a heated lid for oil-free amplifications. For most markers, a "touchdown" PCR cycling regimen and the addition of DMSO (10 % final v:v) was used in order to automatically optimise the hybridisation stringency. Gel electrophoresis in either LE or Metaphor agarose followed by staining in ethidium bromide was used to resolve and visualise DNA fragments. For genotyping of the various polymorphisms primers were used at

200 uM and were designed as described in the references (see *Table 1*). Also the same restriction enzymes as described were used.

Set of polymorphisms in candidate genes: According to various criteria like frequency and technical reasons 16 polymorphisms in genes coding for following proteins were selected from a total of approximately 100 known variances in these genes:

- dopamine receptor subtypes (D1-D5)
- monoaminooxidase A and B (MAOA, MAOAB), dopamine-β-hydroxylase (DBH), catechol-O-methyltransferase (COMT), and tyrosine-hydroxylase
- dopamine transporter
- Gs protein α-subunit, and G-protein β-3 (coupled to dopamine receptors)

See *Table 1* for a complete list of selected polymorphisms.

Table 1: For this association study selected polymorphisms in genes of the dopaminergic metabolism and neuromodulation (SNP= single nucleotide polymorphism, bp = base-pairs relatively to start codon, aa = amino-acids).

Protein	**Description**	**Reference**
dopamine1-receptor	SNP at -48 bp	[23]
dopamine2-receptor	functional deletion at -141 bp in promoter	[24]
dopamine2-receptor	serine to cystine exchange at aa 311	[25]
dopamine3-receptor	serine to glycine exchange at aa 9	[26]
dopamine4-receptor	functional 120 nucleotide duplication in promoter	[27]
dopamine4-receptor	variable 16 aa repeat in the third cytoplasmatic loop	[28]
dopamine4-receptor	SNP at -521 bp	[29]
dopamine5-receptor	dinucleotide repeat	[30]
Gs-protein-α	SNP at 393 bp	[31]
monoaminooxidaseA	30 nucleotide repeat in promoter	[32]
monoaminooxidaseA	SNP at 1460 bp	[33]
monoaminooxidaseA	SNP at 941 bp	[33]
catechol-O-methyltransferase	valine to methionine exchanege at 108 aa	[34]
dopamine-β-hydroxylase	alanine to serine exchange at 304 aa	[35]
dopamin-β-hydroxylase	SNP at 444 bp	[36]
dopamine transporter	40 nucleotide repeat in promoter	[30]

Testing for associations between geno- and phenotype: As behavioural phenotypes the overall median RT in the Stroop task and the RT difference between congruent and incongruent trials in the Stroop task were used. For none of the genes did an a priori hypothesis about the genetic mechanism exist. Therefore an additive gene effect, dominance for each allele and over-dominance were tested for every polymorphism separately. For this purpose the subjects were grouped according to their genotype at that polymorphism following the assumed gene effect. In case of two resulting groups (dominance of one allele, or over-dominance) t-tests, for an assumed additive gene effect ANOVAs were calculated. Here we report only the significant results of these comparisons.

Results

Behaviour Results: The overall median RTs in the colour-word Stroop-test are significantly longer than in the Flanker test ($p <. 00$). In both tasks RTs for the incongruent condition are significantly longer than for the neutral and congruent condition (ANT $p <. 00$, Stroop-test $p < .00$). The efficiency of conflict resolution measured by both tasks are not normal distributed (Lilliefors-test [37] for normal distribution, ANT: maxD = .153, $p < .01$; Stroop-test maxD = .119, $p < .01$, *Figure 2*). The RT-differences in both tasks are not correlated ($r^2 = .0004$, *Figure 3*). In contrast the overall median RTs in both tasks correlate significantly ($r^2 = .51$, $p <. 01$) and also the overall RT and the conflict-resolution in the Stroop-test correlate significantly ($r^2 = .43$, $p <. 01$).

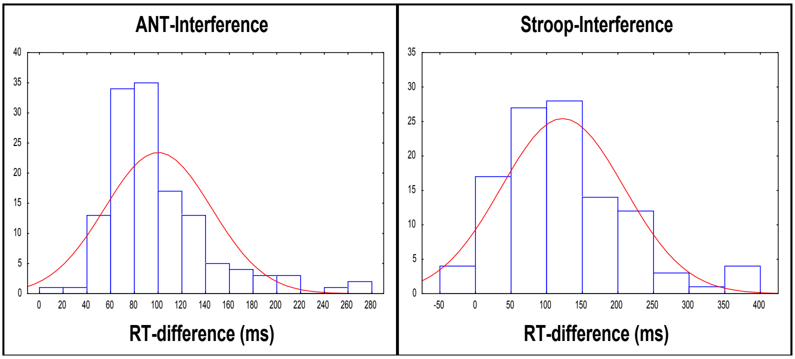

Figure 2: Distribution of the efficiency in inhibitory control measured by the ANT and the Stroop-test (median RT congruent minus incongruent condition).

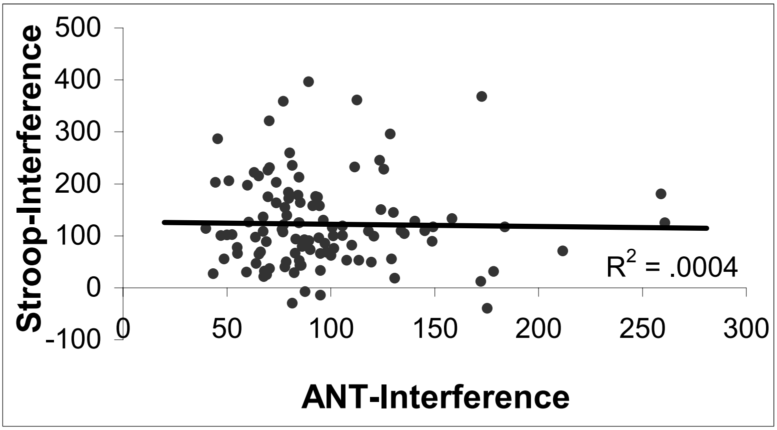

Figure 3: Correlation of the individual efficiencies in inhibitory control measured by the ANT and color-word Stroop-test.

Association of inhibitory control and dopaminergic variability: We found one significant association between performance in the Stroop test conflict and dopaminergic gene variation: assuming complete dominance of the valine-allele of the catchol-O-methyltransferase [34] there is a group difference in inhibitory control measured by the Stroop test (p <. 02, *Figure 4*, right). There is no linear dependency from the genotype as it would be the case for an additive gene effect (*Figure 4*, left).

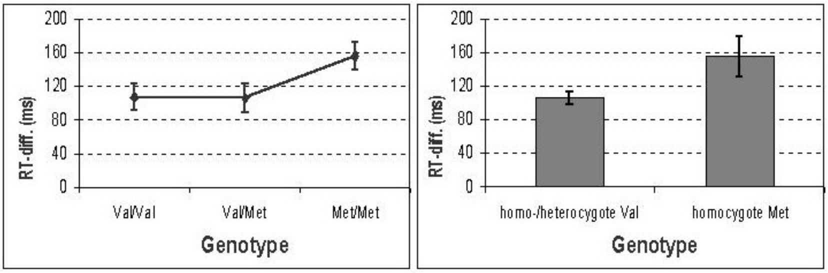

Figure 4: Association of genotypes in the catechol-O-methyltransferase gene polymorphism Val/Met108 and the individual efficiency in executive control measured by the Stroop-test. Left: assumed additive gene effect, right: assumed dominance of the Val-allele.

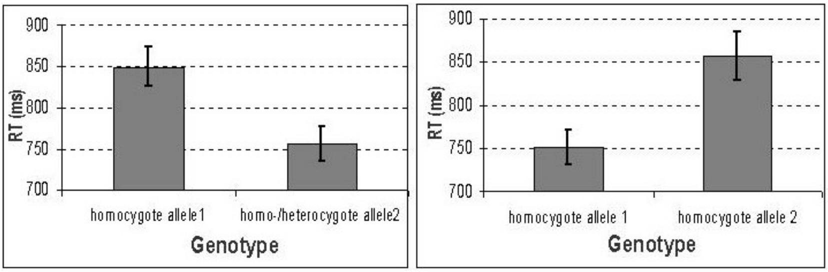

Figure 5: left: association of the polymorphism in the G-protein α-subunit with the overall median RTs in the Stroop-test, assumed dominance of allele 2; right: association of the polymorphism in the MAOA gene with the overall median RTs in the Stroop-test.

Association of overall RT and dopaminergic variability: Assuming dominance of allele 2 and grouping the subjects according to their genotype in the polymorphism in the gene for the G-protein α-subunit [31] results in a significant group difference in the overall RT (p <. 02, *Figure 5,* left). Because the MAOA-gene is located on the X-chromosome there is only one way to group the subjects according to polymorphisms in it. For one of the polymorphisms [33] this results also in a group difference (p < .00, *Figure 5,* right).

Discussion

Behaviour Results: In both tasks, the colour-word Stroop-test and the ANT, the incongruent condition introduces a cognitive conflict, a prepotent response has to be inhibited which leads to the increased RTs. The distribution of the individual efficiencies in resolving this conflict is not normal but unimodal distributed. Surprisingly the individual efficiencies in this inhibitory control do not correlate at all. A correlation was expected because both tests appear to introduce a similar type of cognitive conflict: a competition between for the required response relevant and irrelevant stimulus information. In a recent study [6] these two tasks and an additional conflict task activated similar but not identical areas of the ACC. However as in the current data, the two were uncorrelated. At least two interpretations of this finding are possible: even if both types of conflict seem to rely on the same or very similar cognitive processes it might be the case that the conflict occurs on different independent levels of processing [38], or that both conflicts involve independent parallel processes. In the flanker task subjects must select the relevant stimulus information from a spatial array including relevant and irrelevant information. In the Stroop-test irrelevant and relevant information presents itself in the same spatial location. Here, relevant and irrelevant stimulus information competes based on information type instead of location. The conflict during the flanker task emerges through response competition because subjects must inhibit the response to stimuli located in an irrelevant place. In the colour-word Stroop-test the conflict might emerge from semantic competition [39]. Therefore it might be the case that both tasks represent different independent cognitive sub-functions of inhibitory control that take place independently in the ACC. The other interpretation would be that the ACC is just the area where conflicts are monitored as other authors [7] propose. In that case the ACC wouldn’t play an active role in conflict resolution but just sends signals to brain areas where both conflicts are independently resolved. Both interpretations have in common that the two marker tasks of executive control – or more specific inhibitory control – underlie different cognitive mechanisms of inhibition. They represent different, independent sub-functions of the network of executive control.

Association of inhibitory control and dopaminergic variability: The genotype in the functional polymorphism in the COMT-gene is associated with the efficiency of inhibitory control measured by the Stroop-test. COMT (together with MAOA) is one of the crucial enzymes in the catabolism of dopamine and other monoamines. The polymorphism in the gene leads to a valine to methionine exchange in the enzyme. The Val-allele has a 4-fold higher enzyme activity and increases therefore the dopamine catabolism which leads to a decrease of the dopamine level. There is evidence from various sources that COMT is especially important in the prefrontal cortex for the inactivation of released dopamine. There are many behaviour genetic studies about this polymorphism with a broad variety of phenotypes (e.g., depression, schizophrenia, OCD, ADHD, alcoholism). The findings are heterogeneous but taken together a relative large number of studies report positive associations at least with subpopulations of the samples. Interestingly an impaired executive attention is known to be an endophenotype of at least schizophrenia and ADHD.

In our sample the Val-allele is associated with a more effective inhibition of the pre-potent response in the colour-word Stroop-test. A faster inactivation of prefrontal dopamine would lead therefore to a more effective inhibitory control. This is in contradiction to findings of Egan and colleagues [42] who report in their sample fewer preservative errors in the Wisconsin Card Sorting Test (WCST) for subjects with the less active Met-allele. They conclude that dopamine enhances cognitive functions. Although the Stroop-test and the WCST rely on different cognitive mechanisms, it should be therefore noticed that the way dopamine influences prefrontal cognition remains controversial. Additionally COMT is also involved in the catabolism of the other catecholamines (e.g., adrenalin and noradrenalin), which influence cognitive functions, too.

Association of RT and dopaminergic variability: The genotype in the MAOA and Gs-α-subunit genes are in the sample associated with the overall median RT in the colour-word Stroop-test. This is not the case for the overall median RT in the ANT [40]. The RT measured by the ANT is in contrast associated with the genotype in one of the polymorphisms at the dopamine-beta-hydroxylase gene [34, 40]. As mentioned in the introduction there are several family studies which report consistently a heritability for the so called "speed of information processing" measured as RT in a variety of cognitive tasks. This is not a well-defined cognitive process and a rather broad behaviour phenotype: The overall median RT can be influenced from totally different and independent stages of information processing or response preparation, especially in different cognitive tasks. Therefore there is not one brain area or transmitter system which is responsible for differences in RT. Accordingly there is no obvious hypothesis which genes might be responsible for parts of the normal variance in RTs. Thus all genes which are involved in neural signal transduction in the human brain are candidate genes for association studies with this behavioural phenotype. The fact that the correlation of the overall median RTs in both tasks we administered in this study explains only 25 % of the variance and both are associated with genotypes in different genes support this consideration about the heterogeneity of this behavioural phenotype. Such vague hypotheses for molecular behavioural genetic studies are nevertheless not uncommon due to the fact that the link from behaviour to a particular gene is very complex [e.g., 41]. A heterogeneous behavioural phenotype like the overall RT diminishes the likelihood of a positive finding because a lot of different factors and cognitive operations contribute to the measured behaviour. This decreases the contribution of each with the behaviour associated genetic variance to the found behavioural variability. But on the other hand the overall median RT is a more reliable measure than a subtraction measurement like "inhibitory control" because the reliability of differences of correlated tests (in this case the RT in different conditions) is lower than the origin tests.

The two polymorphisms which are associated with the overall median Stroop-RT in our sample are so called silent polymorphisms: the variation in the DNA-sequence of the gene do not lead to a variation in the amino-acid-sequence of the protein. Therefore these polymorphisms cannot be responsible by themselves for functional differences of the protein. If the found associations are not false positive results these polymorphisms must be in linkage disequilibrium with functional polymorphisms. In the exons of the gene for the G-protein α-subunit this is the only known polymorphism. For this reason the linked functional polymorphism must be in regulatory DNA-sequences of this gene or in an adjacent gene. So far no behavioural genetic study has been published about this polymorphism. The single nucleotide exchange in the MAOA-gene is associated with different levels in enzyme activity [33]: Allele 1 was found to be more frequent in subjects with a less active MAOA. A moderate inhibition of MAOA activity leads, e.g., to motoric hyperactivity [43]. In our sample subjects with allele 1 have an overall faster reaction time in the Stroop-test. The relatively elevated level of catecholamines could be the basis for this behavioural difference. For this polymorphism there exists only three negative findings: one association study with mild mental retardation and two with Parkinsonism as phenotype. Also for other polymorphisms in this gene the findings of association studies with a variety of behavioural phenotypes (e.g., bipolar affective disorder, alcoholism etc.) are still very heterogeneous. If and how the G-protein α-subunit and the MAOA-gene might influence the RT needs therefore further investigations.

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II.

Individual Differences in Brain Activity: EEG, ERP and MEG Studies

A New ERP Paradigm for Studying Individual Differences in the Executive Control of Attention

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Abstract

Event-related potentials (ERPs) provide valuable information about the fast brain dynamics subserving cognitive functions such as attention and working memory. Most ERP studies employ cognitive paradigms with a fixed task-set (i.e., press a button to named targets), but few have measured ERPs time-locked to shifts in set using a task-switching paradigm. The Madrid Card Sorting Test (MCST) is a dual task protocol in which feedback cues signal unpredictable shifts in set (i.e., from “sort cards by colour” to “sort cards by shape”). This protocol offers an integrated analysis of ERPs to both feedback cues and target card events, providing separate ERP indexes for the shifting, updating and rehearsal of attention sets in working memory. Two of these ERP indices are the frontal and posterior aspects of the P300 response. Feedback cues that direct a shift in set also elicit both a frontally distributed P3a potential (300 to 400 ms) and a posteriorly distributed P3b potential (350 to 600 ms). In turn, target card events evoke posterior P3b responses whose amplitude increases as the new task set is gradually rehearsed. In line with current models about the role of prefrontal cortex in the executive control of attention, this P3a/P3b response system appears to reflect the coordinated action of prefrontal and posterior association cortices during the switching and updating of task sets in working memory.

Introduction

Scalp-recorded event-related potentials (ERPs) provide a fine spatio-temporal analysis of brain activation in so-called “oddball” target detection tasks. In these tasks, target events evoke a distinct long latency positive potential (350to 600 ms; P3b) maximal over mid-parietal scalp. The P3b potential reflects task-relevant processes such as context updating [6] or closure of the event-encoding cycle in working memory [22]. An earlier latency positive potential (300 to 400 ms; P3a) indexes attention switching to non-target novel events [7]. Lesion, brain imaging and intracranial studies propose anatomical and functionally distinct neural sources for the switching (P3a) and updating (P3b) mechanisms [12]. For instance, the prefrontal cortex (PFC) plays a key role in triggering the P3a potential [10], but has a less critical involvement in P3b elicitation [11]. In spite of evidence about an implication of PFC in both task set-shifting and the detection of novel events [10, 14, 17, 18], to date there is no functional evidence that these two processes may be subserved by a common brain mechanism. However, one limitation of ERP studies on attention is that brain activity is measured under fixed task-set conditions (i.e., “press a button to named targets”). Further, even if the task’s rules change between successive trial blocks, ERPs are normally not recorded while the task’s rules are being changed. Thus, the critical brain potentials related to the shifting and updating of stimulus-response mappings (or task sets) in working memory still remain to be described.

In the last few years we have developed a task-switching paradigm, the Madrid card sorting test (MCST), inspired by a classic test of prefrontal impairment, the Wisconsin card sorting test (WCST) [9, 15, 17], to study the fast brain dynamics behind task-set switching [2 to 5]. Initially, we found a gradual modulation of P3b amplitudes across “shift” and non-shift (“stay”) trials time-locked to target card stimuli, but no clear evidence of a frontally distributed ERP activation [3]. Subsequent analyses revealed that the actual shift in set takes place at the feedback stage, that is, when a non-target “shift” feedback cue instructs the subject to adopt a new rule for the task at hand. In turn, at the card-matching stage, the task-set is merely implemented or rehearsed [19 to 21]. This has led to a more comprehensive ERP analysis of both contextual processes time-locked to feedback events, and target-related processes time-locked to the card-matching stage of task performance (see *Figure 1b*). This novel ERP paradigm shows that task-switching consists of several cognitive processes, as reflected by a number of ERP components, the most conspicuous of which is the endogenous P300 response [4]. Therefore, the MCST task-switching protocol represents a new and promising tool for examining the putative relationship between attention set-shifting and the frontal (P3a) and posterior (P3b) components of the P300 response system. The interpretation of observed modulations in the frontal P3a and posterior P3b aspects of the P300 response system in terms of attention set-shifting processes may benefit from the solid theoretical grounds yielded by current models about the role of prefrontal cortex in the executive control of attention [15, 16, 19]. To illustrate this new ERP paradigm, here we present a study designed to examine the involvement of the frontal and posterior components of the P300 response in switching (P3a) and updating (P3b) of task-sets in working memory.

Methods

Subjects: Twenty-seven right handed subjects (15 females; mean age 23 ± 4 years, range 18 to 34 years), took part in the study. They all had normal or corrected visual acuity and no history of neurological or psychiatric disorder.

Behavioural procedures: We used a computer version of the WCST designed to assess attention set shifting using ERP recordings [3]. The task protocol used the 24 choice-cards of the original 64 WCST cards that can be matched unambiguously with the four WCST key-cards based on just one stimulus dimension (i.e., either colour, shape, or number of items in the card; Fig. 1a). Unambiguous cards are required for both a sensitive scoring of WCST errors and set-shifting ability [2]. These 24 choice-cards were repeatedly used in 137 trials arranged into 18 series (see *Figure 1*). The correct sorting rule was initially unknown to the subject and changed randomly from one series to the next. The length of each series varied randomly between 6 and 8 trials. Each trial began with the onset of a compound stimulus with the four WCST key-cards on top of one choice-card, all centred on a computer screen. The cards subtended a visual angle of 4° horizontally and 3.5° vertically, and remained on display until a response was given (*Figure 1b*).

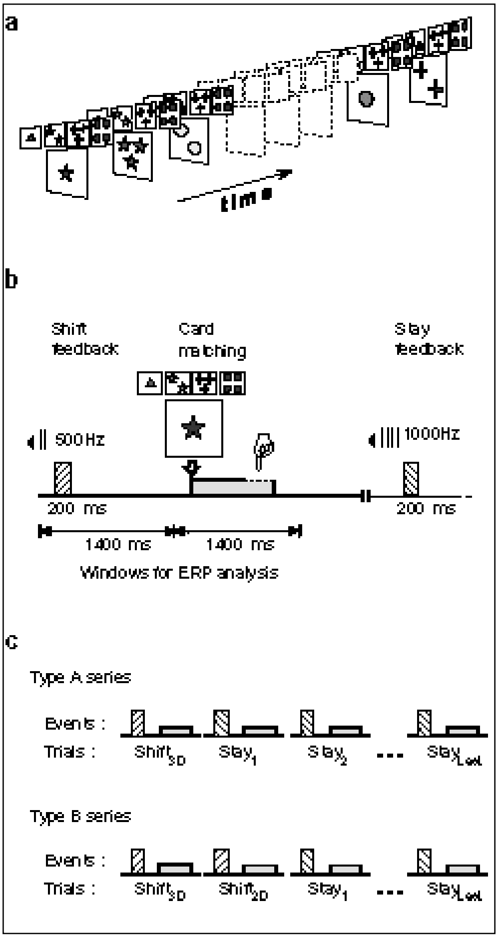

Figure 1: Task design and ERP trial analysis. *1a*, Schematic example of one MCST series. Each choice-card could be unambiguously matched with each key-card based on just one stimulus dimension. *1b*, Feedback stage: A "shift" feedback tone cued subjects to shift the task rule (sound frequency 500 Hz). A "stay" feedback tone cued subjects to use the same rule again (sound frequency 1000 Hz). Card-matching stage: The choice-card remained on display until a response was given. *1c*, Trial analysis based on the subject's responses. In the first trial of a series (shift$_{3D}$ trial), subjects inhibited the old rule and adopted one of the remaining two for responding. In type B series, subjects had to shift set twice to find the correct rule (shift$_{2D}$ trials). In the first stay trial (stay$_{1}$) the subject repeated his previous choice of rule. The last stay trial of a series (stay$_{\mathrm{Last}}$) was preceded by

another three to five stay trials (adapted from [1]).

Subjects were instructed to match the choice-card with one of the four key-cards following one of three possible rules: number, colour or shape. Likewise, subjects were informed that the correct sorting rule would change without notice after a variable number of card sorts, and hence, they would have to shift their sorting rule accordingly. The correct rule was to be determined on the basis of an auditory feedback cue delivered within a variable interval of 1500-2000 ms after the response (200 ms duration, 10 ms rise/fall times; 65 dB SPL; 1000 Hz for “stay” cues, 500 Hz for “shift” cues).

Subjects used their thumbs for responding using a panel with four key-buttons aligned. Subjects performed two blocks of 137 trials each, with a 5 min rest period between blocks. The task was practised for about 5 min, or 5 to 7 series, to make sure that subjects had understood the instructions and could sort cards efficiently (see operational criteria for efficiently completed WCST series below [2]). The sequence of trials used for practice was different from that in the main task. Therefore, in our adapted WCST protocol each correct card match was followed by a “stay” feedback cue prompting the subject to use the same sorting rule again. After a variable number of correct card matches, the rule changed unpredictably and the subject had to adopt a new task rule upon hearing a “shift” feedback cue (e.g., from shape to number, or to colour).

Following prior functional magnetic resonance imaging (fMRI) studies [14, 18], we defined three-dimensional shift trials (shift$_{3D}$) as those where subjects had to handle three task rules in working memory (i.e., inhibit the previous rule and consider the other two for responding; *Figure 1c*). In two-dimensional shift trials (shift$_{2D}$), only two rules were handled, after having discarded one in the previous trial. In stay trials, a “stay” feedback cue prompted the subject to use the same task rule again. This task design allowed us to carry out a separate analysis of attention switching (P3a) and memory updating (P3b) processes. After the first shift feedback cue of a new series (shift$_{3D}$), an ideal subject has 50 % chance of choosing an incorrect task rule, and so needs to shift set again to achieve the remaining correct rule. This is an efficient trial-and-error process in normal subjects, who can use past contextual information to optimise task-set shifting. Here we considered data from efficient series only, with either no errors or just one such efficient error (shift$_{2D}$; *Figure 1c*).

ERPs and data analysis: The electroencephalogram (EEG) was recorded from 29 tin electrodes positioned at Fp1, Fp2, AF3, AF4, F7, F8, F3, Fz, F4, FC5, FC6, FC1, FC2, T7, T8, C3, Cz, C4, P7, P8, P3, Pz, P4, PO7, PO8, PO1, PO2, O1 and O2, and referenced to the left mastoid. The EEG signal was amplified (band pass, 0.01 to 30 Hz; 12 dB/octave roll/off), digitised at 250 Hz/channel and stored for off-line averaging. Electrode impedances were kept below 5 kΩ. The averaging window was 1400 ms for the feedback and card matching epochs, including a 200-ms baseline in both cases (*Figure 1b*). The electrooculogram (EOG) was also recorded for eye blink correction. Epoch trials with EEG exceeding ± 75 μV in amplitude, muscle, or any other artifacts were discarded. ERP averages were obtained from completed WCST series only. A completed series was scored if (a) the new sorting rule was not anticipated (i.e., the first trial in a series was a shift$_{3D}$ trial); (b) the subject shifted set efficiently and found the new rule in the second (type A series) or third trial (type B series, Figure 1c); and (c) the rule was not missed thereafter. In the present sample of normal subjects, individual task performance ranged between 32 to 36 successfully completed WCST series [2]. ERPs were computed time-locked to both feedback cues and card onsets across both shift and stay trials. A linked-mastoid reference was obtained off-line. Mean ERP amplitudes were measured relative to the 200 ms pre-stimulus baseline. For feedback-locked averages, mean amplitude values were computed for the P3a component (375 to 400 ms post-stimulus onset) and P3b (550-600 ms post-stimulus onset). For card-locked averages, only mean P3b amplitudes were measured. The P3a potential was measured at Fz, and the P3b potential at Pz. A significance level of $P < 0.05$ was used in all contrasts.

Results

Figure 2 presents the grand-average ERP waveforms evoked by feedback and card events from shift$_{3D}$ trials as compared to stay$_{Last}$ trials in the MCST series. *Figure 3* displays the mean P300 amplitudes (Figure 3, upper panel) and behavioural task performance (Figure 3, lower panel) across shift and stay MCST trials. It can be observed that feedback cues signalling a shift to a new task rule evoked a distinct frontally distributed P3a potential that was absent after the first stay cue ($P < 0.0001$, for the main Trial effect; Figures 2 and 3). A sharp reduction in P3a amplitude was observed in response to the first ($P < 0.003$), and second stay cues ($P < 0.0001$; Figure 3), but there was no decrement in P3a amplitude from shift$_{3D}$ to shift$_{2D}$ trials ($P > 0.2$; Figure 3). In turn, shift$_{2D}$ cues evoked larger P3a potentials than stay$_1$ cues ($P < 0.003$; Figure 3). Stay$_2$ and later trials evoked similar brain responses in both type A and B series [3, 4]. Finally, P3a amplitudes to shift$_{3D}$ cues did not diminish over successive task blocks, consistent with behavioural evidence that set shifting costs do not decline with practice [20].

Feedback cues also elicited a distinct pattern of P3b activity across shift and stay trials ($P < 0.0001$, for the main Trial effect; Figures 2 and 3). There was a reduction in P3b amplitude from shift$_{3D}$ to shift$_{2D}$ cues ($P < 0.003$), and between stay$_1$ and stay$_2$ cues ($P < 0.001$), but no P3b change was observed between shift$_{2D}$ and stay$_1$ cues (Figure 3). Thus, unlike the P3a, the P3b response to feedback cues was sensitive both to the number of rules held in memory, and to the subject's ability to predict the next task rule. Although the P3a and P3b components have never been compared in a similar task-switching paradigm, the present results reveal a significant interaction between the type of P300 component (P3a vs. P3b) and the type of early task-set trials (shift$_{3D,}$ shift $_{2D}$, stay$_1$), suggesting their differential role in switching (P3a) and updating (P3b) of task-sets in working memory ($P < 0.03$, for the quadratic trend; see Figure 3, upper panel).

At the card-matching stage, we observed the expected P3b response to visual targets, with a gradual P3b increment from shift to stay trials as revealed in the main Trial effect (*P* < 0.0001; Figures 2b and 3), but no evidence of a P3a potential. However, the pattern of P3b responding at the card-matching stage differs substantially from that observed at the feedback stage, as revealed by a significant interaction between Stage and Trial (*P* < 0.0001; see Figure 3). These results suggest that the posterior P3b response system accomplishes rather different functions during the feedback and card-matching stages of WCST performance [18, 21].

The analysis of behavioural responses confirmed the well established costs in speed and accuracy related to task-set shifting [19-21]. Response times were slower during shift as compared to stay trials (up to circa 500 ms; *P* < 0.0001; Figure 3, lower panel), indicating a gradual speed-up in responding from shift_{3D} to shift_{2D} trials (*P* < 0.02), and from shift_{2D} to stay_1 trials (*P* < 0.03). The analysis of errors from failed series indicated that subjects were more likely to miss the task rule in shift_{2D} (*P* < 0.001) and stay_1 trials (*P* < 0.01), as compared to the last trial in the series (*P* < 0.001, for the main Trial effect; Figure 3).

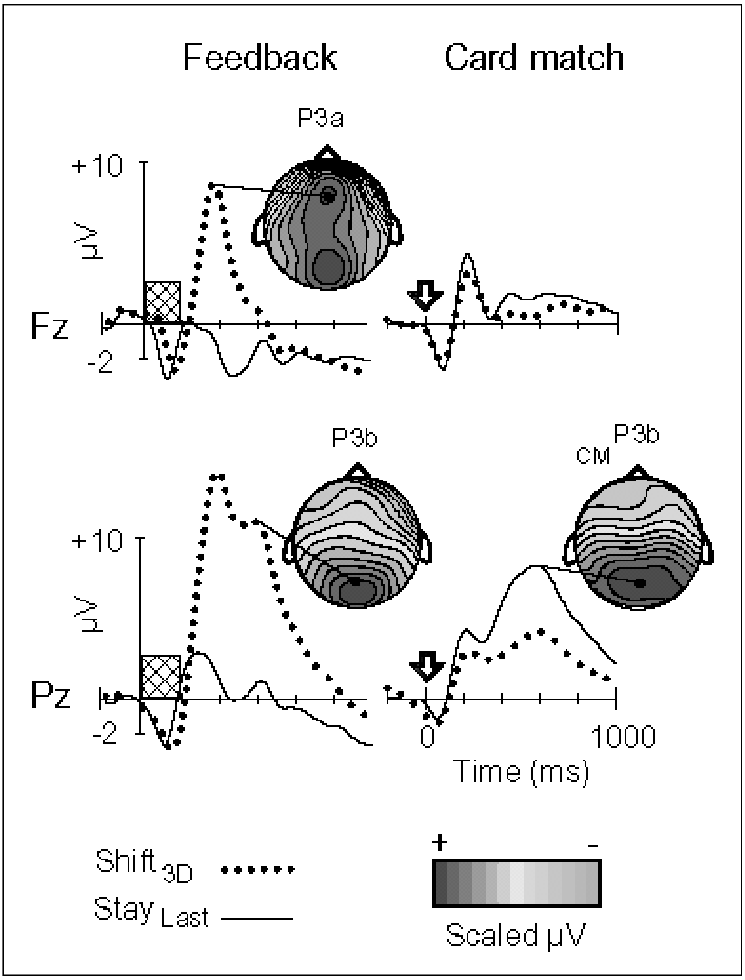

Figure 2: Brain responses to feedback and card events. Mean group-averaged ERPs to feedback cues and card stimuli are displayed for shift$_{3D}$ and stay$_{Last}$ trials, at frontal (Fz) and parietal (Pz) midline electrodes. Voltages are in microvolts (μV). Scalp potential maps are displayed for mean P3a and P3b activity evoked by shift$_{3D}$ feedback cues, and for mean P3b activity evoked by the last card-match in the series ($_{CM}$P3b). The scale is in normalised units (adapted from [1]).

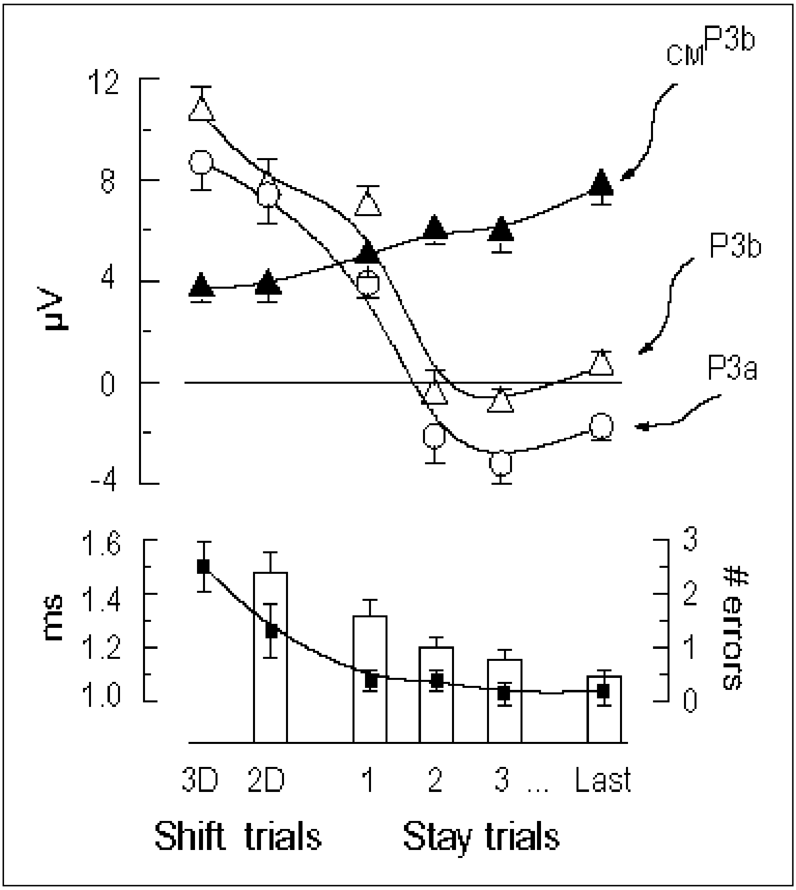

Figure 3: ERPs and behavioural responses across shift and stay trials. *Upper panel:* Group-averaged mean (± s.e.m.) amplitudes in micro-volts of the P3a and P3b responses plotted across shift and stay trials in the MCST series. Mean P3a and P3b amplitudes were measured from the mid-frontal (Fz) and mid-parietal (Pz) scalp regions, respectively. P3a and P3b responses were time-locked to feedback events. $_{CM}$P3b responses were time-locked to card-matching events. *Lower panel:* Mean (± s.e.m.) reaction times (in sec) from completed MCST series (solid squares), and mean number of random of errors from failed series (bars), are plotted across shift and stay MCST trials (adapted from [1]).

Discussion

This study represents the first evidence in the literature suggesting a role of the frontally distributed P3a response in the executive control of cognitive set shifting. Past ERP studies of attention set-shifting either focused on target events only, or failed to link the observed P3a-like activation to task-set switching. In our modified version of the WCST, feedback events that directed a shift in the subject's mental set to new task rules, also elicited P3a responses whose amplitude, latency and scalp topography closely resemble those elicited by non-target novel events in oddball tasks. However, our "shift" feedback tone cannot be defined as a novel stimulus, as it had been learned to denote a shift in the task's rules, and the same tone was used along the practice and test sessions. Instead, the "shift" tone prompted the subject to "think differently", and to flexibly adopt a new solution (i.e., a new task set) for the same card sorting problem. Thus, our results indicate that the same brain system may subserve the processing of both stimulus and task novelty.

While "shift" trials were infrequent relative to "stay" trials (i.e., overall probabilities were 0.25 and 0.75, respectively), "oddball" processes like uncertainty alone cannot explain the observed modulations of P3a brain potentials. First, oddball tasks with a fixed task-set and equally infrequent non-target tones elicit substantially smaller P3a potentials that decline rapidly with repetition. Second, task uncertainty cannot account for the functional dissociation of P3a responses to feedback and card events. Third, "shift" trials from similar tasks evoke peak fMRI activation at PFC regardless of their relative frequency of occurrence. That said, brain responses to the first stay feedback cue revealed that task uncertainty did play a role in the early trials of each new WCST series. Indeed, our feedback cues did not make it explicit which task rule was to be used next. This ambiguity disrupts WCST performance in prefrontal patients, who cannot rely on internal representations to project future actions based on past stimulus-response contingencies. Even normal subjects who can anticipate the next set need to practice it at least once before reaching pre-shift levels of behavioural efficiency. Indeed, the brain responses observed to the first stay cue may reflect residual reorienting and updating to the newly established task set (*Figure 3*). Activation in this P3a response system ceased completely at the second stay cue, after the new set had been rehearsed once. Rostral anterior cingulate (BA 24/32), mid-dorsolateral (BA 9/46) and mid-ventrolateral prefrontal cortices (BA 12/47) become simultaneously active in response to shift feedback cues in similar set-shifting tasks. In turn, the extant lesion, fMRI and intracranial recording data from oddball tasks favours a lateral – rather than a medial – prefrontal source for the P3a potential.

The present results may help us resolve apparent inconsistencies in past brain imaging and clinical WCST research. First, an outdated model of prefrontal function, and the inherently limited temporal resolution of most metabolic brain imaging studies, had led us to expect maximal prefrontal ERP activation during the card matching stage rather than the feedback stage of WCST performance. In contrast, the observed P3a activation suggests that the shift in set actually takes place during the feedback period, and well before the next target card is on display. This new account is consistent with more recent fMRI and behavioural evidence, suggesting that the internal representation of task rules must be activated (i.e., updated) in anticipation of the behaviour they govern (i.e., card sorting). Second, our ERP results provide support for the view that PFC acts in concert with posterior association cortices for the executive control of cognitive set shifting. Indeed, *Figure 2* reveals instant widely distributed neural activation across both frontal and posterior brain generators in response to “shift” feedback cues. This argues against the strict localizationist view conveyed by some studies that present isolated foci of prefrontal activation during WCST performance (i.e., see Figure 5 in [14]). Third, an ERP index of set-shifting may help us integrate apparent inconsistencies in the anatomy reported by different metabolic studies. The stereotaxic coordinates of prefrontal regions with significant fMRI/PET activation during WCST performance show a good deal of variability across studies [14, 18]. One possibility is that different anatomical fMRI activation elicited by the same task reflects disparate cognitive processes. Another possibility is that these different fMRI patterns may be showing “tip-of-iceberg” activation from different parts of the same neural network that gives rise to the P3a response [8]. The present ERP results support the latter alternative. Finally, the finding of feedback-locked frontally-distributed P3a activity helps to complete the picture offered by our previous ERP studies [3], suggesting that efficient WCST performance demands the activation of a widespread network of brain areas, with a key role played by prefrontal cortex. Further research will be necessary to map specific types of WCST deficits to specific anomalies in the frontal and posterior aspects of the P300 components reported here [2, 13, 17].

As in previous studies, a steady build-up in P3b activation to card onset was apparent as the new task set became established and gradually rehearsed. This was paralleled by a steady improvement in response speed and efficiency, indicating a growing degree of automaticity in task performance. Unlike P3b responses to feedback cues, P3b activity during card matching was modulated neither by the number of task-sets in memory, nor by their predictability. This suggests a differential role of the posterior association cortices responsible for P3b elicitation during the updating (feedback) and rehearsal (card matching) of task rules in working memory. It could be argued that long-term memory networks at posterior association cortex need to be differentially engaged both for the rapid retrieval of new task rules during set-shifting and updating, as well as for the gradual rehearsal and consolidation of practised task-sets, leading to proficient task performance. Such a proposal could help us to integrate apparently contradictory accounts of the functional role of the P3b response in terms of either “context updating” [6], or “perceptual closure” processes [22]. Future ERP research with task-switching paradigms should explore further the double dissociation of P3b responses reported here, as well as its likely implication for current models of P300 function.

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The Distraction Potential (DP), an Electrophysiological Tracer of Involuntary Attention Control and its Dysfunction

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Abstract

Attention involves both top-down and bottom-up processes. Top-down processes refer to those driven by the subject's intentions, plans and motivations. Bottom-up processes refer instead to those processes governed mainly by environmental conditions. The present text addresses this later type of attentional processes, as reflected in behavioural and event-related brain potential (ERP) indices. An auditory-visual distraction paradigm has been designed, allowing the recording of the neuroelectric concomitants of the activation of the cerebral network of involuntary attention during behavioural distraction. Subjects are instructed to respond to visual stimuli (i.e., press one response button to letters, and another response button to numbers) while ignoring the shortly preceding, task-irrelevant sounds. When these sounds are deviant or novel with regard to the repetitive auditory stimulation, behavioural distraction, i.e., prolonged reaction time and increased number of errors, is observed. In the ERPs, a triphasic neuroelectric response, the "distraction potential" (DP) is elicited, characterized by the N1/MMN, the P3a and the RON components, signalling, respectively, detection of sound change, orienting of attention and reorienting of attention after temporary distraction. In different conditions of brain damage, such as in alcoholism or after closed head injury, these ERP components reveal cerebral dysfunction of the involuntary attention network even in the absence of

behavioural concomitants, providing an objective tool to assess deficits in the involuntary control of attention.

Introduction

To manage oneself in a challenging environment fulfilled with thousands of stimuli requires an extraordinary ability to select the crucial and to reject the irrelevant. This ability is called attention, and permits us for example to concentrate in the reading of a text in a noisy environment, such as the campus cafeteria, or to listen to a specific instrument of a philharmonic orchestra while playing Symphony #9 (d minor) by Beethoven. This form of attention, which receives the name of voluntary or selective, is complemented with the other face of attention, similarly critical from an adaptive point of view, that is in charge of bringing to the focus of conscious evaluation stimuli initially not attend for their analysis in depth. This other form of attention, the so-called exogenous or involuntary, is responsible for the orienting response, and in general for avoiding that stimuli of vital importance for an adaptive behavioural from remaining unnoticed.

We have developed in the laboratory a simple behavioural "distraction" task that allows to investigate the cerebral mechanisms underlying the exogenous control of attention. Shortly, subjects are instructed to concentrate in the performance of a simple visual task (for example, to classify letters and numbers by pressing the corresponding response buttons) while ignoring the occurrence of irrelevant sounds that are presented one third of second before each visual stimulus. These irrelevant sounds are manipulated conveniently, in such a way that occasionally and with random order, the "standard" stimulus (occurring in 80 % of the cases) is replaced by a "distractor", i.e., a stimulus slightly higher in frequency (deviant) or by an environmental (novel) sound (as for example, a telephone ring, a glass breaking, the tinkle of some keys or that produced by a drilling device). We have observed consistently in several independent experiments that the distracting sounds increase the response time and the number of incorrect choices in the visual classification task, revealing behavioural distraction in the performance of such visual task (*Figure 1*) [1, 4, 6, 7, 17, 22, 23, 24; see review in reference 5].

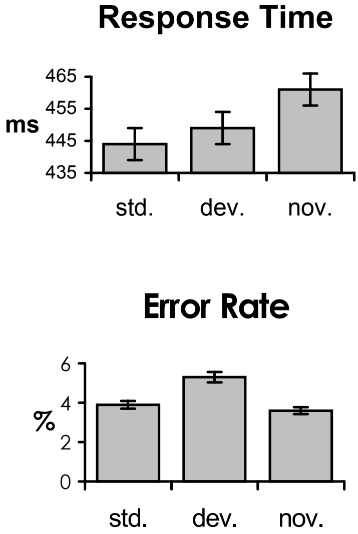

Figure 1: Mean response time (top) and error rate (bottom) to visual stimuli occurring after standard tones (std.), deviant tones (dev.), or novel sounds (nov.) in the distraction paradigm. The bars indicate the standard error of mean. Adapted from [4].

The concomitant recording of event-related brain potentials (ERPs) during the execution of the distraction task allows us to investigate the spatio-temporal dynamics of activation of the cerebral network underlying the exogenous control of attention. The typical ERP recorded in this scenario shows a complex morphology, both for the standard and the distracting trials. This is caused by the overlapping of the neuroelectric responses related to the processing of the physical features of the auditory stimulus, its distracting features, the visual stimulus and the neuroelectric activity associated to the cognitive processing involved in the task being carried out by the subject with regard to the target stimulus (*Figure 2a*). However, a simple arithmetic computation, i.e., the subtraction of the response elicited to the standard trial from that elicited to the distracting trial, allows us to isolate the neuroelectric activation underlying behavioural distraction; for reasons of convenience, we have termed to this activation *distraction potential* (DP). The distraction potential shows a characteristic tri-phasic shape, with an initial negative wave, followed by a positive wave and a final phase with a more or less sustained negative wave (*Figure 2b*). Each of these phases provides a marker for one of the three main processes involved in the involuntary control of attention: (1) the mechanism of attention capture, associated with the *mismatch negativity* (MMN) and/or with the N1 ERP components, (2) the orienting of attention, associated with the P3a or novelty-P3, and (3) the reorienting of attention towards the main task after a momentary distraction, associate with the so-called *reorienting negativity* (RON). These mechanisms and their electrophysiological concomitants are discussed briefly in the following paragraphs.

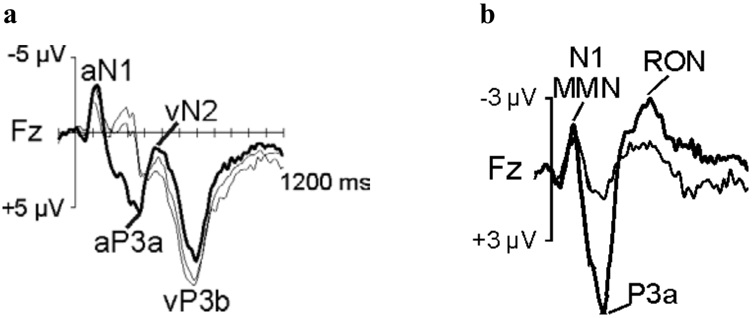

Figure 2: (a) ERPs in the auditory-visual distraction task. Standard (thin), deviant (medium) and novel (thick) trials. The auditory components are labelled as aN1 and aP3a, and those elicited to the visual stimuli as vN2 and vP3b. *(b)* The *distraction potential* (DP), obtained by subtracting the potential elicited to the standard trial from that in the deviant (fine line) or novel (thick line) trials. The distraction potential is characterized by a tri-phasic response including: MMN/N1, P3a and RON ERP components. Adapted from [7].

It has been proposed that there are at least two cerebral mechanisms responsible for directing the focus of attention towards environmental unattended events of potential relevance for competent behaviour [13]. One of them, phylogenetically more ancient, is based on a neurophysiological reaction to transient increment/decrements in the stimulating energy, and operates similarly in the auditory, visual and somatosensory modalities. This mechanism has been associated with the auditory N1 ERP component [15], and is activated, in our distraction paradigm, by the novel stimuli, yielding to an increase in novel-N1 amplitude when compared to the standard N1 (*Figure 2*). The second mechanism is based on the analysis of the implicit regularity of the incoming auditory information, and in the building and maintenance of a neural representation of its features, to react neurophysiologically to any subtle change in the auditory input. This mechanism activates a change-detector process which leads to the generation of the MMN [14, 16, 17], and can be best identified by using distractor stimuli of slight difference with regard to the repetitive stimulation (*Figures 2b* and *3*). In our distraction paradigm, the behavioural data confirm the existence of these two attention capture mechanisms, since the distracting effects are different for novel and deviant sounds. Indeed, whereas novel sounds cause a large (about 25 ms) delay in the response time in the visual discrimination task, deviant sounds cause only a small response time increase (about 5 ms), but a noticeable increment in the number of erroneous classifications as well [1, 4, 7; see *Figure 1*]. ERP recordings show also this differential effect, with a clear MMN generated to deviant distractors and a combined MMN/N1 response elicited to novel distractors [2, 4].

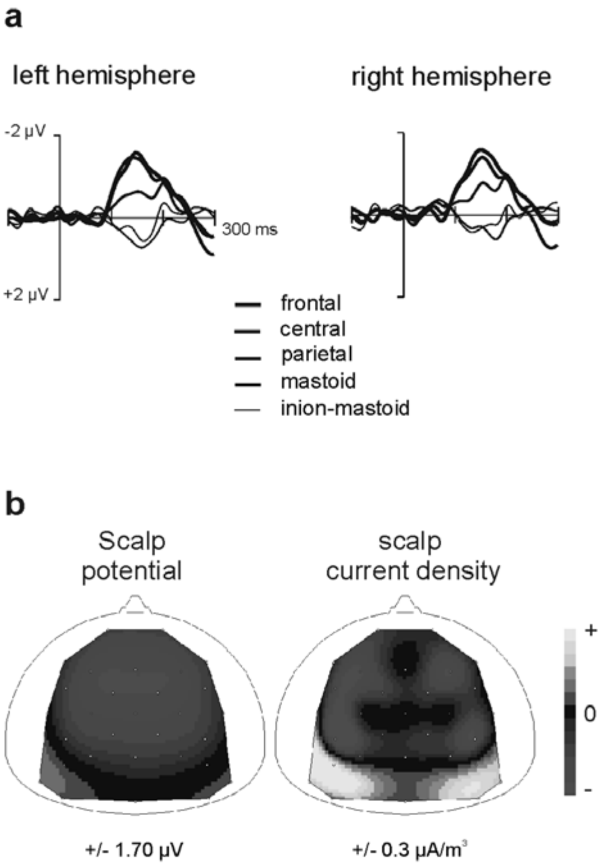

Figure 3. (a) The MMN elicited to frequency deviant stimuli in the distracting paradigm. It appears as a negative-polarity component with a polarity reversal at sites below the Sylvian Fissure (i.e., mastoid, inion-mastoid). *(b)* Scalp distribution of the MMN potential (left) and the corresponding scalp current density map (right). Adapted from [22].

The P3a ERP component, generated with large amplitude to novel stimuli and therefore called “novelty-P3”, has been considered in the psychophysiological literature as a cerebral sign of the orienting response [8, 12, 13]. In our studies, we have observed that novelty-P3 generation is accomplished in two different phases, each of them involving a different scalp distribution, a different latency, and a different sensitivity to attentional manipulations [4, 7]. The first P3a phase, with a peak latency between 220 and 320 ms, has a central bilateral scalp distribution and appears independent of attentional manipulations. On the other hand, the second phase of the novelty-P3, occurring between 300 and 400 ms, has a right frontal scalp distribution, and appears highly sensitive to attentional manipulations: when the subjects can monitor covertly the distracting sounds its amplitude is considerably larger [4]. Recently, we have shown, in agreement with previous results described in the literature [9], that novelty-P3 generation encompasses at least five different cerebral regions (*Figure 4*), engaged in clear spatiotemporal orchestration [24]. As early as 160 ms from novel sound onset, the first contribution to novelty-P3 appears to be the anterior cingulate gyrus; over 200 ms from novel sound onset, a simultaneous activation of the bilateral temporoparietal region and the left frontotemporal cortex is observed; finally, approximately after 300 ms from novel sound onset the superior parietal cortex and prefrontal regions are activated [24].

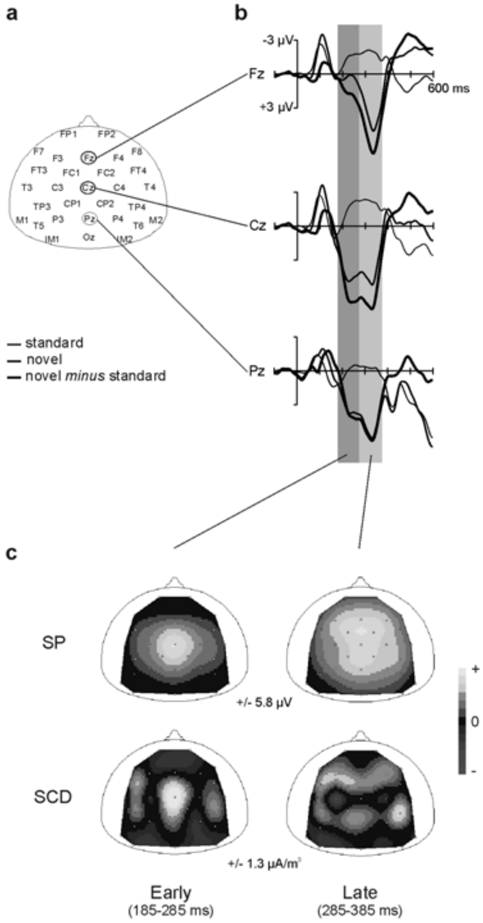

Figure 4: The novelty-P3, *(a)* Distribution over the scalp of the 30 electrodes used in the EEG recordings. *(b)* ERP at midline electrodes elicited to standard and novel stimuli, and the corresponding difference waves. Gray shadows show the two phases of the novelty-P3, in the respective latency ranges of 185-285 ms (dark gray) and 285-385 ms (light gray). *(c)* Scalp potential (SP) and current density (SCD) distributions of the two phases of the nP3. The SCD analyses revealed positive currents over central, bilateral temporoparietal and left frontotemporal areas during the early novelty-P3a, and over superior parietal, bilateral temporoparietal and frontal areas during the late novelty-P3. Adapted from [24].

As important as the flexibility to direct attention towards unexpected potentially relevant events, is the ability to return attention back to original task performance after a momentary distraction. It has been proposed that this attentional process is associate with the generation of another ERP component recorded in distraction tasks, the so-called *reorienting negativity* (RON) [3, 20, 21]. These authors found in their recordings a negative wave, subsequent to P3a, only when the subjects carried out a task where the deviant stimuli acted as distractors, but not when they were asked to discriminate actively these stimuli or when they were instructed to ignore completely the auditory stimulation and to concentrate in an unrelated visual task not concomitant to the sounds. We argued that, to indicate the process of reorienting of attention back towards the main task, RON should be time-locked to the target stimuli in the task, and not with the distractor stimuli. In our experiment, we manipulated the asynchrony between the distractor stimuli and the visual target stimuli, and we observed that the RON latency was of 345 ms, independently of the asynchrony between the auditory distractor and the visual target, which were in different conditions of 245 or 355 ms (*Figure 5*) [7]. Therefore, these data suggest that RON may constitute, indeed, a neurophysiological scalp marker of the process of returning attention back to primary task performance after a momentary distraction.

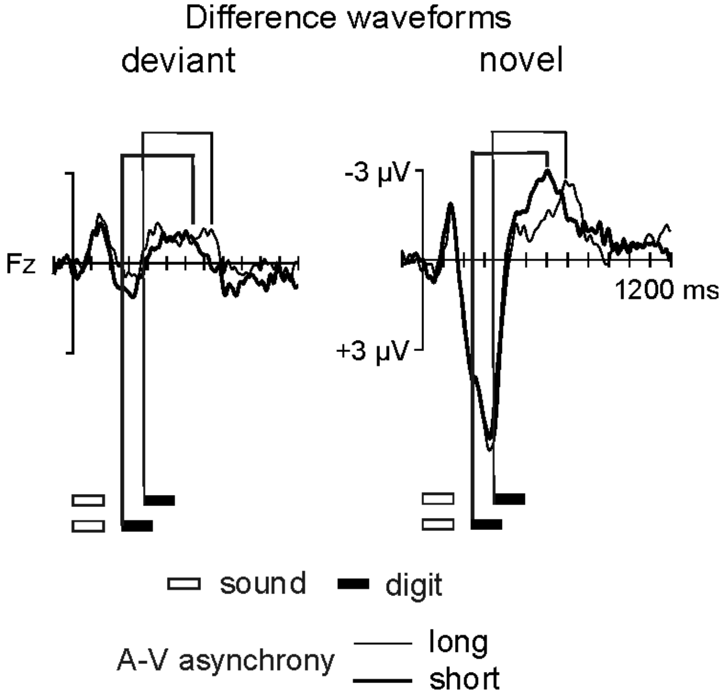

Figure 5: The reorienting negativity (RON) elicited in distracting trials, as seen in difference waveforms at Fz. RON peaks at 345 ms from visual stimulus onset irrespective of distractor asynchrony (short = 245 ms; long = 355 ms). Adapted from [7].

In several recent studies of our laboratory we have been able to show the utility of the distraction potential to reveal attentional impairments in closed head injury patients [10, 18] and chronic alcoholics [17], in the absence of behavioural deficits or evident neuropsychological or neuroradiological signs.

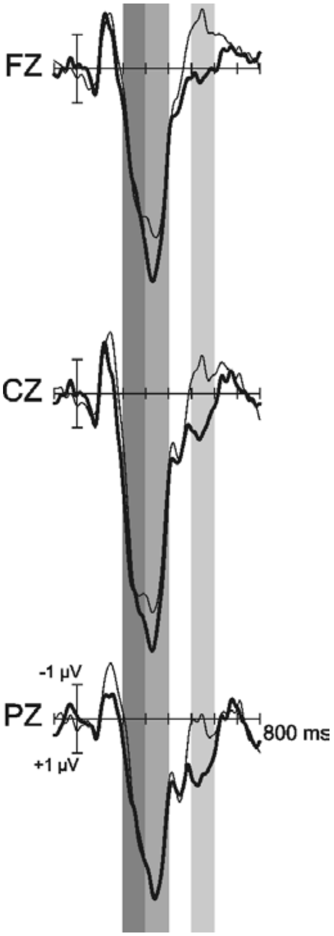

Figure 6: The distraction potential in alcoholic (thick line) and control subjects (thin line). Grey shadows show the early (200 to 300 ms, dark grey) and late (300 to 400 ms, medium grey) phases of the novelty-P3, and RON (500 to 600 ms, light grey). Adapted from [17].

In one of these studies, we compared the results obtained in a sample of detoxified male alcoholic subjects (N = 17, average age: 40 years) and their respective healthy controls (N = 14), matched by age and socio-economic level, during the execution of our distraction task [17]. Both groups showed similar performance in the distraction task, i.e., a similar amount of response time increase in distracting trials, suggesting intact mechanisms of the exogenous control of attention. However, the distraction potential revealed some noticeable anomalies in the exogenous control of attention in the patients, that would confirm their complains of increased subjective distraction and difficulty of concentration. Indeed, in comparison with control subjects, alcoholic patients showed a clearly enhanced novelty-P3 amplitude, particularly over the left fronto-temporal cortex, and a total lack of RON (Figure 6). In agreement with the conceptual framework on the generation of these ERP components, outlined in the present review, these results suggest an exaggerated orienting of attention towards the task-irrelevant novel sounds in alcoholics, as well as a difficulty to reorient attention back towards the main task after a momentary distraction, in agreement with their subjective complains. However, it is possible that in controlled situations, such as those of laboratory testing, they may compensate those deficits to perform in the visual task as control subjects, but nevertheless failing in the executive control of attention in natural conditions, where irrelevant stimuli occur considerably more frequently. In summary, a new distraction paradigm allows to evaluate the neuroelectric activation of the cerebral network involved in the exogenous control of attention, through the distraction potential (DP), which includes the MMN/N1, the P3a and the RON ERP components, in combination with behavioural measures of distraction. A powerful appeal of this new neuroelectric approach to the cerebral activation of attention is that it can disclose neurofunctional impairment even the absence of behavioural concomitants, thus providing indices of neurological dysfunction in cases in which neuroradiological or neuropsychological tests cannot objectify the patient's subjective complaints. Future research in these directions will confirm the power of such a new approach to the cognitive and clinical neuroscience of attention.

Acknowledgment

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Predicting Individual Perception from Individual Brain Responses: Tracing the Neural Correlates of Consciousness

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Abstract

There has long been a belief that activity in primary visual cortex cannot encode any of the subdimensions of our conscious perceptual space [6, 7, 19]. One of the arguments in favour of this position is that V1 represents the physical world in a way that deviates significantly from our perceptual representation. For example, the responses of V1 to chromatic stimuli do not show the same context dependency and colour constancy that has been demonstrated for our perceptual space [18, 23]. V1 even responds to properties of stimuli that we do not perceive, for example it signals disparity even for stimuli with anticorrelated contrast, which do not lead to depth perception [8]. Recently, however, a close correlation between signals in primary visual cortex and certain low-level dimensions of conscious perception have been demonstrated. Signals in V1 have been shown to correlate with low-level dimensions of visual perception such as perceived brightness [20] and perceived texture segmentation [22]. How can these apparently contradictory findings be reconciled? The fact that V1 signals deviate from perception for *some* perceptual dimensions (e.g., colour and depth) does not imply that V1 cannot represent *any* dimension of our perceptual space. One interpretation may be that signals in V1 encode some low-level dimensions of visual space such as perceived brightness, perceived contrast or perceived segmentation, whereas other dimensions such as perceived direction of motion or perceived colour hue are represented in specialised extrastriate visual areas. In

extrastriate visual cortex the representation of visual space has long been known to show such modularity [10, 24].

Introduction

In order to investigate this issue further in awake and behaving humans we compared physiological and perceptual responses of stimuli with varying contrast [16]. It has been shown that population signals recorded from V1 can account for performance in contrast discrimination tasks, where a subject has to judge which of two stimuli whose contrast differs slightly has the higher contrast [2, 14] (*Figure 1*). However, discrimination is not necessarily a good indicator of awareness because subjects are sometimes able to discriminate stimuli despite claiming to see no difference between them [17]. Thus we directly studied the perceived magnitude of contrast using a matching paradigm.

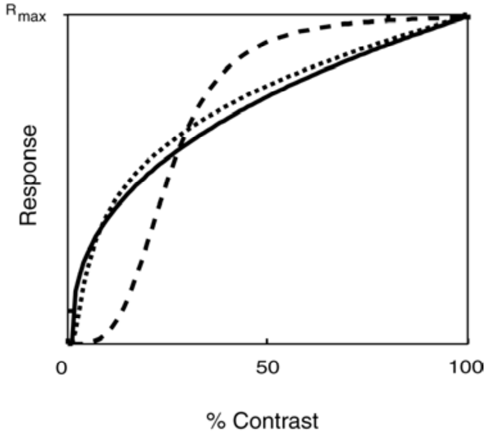

Figure 1: Contrast representation in V1. The dashed line shows an "average" monkey V1 cell (data taken from table 5 in [1]), the dotted line shows the striate fMRI response of one human subject (taken from table 1 in [2]) and the solid line shows a hypothetical contrast transducer function obtained from behavioural data which is used to explain human contrast discrimination performance (taken from [12]). Notice the close match between the hypothetical contrast transducer obtained with psychophysics and the human fMRI response. Contrast discrimination performance can be

explained by assuming a statistically optimal decision based on the mean *population* response in the presence of constant additive noise [2]. The difference between the response of the average monkey single cell and the population response can be explained by the fact that the cells have a large variation in their contrast transfer properties, so that pooling might result in a function similar to the population response.

We concurrently measured contrast-matching psychophysics and evoked neuromagnetic brain responses. We measured the perceived contrast of flashed stimuli with the help of a contrast-matching paradigm and simultaneously measured the electrophysiological transients evoked by such stimuli in human visual cortex. It is known that perceived contrast and contrast discrimination functions show strong individual differences [3, 25]. Thus, when relating brain responses to contrast perception it is necessary to take an individual subject approach and relate individual contrast perception to individual brain responses.

It is well known that the perceived contrast of a target grating can be reduced significantly by the presence of a surrounding grating of higher contrast, a phenomenon also known as “contrast-contrast” [4, 5, 9, 21]. This masking effect is sensitive to the relative orientation between target and surround. Perceived target contrast is reduced more by collinear than by orthogonal surrounds, thus targets with collinear surrounds require additional physical contrast in order to match the perceived contrast of targets with orthogonal surrounds. In analogy to colour vision, we can speak of “contrast metamers” when targets of different physical contrast are matched in terms of perceived contrast (*Figure 2*). By dissociating physical and perceived contrast, contrast metamers let us establish whether the electrophysiological responses of visual cortex reflect physical contrast, perceived contrast, or neither.

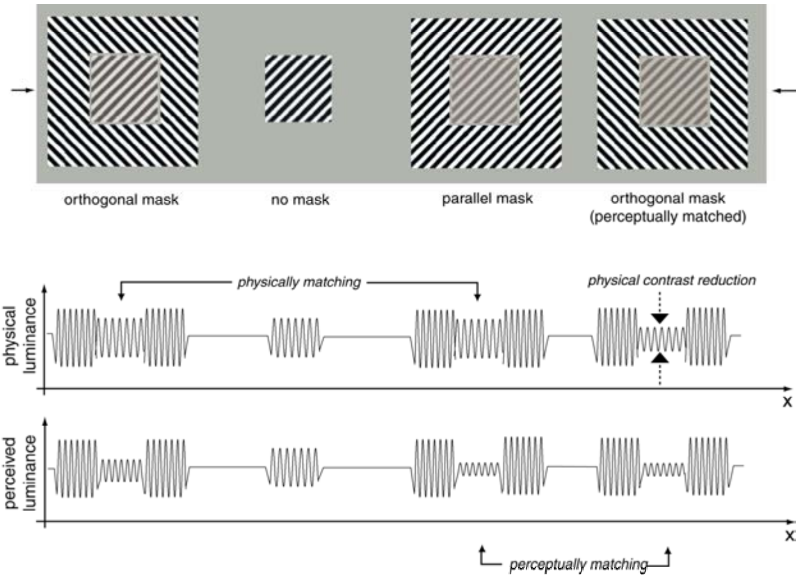

Figure 2: (*Top*) Demonstration of the effect of lateral masking on perceived contrast. The stimulus in the middle left ("no mask") is a standard square-wave grating with medium contrast. If the stimulus is surrounded by a high-contrast masking grating the contrast is perceived to be suppressed (see the 2 adjacent stimuli). The suppression is stronger for iso-oriented ("parallel mask") than for orthogonal surrounds ("orthogonal mask"). The effect had to be artificially enhanced here due to the fact that the luminance transfer characteristics of the print are uncontrolled. (*Middle*) This schematically shows the physical distribution of luminance in a section between the two arrows shown in the top stimulus. The physical contrasts (luminance modulation amplitudes) of the left three targets are equal. The rightmost stimulus shows an orthogonal target whose physical contrast has been reduced so that it perceptually matches the parallel target. (*Bottom*) Despite being physically identical the perceived contrasts are highest for the unflanked central stimulus, lower for the orthogonally flanked stimulus and lowest for the target with parallel surround.

We presented orthogonal and collinear stimuli similar to those shown in *Figure 2* and asked the subjects to judge which had the higher perceived contrast. In order to separate target and mask transients the targets were flashed for 250 ms into a standing background. The physical contrast of the orthogonal stimuli was varied, which allowed measurement of “subjective equality thresholds”. On average subjects matched collinear stimuli with orthogonal stimuli with 40 % less physical contrast, thus the perceived contrast of collinear stimuli was reduced relative to that of orthogonal stimuli.

The left graph in *Figure 3* (thin dashed line) shows the evoked magnetic response recorded from an occipital MEG sensor. A three-phase waveform can be seen with a positive peak around 100 ms, a negative peak around 150 ms and a positive peak around 250 ms. Using equivalent dipole modelling we demonstrated that the first two deflections were dominated by striate sources whereas the third deflection was a mixture of striate and presumably extrastriate sources. Thus we concentrated our analysis on the first two more “pure” striate responses. The amplitudes of the striate dipoles that were fit to the first and second deflections were taken as a measure of striate activity in an early and a late time window. The right graph in *Figure 3* shows the peak amplitude of the early striate response for orthogonal (solid line) and collinear stimuli (dotted line) plotted for different contrast levels. The response amplitudes for collinear stimuli were reduced compared to the responses for orthogonal stimuli at both contrast levels measured, which nicely parallels the reduction in perceived contrast.

Can the individual matching contrasts be predicted from the individual response functions? If the mean response amplitude in V1 encodes the perceived magnitude of contrast then the responses to perceptually matching stimuli should be identical. To put it in a different way, the orthogonal stimulus, which evokes a response of the same amplitude as a collinear stimulus, should be the stimulus that matches the collinear stimulus in perceived contrast. It is possible to interpolate which orthogonal stimulus would have had the same response amplitude as a collinear stimulus by fitting the contrast responses by a suitable function. *Figure 3* (right) shows that the response amplitudes for perceptually matching stimuli are very similar.

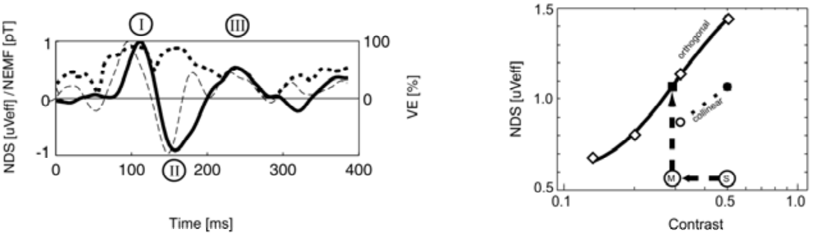

Figure 3: Left: Normalized dipole strengths (bold solid lines, left axis) and percent variance explained (bold dashed lines, right axis) for the striate two-dipole forward solution for one subject. The theoretical dipoles give a good explanation of the two early peaks. For most subjects the peaks of the V1 dipole amplitudes coincide closely with the peaks of the evoked responses (thin dashed line, left axis). The first two deflections (I, II) are clearly dominated by striate cortex. The peak amplitudes of the first two deflections are used to compute early and late striate contrast response functions. Right: Contrast response functions for orthogonal (solid) and collinear (dashed) stimuli of the same subject. The responses to the collinear stimuli are reduced compared to orthogonal stimuli with the same contrast. The filled circle shows the response of a collinear standard stimulus (S) of 0.51 contrast and the arrows and the filled square show how the response of the perceptually matching stimulus (M) is interpolated from the orthogonal contrast response function. Perceptually matching stimuli evoke responses with very similar amplitudes (NDS = normalised dipole strength; NEMF = normalised evoked magnetic field; VE = variance explained).

A different procedure is to predict an orthogonal matching contrast as that orthogonal stimulus that evokes the same response amplitude as the collinear stimulus. *Figure 4* shows a scatterplot of psychophysically measured matching contrasts and matching contrasts predicted from the contrast response functions. The distance between the data points and the identity can be read as the difference between stimuli that are psychophysically measured to match and the prediction based on the striate response amplitude. The data clearly show that the prediction is very good both for the early and the late striate responses, but slightly better for the late striate response (for more details see [16]).

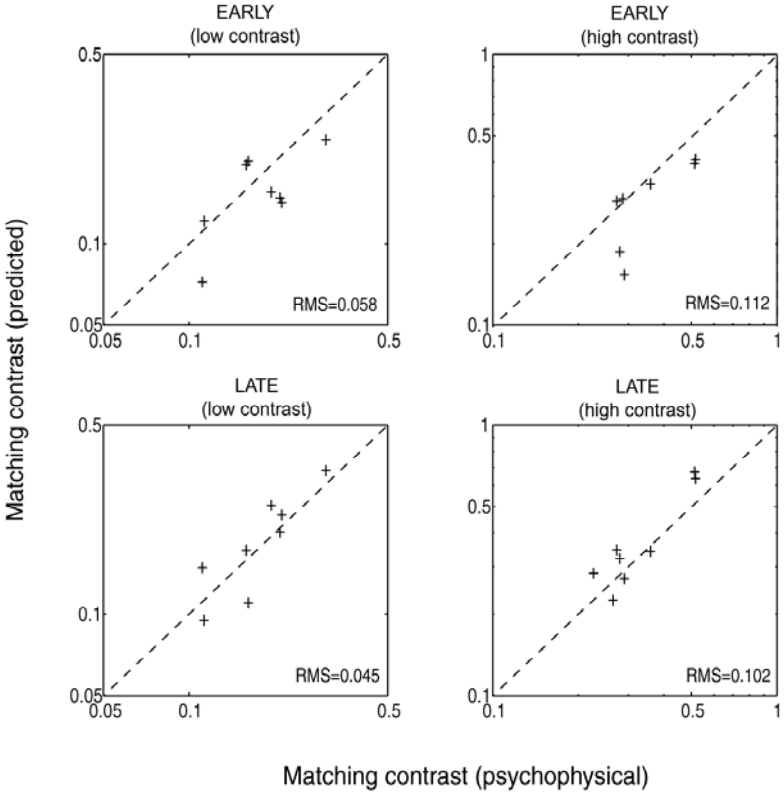

Figure 4: Scatterplot of psychophysically measured matching contrast and the matching contrast predicted from the contrast response function (all 8 subjects). The dashed line shows the identity line f(x) = x. If the prediction was perfect the predicted and measured matching contrasts would be equal and all points would lie on the dashed line. The graphs also show the root mean square values for the difference between predicted and measured matching contrast.

This presents evidence that the perceived magnitude of contrast might indeed be represented as the mean amplitude of responses in V1. Previous studies have shown that human steady state potentials show a contrast dependency similar to human perception [11, 13]. However the relationship between steady state VEPs and V1 activity is currently not yet clear. An approach more closely related to our study was used by Goodyear et al. [15]. Using BOLD-fMRI they demonstrated for one clinical subject with a monocular reduction of perceived contrast due to amblyopia that stimuli matched for perceived contrast generate similar responses in early visual cortex (presumably V1/V2). With our lateral masking paradigm we have been able to confirm this finding in normal subjects, and investigate the temporal properties of the striate response. The fact that the later striate component predicts perceived contrast better may point towards the importance of feedback processing which has previously been shown to be a necessary condition of conscious perception [22].

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Inter-individual Differences in Oscillatory EEG Activity and Cognitive Performance

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Abstract

Empirical evidence is reviewed showing that EEG oscillations in the alpha and theta band reflect cognitive performance if a double dissociation between two types of power measurements (resting and event-related power) and two frequency bands (theta versus alpha) is taken into account. This double dissociation is given by two facts. First, with increasing task demands, event-related band power increases in the theta but decreases (desynchronises) in the alpha frequency range. Second, the extent of an event-related EEG response depends at least in part on the extent of resting power but in opposite ways for theta and alpha. Whereas small resting theta power enhances theta synchronization, large resting alpha power enhances alpha desynchronisation. Results from a transcranial magnetic stimulation (TMS) study show that TMS pulses applied at individual alpha frequency (IAF) during a period preceding the performance of a mental rotation task improves cognitive performance. The influence of TMS pulses at IAF on the EEG mimicked exactly that situation which is typical for good performance: Increased reference power, decreased event-related power and, consequently, a large extent of event-related desynchronisation (ERD). These findings suggest that oscillations play a causal role for cognitive performance. In addition, when considering results about evoked oscillations and the finding from a recent study showing that the extent of phase locking increases with cognitive demands, the general conclusion is that oscillations play an important role for the timing of cognitive processes.

Physiology and functional meaning of theta and alpha oscillations

The physiology and neuroanatomy of hippocampal theta oscillations (with a frequency of about 4 to 12 Hz) and thalamocortical spindle activity (with a frequency of about 7 to 14 Hz, cf. [2]) is well described in animal research. The functional meaning of these oscillations is strikingly different.

In awake animals, hippocampal theta oscillations can be observed during exploratory behaviour and orienting responses [22], but not during automatic behaviours, such as eating or drinking. Furthermore, theta oscillations can be observed during REM-sleep where dreaming episodes occur [32]. Most interestingly there is meanwhile clear evidence that the phase of theta oscillations plays an important role for the encoding of new information and that during dreaming episodes hippocampal theta allows for a "replay" and, thus, consolidation of that information which was acquired during exploratory behaviour. These findings provide evidence for the hypothesis that theta oscillations are related to the processing of new episodic information. Although it has been questioned for a long time, there is meanwhile converging evidence that theta oscillations can also be observed in humans. This evidence comes from studies with patients using subdural electrodes [8] as well as from studies with normal subjects using scalp electrodes [5] and MEG [7, 29]. Results from our laboratory have shown that in human scalp EEG, theta responds selectively (with an increase in band power) to the encoding and retrieval of episodic information [9, 12]. These findings support the hypothesis that episodic encoding processes are reflected by theta oscillations in hippocampo-cortical re-entrant loops.

Spindle oscillations were studied primarily in animals under anesthesia. The basic finding is that thalamocortical cells show two types of firing modes, a tonic (non-oscillatory) and a bursting (oscillatory) mode. Traditionally it was believed that only the tonic-firing mode is related to cognitive processing whereas the burst mode which is typical for spindle activity reflects the interruption of sensory and cognitive processing. Recent research, however, indicates that a burst mode can be observed also during alert wakefulness. In rodents this burst mode occurs during periods of pronounced alpha like oscillations that are commonly referred to as the mu-rhythm. It is functionally related to a behavioural state of "whisker twitching" which can be best described as a "preattentive state" during which an animal is prepared (or expects) to process sensory information. From the human scalp EEG it is known that the mu-rhythm becomes blocked (desynchronises) during actual sensory processing. Results from our laboratory indicate that the upper frequency range (of about 10 to 12 Hz) of the posterior alpha rhythm is particularly responsive to sensory-semantic processing demands.

As a working hypothesis, we assume that theta and alpha (like) oscillations reflect information processing in large-scale networks with reciprocal connections that establish complex re-entrant loops (e.g., cortico-cortical, cortico-hippocampal and thalamo-cortical loops). The general view is that neuronal networks of different sizes can be functionally tied together by coherent synchronous oscillatory activity (cf. [30] for a comprehensive review). It is assumed that the size and complexity of neuronal networks are related to frequency in a sense that large networks operate in a slow frequency and small networks in high frequency ranges.

Whereas animal research offers the big advantage of a detailed analysis of the physiological and neuroanatomical basis of oscillations, the human scalp EEG is a valuable tool to investigate their functional meaning in complex cognitive tasks. Although it is still an open question, whether theta and alpha like oscillations recorded from animal brains play a similar functional role in humans, there is some evidence for a functional correspondence [21].

Findings from the human scalp EEG about event-related band power changes in the theta (of about 4 to 6 Hz) and alpha range (of about 7 to 12 Hz) demonstrate that in response to respective task demands theta band power increases (synchronises) whereas alpha band power decreases (desynchronises). Most interestingly, this dissociation between frequency (in the theta versus alpha range) and type of event-related response (synchronization versus desynchronisation) is of outstanding functional significance. Whereas theta appears to be related to encoding and retrieval processes of a complex working memory system (WMS), upper alpha (of about 10 to 12 Hz) responds selectively to sensory-semantic memory processes of a complex long-term memory system (LTMS) and the lower alpha to attentional processes (cf. [9] for a review). It is important to emphasize that the functional specificity of these frequency bands can be observed only if frequency boundaries were adjusted to individual alpha frequency (IAF).

Inter-individual differences in alpha and theta oscillations are related to cognitive performance

Several early experiments, carried out by Surwillo have shown that individual alpha frequency (IAF) is negatively correlated with reaction time (RT) in a variety of different tasks (e.g., [28]). These findings demonstrate that high alpha frequency is associated with short (fast) RTs whereas low alpha frequency is associated with long (slow) RTs (for similar findings cf. [13]). In addition, experiments from our laboratory indicate that the IAF of good memory performers is about one Hz higher than the IAF of age matched samples of bad performers [10, 11]. These findings agree with the fact that alpha frequency declines with age [18] in a similar way as response speed does and suggest that IAF is an indicator of cognitive performance.

Alpha power too appears to be related to cognitive performance. Whereas event-related band power is negatively associated with memory performance [14], spectral estimates obtained during a resting condition are positively associated with performance [3, 15, 31]. An example for performance related differences in upper alpha desynchronization during a semantic memory task is shown in *Figure 1*. Good memory performers show a larger magnitude of event-related desynchronisation (alpha power suppression) and hence smaller band power during task performance as compared to bad performers. In contrast to event-related band power measures, estimates of alpha power obtained during a resting condition reveal a positive association with performance as depicted in *Figure 2*. Under this condition, alpha power is positively associated with memory performance. For theta oscillations a similar but opposite relationship holds true. Whereas a large event-related increase in theta reflects good performance during actual processing of a task, small theta resting power is negatively correlated with performance.

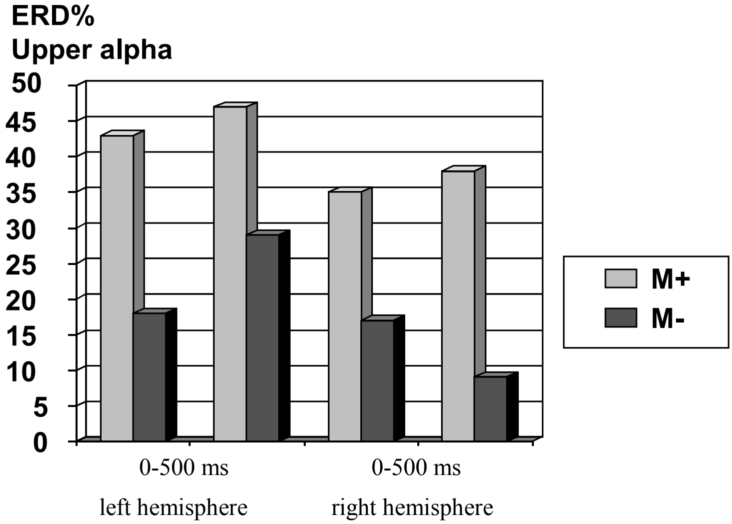

Figure 1: Event-related desynchronisation (ERD; percentage of a band power change during the performance of a task in relation to a reference interval) in the upper alpha band is significantly larger for good (M+) as compared to bad memory performers (M-). Subjects performed a semantic association task in response to a concept word. Data are replotted from [14].

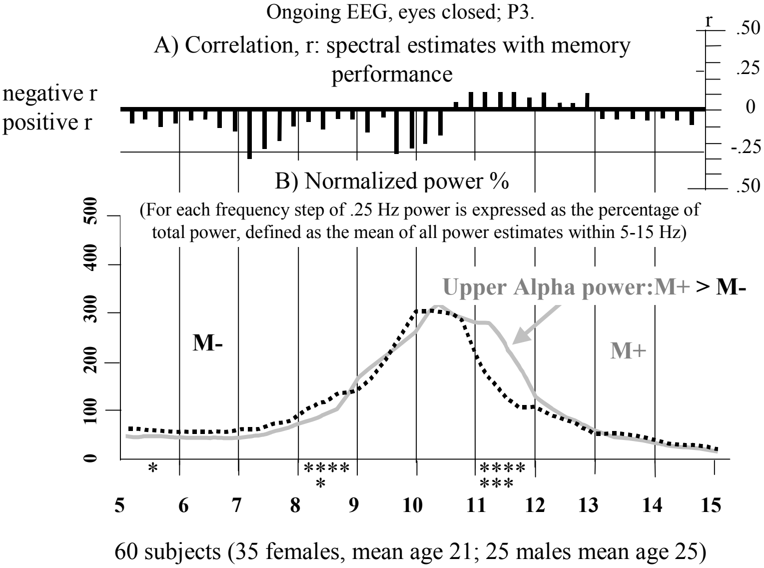

Figure 2: Good and bad memory performers (M+; M-) show different power estimates in a resting situation particularly in the frequency range of upper alpha (of about 11.5 Hz). The black bars in the upper panel represent correlation coefficients between spectral estimates and memory performance as determined in a word recognition experiment. Note that only power estimates in the upper alpha frequency range show a positive correlation. The averaged (normalized) power spectrum of the two groups is depicted in the lower panel. Data are replotted from [31].

In a recent review [9] it was demonstrated that resting alpha power is increased under conditions that are associated with enhanced cognitive processing capacity or situations where subjects try to increase their capacity (e.g., during states of increased attention or in young healthy as compared to elderly subjects), but is decreased under conditions that are associated with reduced capacity (in neurological diseases, during drowsiness and sleep onset). In assuming that the magnitude of alpha desynchronization depends at least in part on the extent of alpha power as measured during a resting (or reference period), we expect a negative correlation between these two measures. In a recent experiment [17] we have found empirical evidence for the expected negative correlation between these two different types of power estimates. The principle underlying this negative association between resting and event-related power is depicted in *Figure 3*.

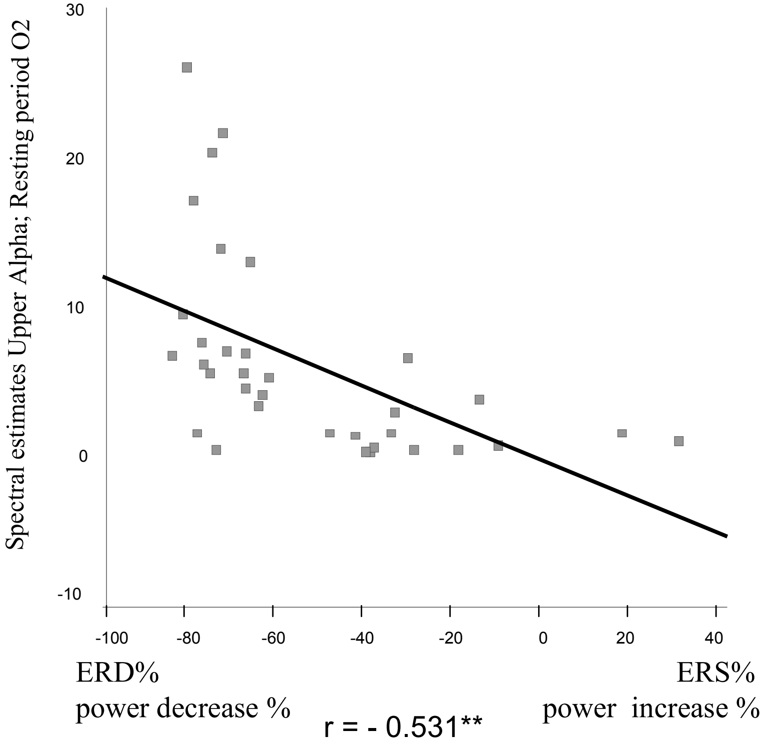

Figure 3: The extent of event-related desynchronisation (ERD) depends at least in part on resting (or reference) power. The example is from a picture recognition task and shows the extent of upper alpha ERD (at = 2 for 250 to 500 ms post stimulus). Data are replotted from [17].

The nature of the relationship between oscillations and cognitive performance: Causal or correlative?

Is the observed relationship between alpha oscillations and cognitive performance of correlative or causal nature? As an example, if we would assume that alpha oscillations are due to passive resonance properties of neural networks, the relationship between alpha and cognitive performance would be correlative. Even in that case, however, IAF would still reflect some important properties of cortical connectivity in the sense that highly interconnected networks allow for a higher resonance frequency. Thus, the higher alpha frequency of good performers could be an indicator of a more intensively interconnected brain. If, on the other hand, alpha is a mechanism for the timing of cortical processes in the sense that oscillatory activity is actually needed during certain stages of information processing (e.g., to control the timing of information processing in different neural networks), the observed relationship between alpha and cognitive performance would be causal rather than correlative.

In a recent study [16], we used transcranial magnetic stimulation (TMS) to investigate this question. The basic idea was to induce rhythmic activity into the cortex by a brief series of TMS pulses with a frequency at IAF in an attempt to increase cognitive performance. This repeated application of single TMS pulses is termed rTMS. Because it is well known that TMS and rTMS have disruptive effects when applied during task performance, we applied rTMs at IAF during a brief period before a mental rotation task is performed.

The rationale of the experimental procedure was derived from the following findings about the human EEG alpha rhythm, which have been reviewed in the preceding paragraphs. (i) Inter-individual differences in mean or peak alpha frequency are large (7 to 13 Hz; mean for young adults is about 10 Hz) and are related to memory performance and the speed of information processes. (ii) The magnitude of alpha desynchronisation (as measured e.g., by event-related desynchronisation or ERD; cf. [23]) depends on the amplitude of alpha oscillations during a resting or reference period that precedes task performance.

(iii) These findings are frequency sensitive and can be observed primarily in the upper alpha band (width of 2 Hz) but only if frequency boundaries are adjusted to IAF (e.g., for a subject with fast IAF of 12 Hz, the upper alpha band is 12 to 14 Hz).

Thus, the conclusion from these findings is that a period of pronounced (upper) alpha activity – preceding task performance – Is associated both with a large ERD (alpha suppression or reactivity) and good performance. Thus, the logic underlying the present experiment was to apply rTMS at individual upper alpha frequency (IAF + 1 Hz) in a period preceding task performance. We used a mental rotation task and applied rTMS at IAF + 1 Hz over a frontal (Fz) and a right parietal site (P6). Control conditions were rTMS at IAF – 3 Hz (lower alpha, individually adjusted) and at 20 Hz (beta frequency, not adjusted individually).

The findings indicate that only rTMS delivered at the subjects' individual alpha frequency (IAF) leads to a significant improvement in performance (i.e. the accuracy but not speed of mental rotation) when compared with sham. Furthermore, the influence of rTMS at IAF on EEG parameters mimicked exactly that situation, which we know is typical for good performance: increased reference power, decreased test power and, consequently, a large ERD.

The interesting conclusion is that rTMS at IAF improves performance by way of those factors which are known to be of importance under normal conditions. Thus, the present findings suggest that the relationship between the dynamics of alpha desynchronisation and cognitive performance is not correlative but causal in nature.

Evoked oscillations and cognitive performance

The results obtained from analyses in the time and frequency domain usually are considered to represent completely different phenomena of the EEG. There is, however, evidence that ERPs (as the most prominent example for analyses in the time domain) are generated at least in part by evoked oscillations (c.f. the pioneering work of Basar; c.f. [1] for a review and [19] as an example of a more recent study).

If we proceed from the hypothesis that particularly early ERP components are generated by evoked oscillations and consider the conclusion from our rTMS study (see above) that oscillations play an important role for the timing of cognitive processes, we might expect that high cognitive performance and/or increased performance demands lead to an increase in synchronous oscillatory activity. There is some evidence for this idea as the results from a memory-scanning task, analysed in the time and frequency domain, indicate [26]. It was found that during the retention period alpha oscillations (at about 12 Hz) increased with load and that exactly this frequency exhibits a load dependent increase in phase locking – measured by a specially developed phase locking index (PLI) – during retrieval. Most interestingly, the P3b – presumably reflecting the read out from WMS – coincided with the last of three evoked alpha peaks that were clearly visible in the ERP's (particularly at Pz and P4). It is important to note that during retrieval, alpha phase locking (or evoked alpha activity) was the only EEG parameter that increased with performance demands. Phase locking in the delta and theta frequency range decreased with load as did evoked delta and theta power and P3 amplitude. These findings suggest that alpha oscillations play an important and selective role for the timing of cognitive processes during encoding and memory scanning. Thus, we may conclude that alpha oscillations coordinate the encoding of the probe, scanning, and the evaluation of the read-out process that most likely is manifested by the P3b.

Conclusions

The general conclusion is that oscillations underlie the timing – and are not an epiphenomenon – of cortical information processing. This is well in line with animal research showing that action potentials can be observed particularly during the depolarising phase of the local field potential. This relationship is best described for the hippocampal theta rhythm and the phase dependent firing of place cells [20]. It is, however, important to emphasize that oscillations may control the timing of information processing by way of a variety of different mechanisms. One example is coherent oscillatory activity during a "preattentive" preparatory period (such as possibly induced in the rTMS study described above). another is phase locking (or phase resetting) of an oscillation with respect to the presentation of a stimulus (such as found for alpha in the memory scanning experiment, described above). Yet another example is phase synchronization of different areas of the brain by zero phase lag oscillations of the same frequency (e.g., [4, 27]) or by oscillations of different frequencies that are phase coupled (e.g., [25]). The investigation of these different timing mechanisms with respect to inter-individual differences in cognitive performance will be a promising task for future research.

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Inter-individual Differences in Oscillatory Brain Activity in Higher Cognitive Functions – Methodological Approaches in Analysing Continuous MEG Data

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Abstract

Inter-individual differences of psychophysiological parameters often exceed the possibilities of the methods used in analyses. Both the subtle nature of higher cognitive functions due to the complexity of the underlying neural networks as well as the relatively small measurable physiological signals require appropriate and sensitive strategies in analysing the data. Therefore a better definition of the topic that actually has to be examined in the data set might be helpful. In order to get a better approach to that issue we introduced a model-based multiple dipole-density strategy on band-pass filtered continuous MEG data recorded during three different mental tasks. The frequency ranges were individually determined by pre-selection of the power spectra of the data sets. In comparison to three alternative methods performed on band-pass filtered data of fixed frequency bands the proposed strategy leads to a better regional characterization of the different mental conditions.

Introduction

It is a well-known fact that methodological problems in psychophysiological data very often arise by inter-individual differences due to

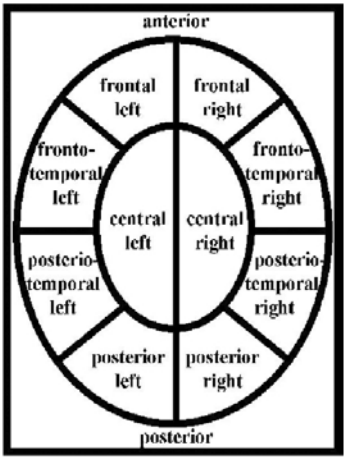

Figure 1: Schematic illustration of ten regions used to cluster the power data

the variations in statistical procedures. Even in well-defined paradigms that analyse specific electrophysiological aspects (e.g. tonotopic brain maps) inter-individual differences often play a crucial role. The problem becomes more severe when continuous data have to be analysed. Additionally, complexity in the data set reflecting the complexity of higher cognitive functions makes it difficult to model the underlying hypotheses. Dipole-density and minimum-norm algorithms were successfully used on continuous band-pass filtered data to examine differences between psychiatric patients [1] and controls and/or to determine pathologic foci e.g. of brain lesions [5, 6]. Activation patterns in relation to pathology are mostly characterized by high amplitudes and, therefore, may be examined by relatively insensitive methods. The same strategies, however, are not adequate to assess more subtle and presumably greater inter-individual differences in higher cognitive functions with high accuracy. The pre-selection of specific individual properties of the data might be helpful to find the issue that actually has to be examined. This work shortly describes four strategies in analysing continuous MEG data acquired during three mental conditions.

Methods

Data acquisition, subjects and tasks

Whole-head (148 channels) magnetoencephalographic recordings (MAGNES® 2500 WH, 4D Neuroimaging, San Diego, USA) were obtained from 9 healthy female adults (mean age: 22.6 ± 5.2 years; 20 to 27 years) during a resting condition and two conditions during which the subjects had to perform mental activities. These activities consisted of luxuriating/indulging in positive fantasies and contrasting positive fantasies with real-life decisions during their study at the university (in detail described elsewhere; Achtziger, in preparation).

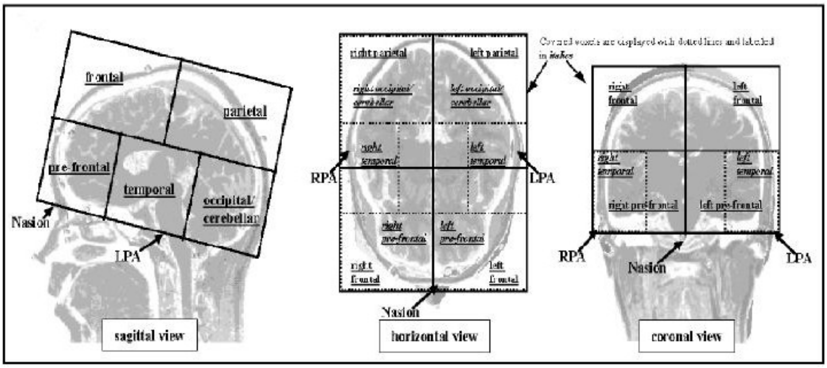

Figure 2: Schematic illustration of the ten regions used to cluster the dipole density (DDP) data

Subjects were asked to fixate a coloured fixation point on the ceiling of the chamber in order to reduce eye- and head-movements. The MEG was recorded with a 678.17 Hz sampling rate, using a band-pass filter of 0.1 to 200 Hz. The total recording time for each condition was 5 minutes. For artifact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye.

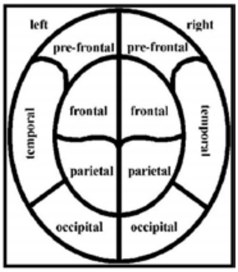

Figure 3: Schematic illustration of the ten regions used to cluster the minimum-norm (MMN) data

Regional Fast Fourier Transformation (FFT)

For each subject a Fast Fourier Transformation (FFT) was performed. FFT results were averaged over all 148 MEG-channels and then divided in 17 frequency bands: delta (1.5 to 4 Hz), theta (4 to 8 Hz), alpha-low (8 to 10.5 Hz), alpha-high (10.5 to 13 Hz), beta-low (13 to 21.5 Hz), beta-high (21.5 to 30 Hz) and 11 gamma bands (width 6 Hz) between 30 and 100 Hz (without 48 to 50 Hz). To get regional power values of each data set separately FFT results were averaged for 10 channel groups (see *Figure 1*). Absolute and relative global and regional FFT band power was analysed by ANOVAs examining regional and frequency band related condition differences.

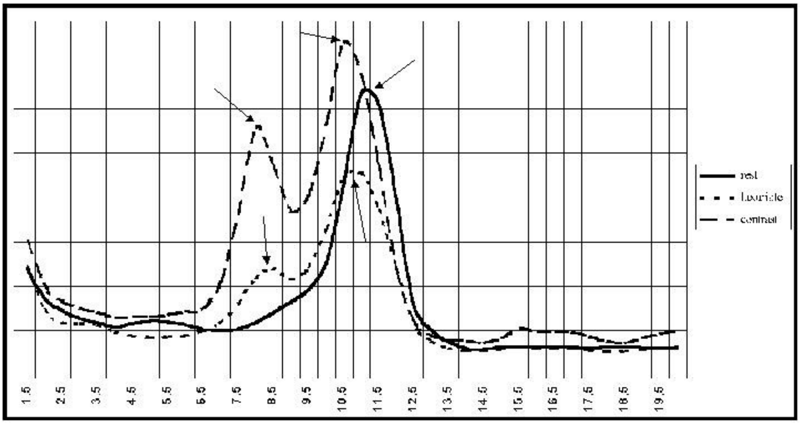

Figure 4: Example of three power spectra (resting, luxuriating and contrasting) in one subject. The different conditions show specific deflections

Dipole Density (DD)

Time segments – low on artifacts – of band-pass (delta [1.5 to 4.0 Hz] and theta [4.0 to 8.0 Hz]) filtered data were determined by visual inspection.

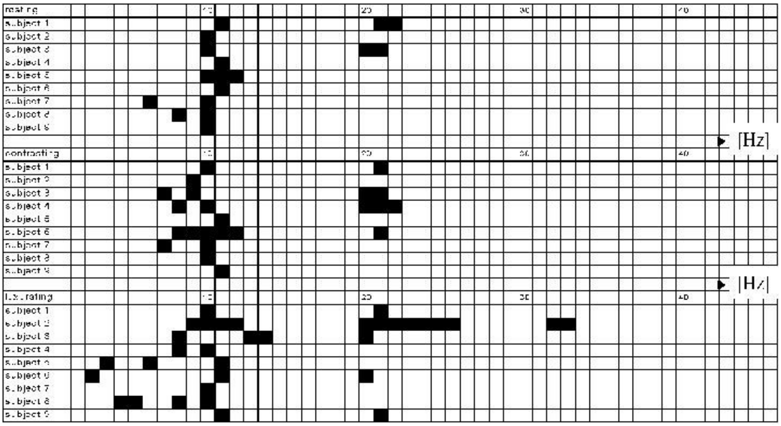

Figure 5: Frequency ranges in which prominent deflections occur were shadowed for each subject and condition

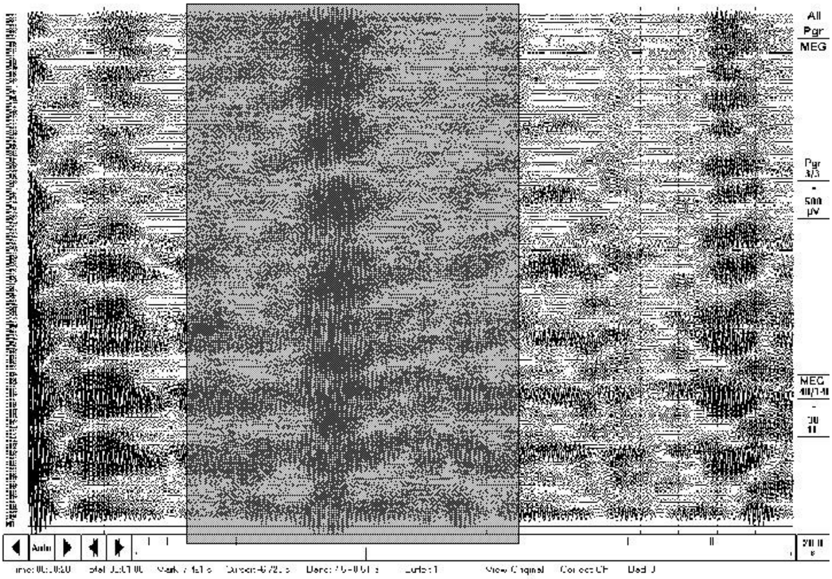

Figure 6: Example for a selected time epoch (box) of band-pass-filtered data in which all channels (wave forms arranged in lines) show clear activity

Single equivalent dipoles in a homogeneous sphere were fitted for each time point only in the selected epochs of various length. All 148 channels were used for source estimation. Only dipole fit solutions at time points with a root mean square between 100 and 300 ft, a goodness of fit (GOF) over 0.90 and a dipole moment over 50 nAm were accepted for further analysis. For statistical analysis the brain was divided into ten regions of interest (ROI, see *Figure 2*). The percentage of time during which a dipole model would fit in the delta and in the theta band was determined for each subject, condition and region.

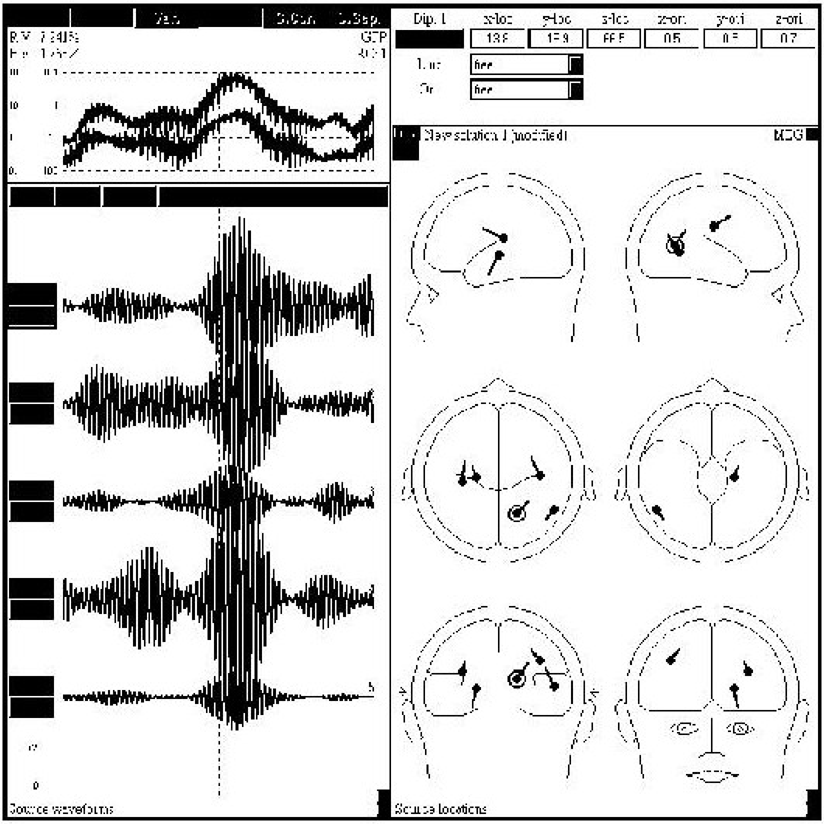

Figure 7: Source wave forms and locations of a 5-dipole model based on a 6 second band-pass-filtered data epoch

Minimum Norm L2 (MMN)

For multiple source detection the MMN-method [2; 3] was performed on a 30 second band-pass filtered (delta [1.5 to 4.0 Hz], theta [4.0 to 8.0 Hz], alpha low [8.0 to 10.5 Hz], alpha high [10.5 to 13.0 Hz], beta [18 to 22 Hz], gamma1 [28 to 32 Hz] and gamma2 [38 to 42 Hz]) data epoch for each subject and condition. Over all data time points with a global field power between 3000 and 18000 fT that did not correlate with a prominent eye-blink pattern a MMN solution was calculated.

MMN values were estimated at 87 positions (each consisting of two orthogonal dipoles tangentially oriented to the surface) on a concentric shell that was computed as a rough approximation of the brain volume. Thereafter, the source activity of each position was collapsed by averaging the absolute values of both dipole orientations.

The MMN solutions were then averaged over all data time points. For statistical analyses the resulting MMN-Maps were attributed to 10 ROIs by averaging clusters of MMN-values roughly representing particular brain regions (see *Figure 3*). The whole procedure was also performed on the lower, middle and stronger magnetic fields of each data set separately. First for each band-pass filtered data set the global field power of each data time point was calculated and the highest global field power value was determined. Thereafter, minimum-norm estimates were calculated separately for the lower, middle and higher third activity data time points and averaged for statistical proceedings.

Multiple Dipole Density (MDD)

(1) For each subject and condition a fast Fourier transformation (FFT) was performed on the data. FFT results were averaged over all 148 MEG-channels. The resulting power spectra were plotted for each subject and condition (see *Figure 4*).

(2) Power spectra were visually inspected and prominent deflections of each spectrum were noted as possible effects of generators underlying background and/or condition related activity (see *Figure 4* [arrows] and *Figure 5* for critical frequency ranges).

(3) Original data sets were band-pass-filtered separately for all critical frequency bands and visually inspected for epochs in which all channels show activity (e.g. *Figure 6*). More precise, data were filtered 1 Hz around identifiable peaks in the power spectrum or for more extensive cohesive frequency ranges in which a particular condition clearly showed more power than the others. In those epochs (about 5 seconds) stepwise multi-dipole analysis was performed using the software BESA2000. First a spatio-temporal PCA was calculated to get a first impression of how many dipoles approximately have to be

expected to explain the data in the actual model. During the next step the epoch with the highest deflections in the eigen-value curve was marked to fit the first dipole(s). Thereafter, additional dipoles were added one by one and fitted on partial epochs showing the highest residuals. The number of dipoles was increased until 90 percent of variance was explained (by a maximum of 15 dipoles, see *Figure 7* for illustration). Afterwards, all dipoles were fitted simultaneously for the whole epoch to tune the position of each dipole in the model.

In dipole fit procedures using the BESA software dipoles were first set to different positions in order to search the best starting position. This prevents that dipoles are fitted to local minima.

Fitting the first single dipole sometimes resulted in a dipole position located in the middle of the sphere model. Those solutions often represent a sum of source activities at different positions. This could be confirmed by the huge moment of those dipoles that could not be generated by a valid physical source in the middle of the brain. A manual arrangement of two or three dipoles in positions around the centre of the sphere often provided a more appropriate starting condition for the fitting procedure.

Oscillatory activity in gamma range (above 30 Hz) could not be fitted using the model criteria and were therefore excluded of further analyses.

(4) The multi-dipole model reaching the criterion explained above was then used to fit the complete data (60 seconds) epoch. The resulting source wave forms served as a basis for the statistical analysis.

(5) For statistical analyses the brain was divided into ten ROIs (comparable to *Figure 2*). In a first approach each data time point of the source wave forms was examined as follows: assuming, n is the number of dipoles in the present model, a dipole has to reach more than the n-th part of the sum of current equivalents at that data time point to be considered for statistics. Thereafter, the regional densities of

dipoles were then calculated with respect to differences in mental conditions by ANOVAs.

The central aspect of the described strategy consisted in bypassing the problem of high interindividual variability of activities within fixed ranges of frequency bands. Based on the assumption that subjects proceed in different frequency bands but in the same ROIs due to the same semantic condition a FFT was performed in order to determine individual task-related frequency ranges of activity for each data set. Afterwards only those frequency ranges were analyzed in terms of source analyses. Considering interindividual differences in oscillatory brain activity consistent task-related regional variations should be evident.

Results

Regional Fast Fourier Transform (FFT)

ANOVAs calculated over regional absolute (REGION x FREQUENCY-BAND x CONDITION: F[288,3456] = .41, p = .67; Greenhouse Geisser (GG): p = .87; Huynh-Feldt (HF): p = .90) and relative (REGION x FREQUENCY-BAND x CONDITION: F[288,3456] = .86, p = .59; GG: p = .89; HF: p = .94) power values clearly did not reach significance. Exploratory post hoc least significance tests only showed trends but no significant differences between the conditions.

Dipole Density Plot (DDP)

As shown by Achtziger (in preparation) luxuriating/indulging and contrasting generally reduced delta dipole density relatively to the rest condition. These changes, however, did not reach significant main effects or interactions. There was still a tendency for the contrasting condition to reduce delta activity mainly in right hemispheric frontal, prefrontal and temporal regions when compared to the luxuriating condition.

Minimum Norm L2 (MMN)

ANOVAs calculated over regional minimum-norm (FREQUENCY-BAND x REGION x CONDITION: F[108,1296] = .38, p = .71; Greenhouse Geisser (GG): p = .97; Huynh-Feldt (HF): p = .99) values clearly did not reach significance (see *Table 1* for details). Exploratory post hoc least significance tests only showed trends but no significant differences between the conditions.

ANOVAs calculated over regional minimum-norm values estimated over weak (FREQUENCY-BAND x REGION x CONDITION: F[108,1296] = .39, p = .69; GG: p = .97; HF: p = .99), medium (FREQUENCY-BAND x REGION x CONDITION: F[108,1296] = .48, p = .63; GG: p = .91; HF: p = .95) and stronger (FREQUENCY-BAND x REGION x CONDITION: F[108,1296] = .51, p = .61; GG: p = .91; HF: p = .96) magnetic fields (global field power=GFP, see methods) separately did not reach significance (see *Tables 2, 3* and *4* for details). Exploratory post hoc least significance difference tests only revealed trends but no significant differences between the conditions.

all data time points averaged (condition x region; F(18,216)=F)				
band [Hz]	**F**	**p**	**GG**	**HF**
delta [1.5-4.0]	.21	.82	.99	.99
theta [4.0-8.0]	.67	.70	.91	.94
alpha low [8.0-10.5]	.50	.62	.77	.80
alpha high [10.5-13.0]	.39	.69	.85	.88
beta [18.0-22.0]	.19	.83	.94	.96
gamma 1 [28.0-32.0]	.54	.59	.80	.84
gamma 2 [38.0-42.0]	.61	.55	.76	.80

Table 1: ANOVAs over regional MMN-values of several frequency bands; uncorrected (p), Greenhouse-Geisser (GG) and Huynh-Feldt (HF) corrected p- values.

low GFP data time points averaged (condition x region; F(18,216)=F)

band [Hz]	F	p	GG	HF
delta [1.5-4.0]	.24	.79	.95	.98
theta [4.0-8.0]	.47	.63	.86	.89
alpha low [8.0-10.5]	.45	.65	.86	.90
alpha high [10.5-13.0]	.34	.71	.90	.93
beta [18.0-22.0]	1.00	.38	.44	.44
gamma 1 [28.0-32.0]	.67	.52	.70	.73
gamma 2 [38.0-42.0]	.73	.49	.66	.70

Table 2: ANOVAs over regional MMN-values (only time points with low GFP) of several frequency bands; uncorrected (p), Greenhouse-Geisser (GG) and Huynh-Feldt (HF) corrected p- values.

middle GFP data time points averaged (condition x region; F(18,216)=F)

band [Hz]	F	p	GG	HF
delta [1.5-4.0]	.24	.79	.98	.99
theta [4.0-8.0]	.57	.58	.76	.80
alpha low [8.0-10.5]	.63	.54	.73	.76
alpha high [10.5-13.0]	.39	.68	.88	.91
beta [18.0-22.0]	.63	.54	.70	.74
gamma 1 [28.0-32.0]	.65	.53	.70	.74
gamma 2 [38.0-42.0]	.81	.47	.59	.62

Table 3: ANOVAs over regional MMN-values (only time points with medium GFP) of several frequency bands; uncorrected (p), Greenhouse Geisser (GG) and Huynh-Feldt (HF) corrected p- values.

high GFP data time points averaged (condition x region; F(18,216)=F)

band [Hz]	F	p	GG	HF
delta [1.5-4.0]	1.11	.35	.36	.36
theta [4.0-8.0]	.65	.53	.69	.72
alpha low [8.0-10.5]	.50	.61	.80	.84
alpha high [10.5-13.0]	.27	.76	.95	.97
beta [18.0-22.0]	.51	.61	.80	.84
gamma 1 [28.0-32.0]	.68	.52	.69	.73
gamma 2 [38.0-42.0]	.55	.59	.84	.89

Table 4: ANOVAs over regional MMN-values (only time points with high GFP) of several frequency bands; uncorrected (p), Greenhouse Geisser (GG) and Huynh-Feldt (HF) corrected p- values.

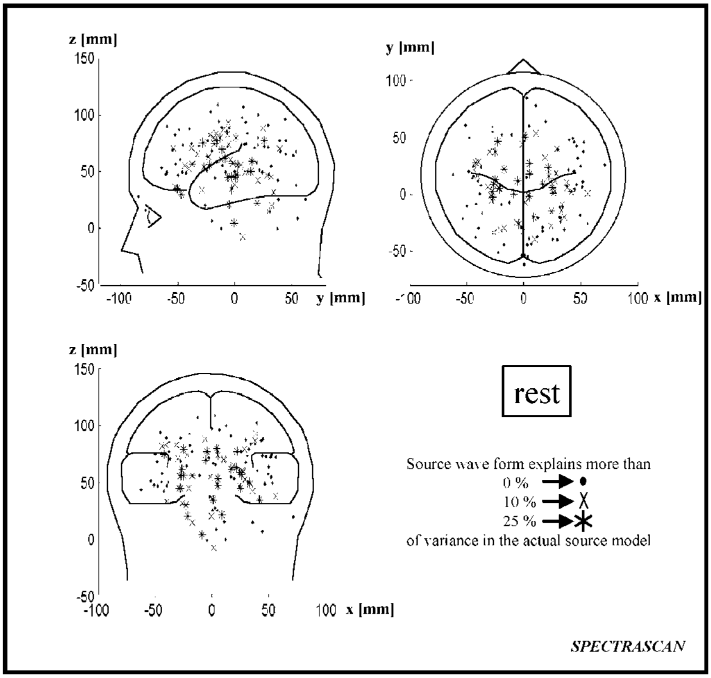

Figure 8: Multiple dipole locations (MDD) over all subjects weighted due to the source wave forms; rest condition

Multiple Dipole Density (MDD)

The subjects showed specific deflections in the power spectra due to the different conditions (see *Figures 4* and *5*). Oscillatory activity in the gamma range (above 30 Hz) could not be fitted using the maximum criterion of 15 dipoles and were therefore excluded of further analyses. At mean there were 5.4 (±2.8) dipole locations fitted per model. Subjects showed 14.9 (±8.4) dipole locations over all models. 2.0 (±0.8) frequency bands were examined per condition and subject.

For multiple dipole density (fitted dipoles per second) in the ten ROIs (see *Figure 2*) a significant CONDITION x REGION (ANOVA) effect could be shown ($F(18,216) = 1.98$; $p < .05$) for uncorrected statistics. Greenhouse-Geisser ($p < .10$) and Huynh-Feldt ($p < .10$) correction lowered the main effect to a trend. Post hoc analyses showed significant more dipoles per second for the contrasting condition than in the resting and the luxuriating condition especially in right frontal and temporal regions (for details see *Table 5*; for illustration see *Figures 8* to *10*).

MDD – multiple source density		
region	**left**	**right**
pre-frontal	cont>rest *	
frontal		cont>rest ** cont>lux **
temporal	cont>rest ** cont>lux **	cont>rest ** cont>lux **
parietal		cont>rest * cont>lux *
occipital	cont>rest *	cont>rest ** cont>lux *

Table 5: Least significant differences tests; rest: resting; cont: contrasting; lux: luxuriating; *=p<.05; **=p<.001.

region	**hemisphere**	**rest**	**luxuriating**	**contrasting**
pre-frontal	**left**	28±39	53±87	354±649
	right	109±165	67±122	205±328
frontal	**left**	112±150	163±193	253±206
	right	430±307	480±482	1054±1084
temporal	**left**	226±174	415±510	1004±985
	right	383±406	491±481	1271±1068
parietal	**left**	30±60	88±98	114±121
	right	35±47	26±42	372±344
occipital	**left**	45±56	135±139	355±350
	right	76±93	180±152	530±668

Table 6: MDD – group means of regional "dipoles per second"-values and standard deviations for ten ROIs.

Conclusions and discussion

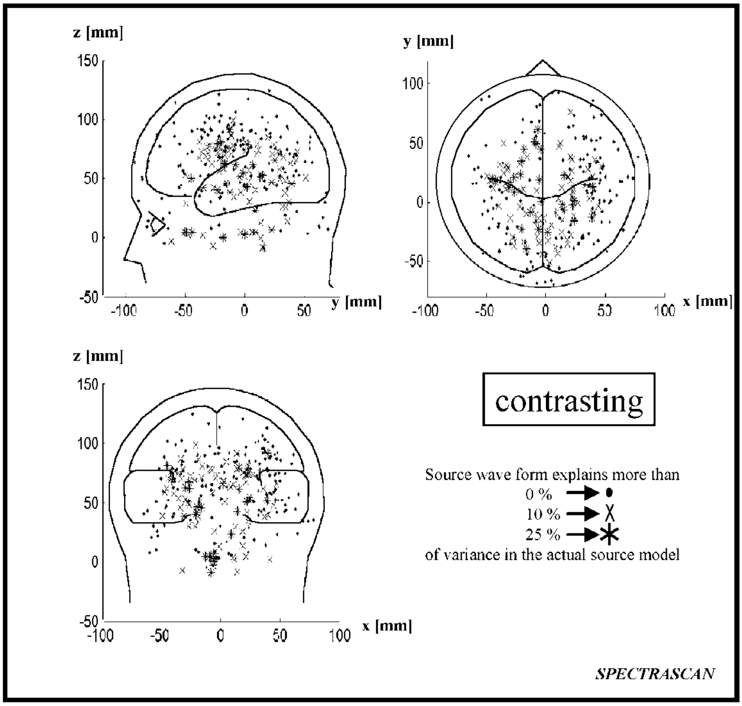

Figure 9: Multiple dipole locations (MDD) over all subjects weighted due to the source wave forms; contrasting condition

The present data clearly indicate that the finally performed strategy (MDD) based on the knowledge of individual oscillatory deflections in the power spectra and multi-dipole analyses leads to a solution that allows a good regional characterization of the different mental conditions. Further investigations have to show reliability and validity of the performed strategy of data analysis.

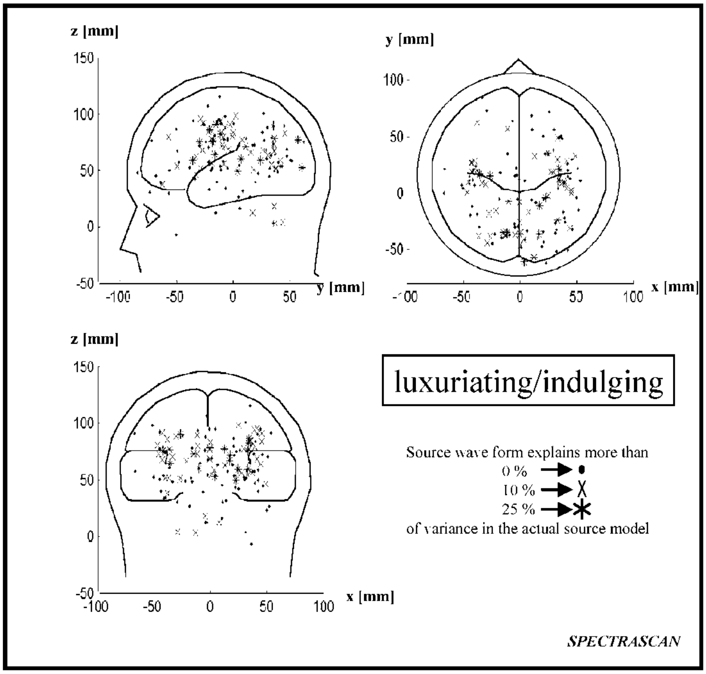

Figure 10: Multiple dipole locations (MDD) over all subjects weighted due to the source wave forms; luxuriating condition

Several aspects of this approach have to be improved. Power spectrum ranges above 30 Hz usually need more than 15 dipoles to be fitted and, therefore, they were handled as diffuse activities and excluded from further analyses. Signals in higher frequency bands reflecting brain activity become less pronounced in comparison to the noise in higher frequency bands. This fact leads to a less marked identification when compared to the oscillatory brain activity of lower frequency ranges. Thus, an *exhaustive* analysis of oscillatory brain activity in higher frequency ranges remains underestimated. A combination of both methods might be helpful in this case. According to the subtle nature of higher oscillatory activity methods like LORETA [4] are possibly more appropriate with respect to the characterization of more distributed and weaker brain activity. The LORETA algorithm aims at 3-dimensional distributions of current density without making assumptions regarding the number of sources. At present, an appropriate method fitting all our requirements is not available. In the same way, an extension of the criterion reflecting the amount of dipoles (more than 15) might be helpful. It has to be noted that this criterion is set in an arbitrary way.

The decision of the respective relevance of a frequency band should be automatised in order to enhance the objectivity of the method. In the present study simple visual inspection provided the basis for the band-pass filters in use.

Multiple dipole density (MDD) was generated only by recognizing dipole locations with source wave forms reaching more than their n-th part of the current equivalent at all time points. Absolute criteria using "current equivalent" or "variance of explanation" thresholds might be also a topic of discussion. At present, however, there is a lack of information with respect to valid normative thresholds. Further investigations will have to develop appropriate criteria.

To provide a comparable parameter for the *multiple-dipole-density* statistics the amount of dipoles counted were transformed into *dipoles per second*. Different subjects, however, showed a different number of generators and dipole locations across the conditions.

To avoid statistical biases due to the use of redundant information arising from different frequency ranges the association between activities in different frequency bands should be examined. Moreover, possible associations based on the harmonics between activities of different frequency ranges should be considered in further processing.

The present methodological approach aimed at a comparison of the output of different *strategies* in analysing continuous data and not at the currently used *methods*. If *dipole-density* and *minimum-norm* would be performed on the same pre-defined band-pass filtered data sets as the *multi-dipole-density* method they might possibly provide an equivalent data basis for a better regional discrimination.

Although the present approach did not use explicitly hypotheses on the regional distribution of different patterns of brain activity it could be shown that the subjects presented more source activity in widespread right hemispheric and right temporal regions during the contrasting condition. Brain activity during luxuriating was comparable to the resting state.

Acknowledgments

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III.

Individual Differences in Brain Activity: fMRI Studies

Functional Imaging and Training Effects

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Abstract

This article reviews functional brain imaging studies of declarative (episodic and semantic) memory. It is shown that prefrontal and medial temporal brain regions are associated with declarative memory. Studies on training-related changes in brain activity are then reviewed. These studies show consistent decreases in prefrontal and medial-temporal regions as a function of repeated task performance. Such decreases may reflect reduced demands on executive/attentional control. Finally, studies on spontaneous and training-induced changes in functional brain activity in older adults are discussed. It is concluded that studies of training effects may provide useful information for the construction of training programs for patients with brain damage.

Introduction

During the last decade, functional neuroimaging with PET (Positron Emission Tomography) and fMRI (functional Magnetic Resonance Imaging) has been used extensively to examine the neural correlates of various cognitive functions [7]. We have focused on declarative long-term memory functions, i.e., memory for general knowledge (semantic memory) and memory for specific events (episodic memory). In this article, I will briefly review some main findings from these studies. Thereafter I will consider the question of how training may affect the neural correlates of declarative memory. Finally, results from studies comparing older and younger adults will be discussed from the perspective of experience-related changes in functional brain activity.

Declarative memory and prefrontal brain activity

A striking outcome of many PET and fMRI studies of declarative memory is that they show a consistent involvement of prefrontal brain regions [5, 7]. This finding may appear at odds with the notion that prefrontal lesions have little effect on declarative item memory and pronounced effects on source memory. However, meta-analytic evidence convincingly shows that prefrontal lesions interfere with declarative memory performance, with a more pronounced effect on more difficult (less supported) tests [34].

There is much evidence for systematic process-related differences in prefrontal activity. In 1994, Tulving and colleagues observed a tendency for activations related to episodic encoding and semantic retrieval to be left-lateralised, whereas activations related to episodic retrieval were right-lateralised [31]. This asymmetric relation between prefrontal activations associated with episodic encoding and retrieval was referred to as the HERA (Hemispheric Encoding-Retrieval Asymmetry) model. In a subsequent paper [17], additional support for the model was obtained, and it was proposed that the model holds for both verbal and nonverbal information. The model is illustrated in *Figure 1*.

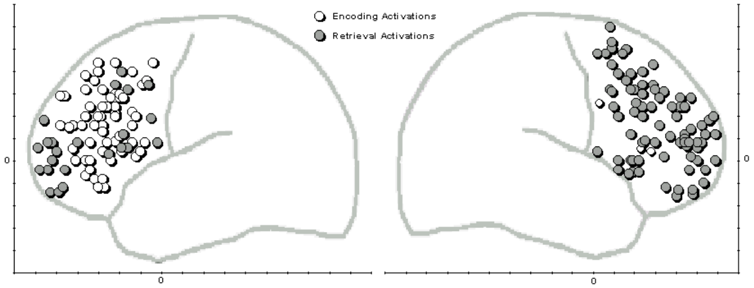

Figure 1: Summary of results from PET and fMRI studies of episodic encoding and retrieval. Circles represent reported activations from published studies (data from [7]).

The notion of an asymmetric relation of prefrontal regions with encoding and retrieval received support from a study by Rossi and colleagues [28], in which Transcranial Magnetic Stimulation (TMS) was used to temporarily interfere with left and right dorsolateral prefrontal cortex during encoding and retrieval of pictures. It was found that TMS applied at left but not right prefrontal cortex interfered with encoding processes (as indicated by subsequent retrieval performance). In contrast, TMS of right but not left prefrontal cortex impaired retrieval of previously encoded information.

Much research has been directed at understanding the functional contribution of left and right prefrontal cortex during episodic encoding and retrieval. There is evidence to suggest that left prefrontal activity during encoding reflects a tendency to analyse to-be-remembered information at a semantic (conceptual) level. For example, Wagner and colleagues showed that encoding-related activity in left prefrontal cortex predicted subsequent episodic memory performance, and they suggested that verbal experiences may be more memorable when semantic and phonological attributes of the experience are extensively processed via the participation of left prefrontal regions [33, p. 1190].

Right prefrontal activation during retrieval of verbal and nonverbal information has been related to the maintenance of “episodic memory retrieval mode” (REMO) [13]. REMO can be defined as a state in which one mentally holds in focal attention a segment of one’s personal past. Support that regional-specific right prefrontal activity is reflecting REMO comes from observations that such activity is seen whether or not retrieval is successful [16]. Thus, by this view, right prefrontal activity during episodic retrieval may be seen as a reflection of a state-related attentional set. In this context it is interesting to note that it has been argued that vigilance is one component of human attention that is right lateralised [22].

A final point regarding prefrontal activation during episodic encoding and retrieval is that although left prefrontal activity is prominent during encoding and right prefrontal activity during retrieval, the picture is more complex than that. Right prefrontal activity has been observed during episodic encoding of nonverbal information [10] and, in addition to right prefrontal activity, left prefrontal activation has been observed during demanding retrieval conditions [14].

Declarative memory and activity in posterior regions

Prefrontal activation during episodic encoding and retrieval is a very consistent observation, but other regions have also been frequently activated [7]. These include medial temporal regions [29]. Medial temporal regions, including the hippocampus, have since long been implicated in declarative memory [30]. Results from brain imaging studies suggest that medial temporal activity is salient during encoding [33] as well as during retrieval. Retrieval-related medial-temporal activity has been associated with actual recovery of information rather than with retrieval mode [18].

Medial-temporal regions have been proposed to interact with neocortical regions during encoding and retrieval [1]. In line with this proposal, various neocortical association areas have been shown to be activated during both encoding and retrieval [15]. The specific site of activity is largely dependent on type of information, such that parietal regions are active during encoding and retrieval of spatial information [23], auditory regions during encoding and retrieval of sound information [19], etc.

Training effects

As summarized above, prefrontal and medial temporal activation is commonly observed in functional neuroimaging studies of declarative memory. Although limited, the available empirical evidence indicates that activity in these regions is changed as a result of training (in most studies, “training” means that the same cognitive operation is repeated on the same set of items).

Training-related changes in prefrontal cortex have been observed during semantic retrieval tasks. An early example comes from a study by Raichle and colleagues [27]. In that study, PET was used to measure brain activity during naïve and practiced performance of a verb-generation task (this task is also an effective incidental encoding task; see [17]). Increased activity, relative to a control task involving word naming, was initially observed in anterior cingulate, left prefrontal and left posterior temporal cortices. After practice (for less than 15 minutes), activity in all these areas was significantly reduced.

Further examples of training-induced changes in prefrontal cortex come from studies of episodic memory retrieval [2, 3]. In these studies, one week before PET scanning, subjects were trained to perfect recall of a story and a list of words. Subsequently, immediately before PET scanning, they were exposed to a second narrative and word list. During scanning, subjects freely recalled the words and the narratives. For both types of to-be-remembered information, frontal activity was observed when the naïve and practiced retrieval conditions were compared with a resting baseline condition. Importantly, when the naïve and practiced conditions were directly contrasted, it was found that frontal activity was lower for the practiced condition. That is, recall of well-learned material recruited less frontal resources than novel retrieval.

A final example of practice-related changes in prefrontal brain activity comes from a study by Klingberg and Roland [11]. In that study, subject repeatedly encoded and retrieved pairs of sounds and pictures (i.e., encoding and retrieval were intermixed within scanning blocks). One PET scan was done during initial training, whereas another PET scan was performed after a period of extensive training (training was terminated when the subjects had reached a criterion of near perfect performance). When the initial training condition was contrasted with the well-practiced condition, increased activity was observed in several regions including frontal cortex. Thus, these results provide additional evidence that frontal activity is more pronounced during initial task performance compared to well-practiced task performance.

Training-related changes have also been observed in medial temporal cortex. Petersson, Elfgren and Ingvar [24] studied medial-temporal activity with PET in a less practiced and a well-practiced (well-encoded) memory state (recall of abstract designs). When the less practiced memory state was contrasted with the well-practiced state, increased activity was observed in several medial temporal regions (in line with the studies reviewed above, increased activity in this contrast was also observed in several frontal regions). These findings indicate that the functional role of medial temporal brain regions in declarative memory changes as a result of practice (for a discussion of changes in other regions, see [25]).

In a subsequent study, Petersson and colleagues replicated and extended their findings [26]. In a first experiment, further evidence for training-related reductions in medial-temporal activity was obtained from an object-location recognition task. Interestingly, a second experiment involved recall of pseudo-words. In that experiment, no training-related changes in medial temporal activity were observed, suggesting that practice-related decreases might be more clearly expressed for information that is meaningful and will lead to associative-relational processing. At least in part, this may relate to the relative novelty/familiarity of the information.

Functional role of training-related reductions in brain activity

The training effects that have been considered up to now suggest that a neural consequence of repeated task execution is that regional brain activity is reduced – notably in frontal areas. A possible functional correlate of this reduction is reduced demands on executive/attentional control [26]. That is, in novel (unpracticed) states there are relative greater demands for controlled frontally-mediated processing, but as performance becomes more automatic there is less need for frontal control.

It should be emphasized that the results here concern repeated task performance *on the same items*. Thus, the results cannot be seen as reflecting a re-organization of the neural system that mediates a certain process such as episodic retrieval, but rather as an item-specific change. Results from procedural learning indicate that practice-related effects are highly item-specific [9], and similar findings have been obtained in the domain of declarative memory [27].

In this context it should be noted that other forms of training effects, that generalize to novel items, are conceivable. One form, that will be discussed in some detail below, has to do with learning techniques that facilitate cognitive performance. Another form has to do with training of basic processing components, such as working memory capacity [12]. These forms of training can facilitate performance more generally, and not only the processing of specific items. However, to date, relatively little is known about the neural correlates of such training.

Age-related changes of functional brain activity

Studies of younger subjects show reduced frontal activity as a function of repeated task performance, and this may be a reflection of reduced demands on controlled processing. This pattern of results can be contrasted with results from studies of declarative memory involving older adults. Several studies have found that older adults show relative greater activity in some frontal regions compared to younger adults [6]. This has been interpreted in terms of compensation for age-related deficits in declarative memory. By this view, since normal aging is associated with impaired declarative memory, especially episodic memory [20], it is necessary for the aging brain to counteract these impairments by recruiting additional processes. Increased activity in specific frontal regions for older compared to younger adults could be a reflection of such compensatory processes (for a discussion of alternative interpretations, see [6]). Assuming that increased age-related frontal activity reflects compensation, such compensation seems to develop spontaneously, and there is data to suggest that compensatory processes do not develop in all older adults [8].

Little is known about the neural correlates of directed/guided training in older adults. To my knowledge, there have been no neuroimaging studies involving older subjects that have examined training in the form of repeated processing of the same items. Thus, it is not known whether older adults show the same pattern of decreased regional activity following training as younger adults do, and whether the rate of changes is the same in older and younger adults.

With regard to other forms of training, we have recently conducted a PET study of the neural correlates of acquiring and using a traditional mnemonic [21]. The mnemonic we used was the method of loci [4], which involves learning to associate to-be-remembered information with a landmark structure. We found that both the younger and older adults could acquire the mnemonic. However, in line with the findings of previous behavioural studies, the younger adults benefited more from the mnemonic. In fact, half of the older adults did not benefit at all from the mnemonic. The other half did benefit, but did not reach the same level of performance as the younger adults.

At the neural level, we found that the younger and the older adults who did benefit from the mnemonic showed increased activity in posterior occipito-parietal brain regions when the mnemonic was used for word encoding compared to a control condition involving non-guided encoding. Activity in this region has previously been associated with the formation of mental visual images [7] and may reflect the formation of associations between the to-be-remembered information and the cue structure. In addition, it was found that dorsal frontal activity was specific for the younger adults. Such activity may reflect working memory processes.

The results of this training study may be interpreted as suggesting that a reduced ability of older adults to benefit from the loci mnemonic reflects both a processing and a production deficit. That is, those elderly who did not benefit at all from the mnemonic may have failed/ chose not to use the mnemonic (i.e., a production deficit, cf. [32]), and correspondingly did not activate occipito-temporal cortex. All elderly subjects may have been less proficient in using the mnemonic due to age-related deficits in working-memory capacity (i.e., a processing deficit), and this was reflected in the absence of increased frontal activity.

Conclusion

The few brain imaging studies of training-related alterations in functional brain activity that have been done to date suggest that such changes can occur fast. Most of the prior studies concern training in form of repeated task performance with the same items. Future studies on other forms of training are needed, as are studies on whether it is more difficult to induce changes in old age. The results of such studies may provide important insights into the construction of training programs to facilitate the recovery of patients with brain damage.

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Individual Differences in Cognitive Strategies and Attentional Effects During Stimulus Uncertainty: Evidence from Psychophysics and fMRI

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Abstract

Using an uncertainty paradigm and fMRI (1.5 T; Siemens Vision) we studied the effect of visual selective and divided attention on cortical activation patterns evoked by near-threshold stimulus discriminations. The stimuli consisted of an oval that differed from an implicit standard oval either in colour or width. The subjects' task was to classify the actual stimulus as one of two possible alternatives per stimulus dimension. Three different experimental conditions were conducted: "colour-certainty", "shape-certainty" and "uncertainty". In all experimental conditions, the stimulus differed in only one stimulus dimension per trial. In the two certainty conditions, the subjects knew in advance which dimension this would be, while during the uncertainty condition, they had no such previous knowledge, so that they had to monitor both dimensions simultaneously. The results of the statistical analysis of the fMRI data (with SPM99) show pronounced differences in cortical activation patterns depending on the attended stimulus dimension. Furthermore, the psychophysical as well as the fMRI results point towards individual differences in cognitive strategies during stimulus uncertainty: Subjects with a relatively small psychophysical uncertainty effect exhibit nearly no differences in their cortical activity between certainty and uncertainty conditions, while subjects with a relatively large psychophysical uncertainty effect show

marked differences in these same comparisons. Foci of higher cortical activity during stimulus uncertainty mainly lie in areas known to be related to attentional and working memory processes, like dorsolateral prefrontal and posterior parietal cortex.

Introduction

Objects in the real world can be defined along numerous physical dimensions. The images these objects generate on the retina can also be defined along an equally large number of dimensions, which are to some degree processed separately by the visual system. In the human visual cortex, various areas have been found to be specialised in the processing of certain aspects of visual information, like the colour (e.g., V4 [3]) or shape (e.g., lateral occipital complex [23, 24]) of an object. From these areas, the information is processed to higher order association cortices, where it is semantically encoded, for example by combination with knowledge about previous experiences.

During each fixation period, countless bits of visual information fall on the retina, exceeding that which can be processed extensively by the brain. In order to make a selection among these different sources of information, we rely on *attention* to direct our processing resources to behaviourally relevant features of visual scenes. Among these attentional selection mechanisms are *selective* and *divided* attention: during selective attention, only one channel of information is attended, whereas during divided attention, at least two different channels are monitored at the same time.

There is accumulating evidence suggesting that the exact pattern of cortical activation varies depending on which features subjects selectively attend to during a discrimination task. If such differences are evident, where in the visual pathway does stimulus selection occur? Underlying this question is the issue concerning the *locus* of attention, i.e. the stage of visual information processing modulated by stimulus selection. Two major theories related to this problem have evolved. The so-called *early selection* theory suggests that attentional selection acts at a relatively early stage of visual processing and is based on simple stimulus features [6, 7, 21], whereas the *late selection* theory suggests that selection takes place between the semantic encoding stage and a further stage of visual information processing [14, 32]. Behavioural and physiological studies related to this issue have produced conflicting results, some showing attentional modulations of neural activity either exclusively in extrastriate visual cortex [27] or also in primary visual cortex (e.g., [26, 31]; see [22] for a review).

Simultaneous discrimination of stimuli that can differ along the one or the other dimension has been used in psychophysics to explore the independence of visual processing. When subjects simultaneously attend to different features of the same object, another question arises: Are the same cognitive processes carried out as during selective attention, except that they are conducted in parallel[1], so that divided attention could be considered to be the sum of different simultaneously performed selective attentional processes? Or are there further differences between these two attentional mechanisms? One paradigm used to investigate this phenomenon has been referred to as *stimulus uncertainty*. For the case of the colour and shape of a given object, it has been shown that judgements about variations can be made independently, provided the differences are large and the observer has prior information about which dimension should be judged (see [37]). What happens when the differences to be discriminated are small and the observer is uncertain along which dimension a change will occur? In the stimulus uncertainty paradigm, observers have to allocate their attentional resources across at least two different stimulus features. Owing to the effects of internal noise, uncertainty has been shown to increase discrimination thresholds in detection and discrimination tasks [36, 18, 34].

Functional imaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) attempt to answer these questions by recording changes in haemodynamic or metabolic measures of brain activity while subjects attend to different

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[1] "parallel" in the sense of independent, not in the sense of "parallel vs. serial processing".

stimuli or different features of these stimuli. In the vast majority of the studies conducted so far, the special case of *spatial* selective or divided attention has been investigated, either with or without the involvement of eye movements, where attentional selection is based on spatial location (e.g., attend left or attend right). Here again the findings concerning the issue of the locus of visual attention are contradictory, with some studies showing attentional influences already in area V1 (e.g., [8, 5, 16, 28]), while others revealed selection not earlier than in extrastriate visual cortex (see [22]).

Only few functional imaging studies so far have tried to examine the effect of *nonspatial* visual selective or divided attention on the neural processing of visual stimuli. In a very widely acknowledged PET study, Corbetta et al. [11, 12] showed that dependent on the attended stimulus feature (colour, shape or speed) different extrastriate visual areas become activated and that dependent on the kind of attentional mechanism (selective or divided) different parts of the frontal lobes and the basal ganglia are active. A problem here is that while the subjects were instructed to attend to subtle changes in one stimulus feature, the other two features could change as well and it remains controversial to what extent the subjects ignored these irrelevant stimulus changes. Le et al. [25] measured BOLD responses during sustained or alternately shifted selective attention to the colour or shape of foveally presented stimuli. They found evidence for feature-specific activations in occipital and temporal visual areas and greater activity in the posterior superior parietal lobule, cuneus, precuneus and different parts of the cerebellum during shifts of attention than during sustained attention. However, they measured cortical activity only in the posterior half of the brain, so that nothing could be inferred about the involvement of prefrontal areas in the attentional control system. With respect to the investigation of the effects of attentional selection on feature-specific activations, the use of large stimulus differences (red vs. green, circle vs. square) is problematic, since several psychophysical studies showed larger attentional effects for near-threshold discriminations (e.g., [39, 4]. Furthermore, the large stimulus differences themselves might – at least partially – explain differential cortical activations.

In our study, we examined the effects of nonspatial visual selective and divided attention on the discrimination of subtle differences in colour and shape and compared these to the cortical activation patterns evoked by these stimuli. We employed an uncertainty paradigm and fMRI in order to identify cortical areas showing changes in the BOLD signal dependent on the attended stimulus feature and on the attentional mechanisms involved. By dividing the subjects according to their discrimination performance during stimulus uncertainty and separately analysing their fMRI data, we found evidence for individual differences in attentional effects and cognitive strategies.

Methods

Subjects: Four female and two male students, aged 24 to 26 years, participated in this study after providing written informed consent. All of them are right-handed and have normal or corrected-to-normal (with contact lenses) visual acuity. Their colour vision was tested before the experiment with the test plates No. 1 to No. 25 of "Ishihara's tests for colour-blindness" [20], where all subjects gave 100 % correct answers, indicating normal colour vision.

Stimuli and task paradigms: Data were gathered with an uncertainty paradigm. The stimulus consisted of an oval of fixed height and luminance (50 cd/m^2), which was presented centrally for 250 ms against a dark background. In each trial, the presented oval differed slightly from an implicit, but never shown, standard oval in either colour or shape by an individually adjusted fixed amount. See Morgan et al. [30] for the usefulness of an implicit standard instead of an explicitly presented reference stimulus in visual discrimination experiments. The task of the observer was to classify the deviation as one of two alternatives per stimulus dimension, as described below. The deviations were small enough that accuracy was less than perfect, i.e., discrimination performance was noise limited. The subjects knew on which dimension the deviation would occur in the two certainty conditions (one for colour and one for shape), but not in the uncertainty condition (in which colour and shape deviations were randomly intermixed from trial to trial).

The stimulus colour was specified in CIE xyY coordinates [10]. The implicit standard was pink in appearance with the coordinates 0.43, 0.224, 50. The two different alternatives were either bluer or redder, where the extent of the difference between these two alternatives varied between subjects. The individual differences ranged from 0.017 to 0.059 in the x value and from 0.008 to 0.028 in the y value.

The shape of the standard oval was set at a height of 4.38° and a width of 3.09° visual angle. Increasing or decreasing the width of the oval by a small amount specified the shape of the actual stimulus presented to the subject. The extent of the difference between the two alternatives varied again between subjects and ranged from 0.09° to 0.26°. *Figure 1* shows exaggerated examples of the two possible alternatives per stimulus dimension.

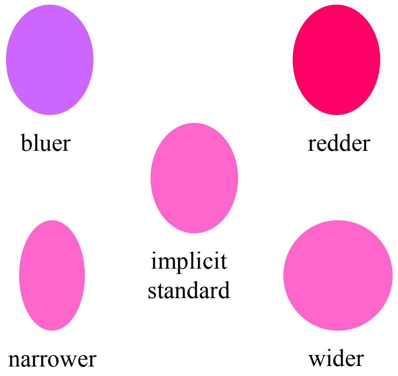

Figure 1: The implicit standard stimulus and exaggerated examples of the four different stimulus alternatives. One alternative was presented centrally on each trial.

Each stimulus was presented against a dark background for 250 ms, such that stray light and eye movements during stimulus presentation should have only a minimal effect. The dark background was 13.13°

wide by 8.75° high and framed by a thin (width = 2.19°), white (xyY = 0.27, 0.28, 75) border.

The main experiment consisted of three different experimental conditions: In the colour-certainty condition, the stimulus presented on each trial differed from the standard in colour. The subjects indicated whether the stimulus was bluer (response = 1) or redder (response = 2) than the standard. In the shape-certainty condition, the stimulus presented on each trial differed from the standard in width. The subjects indicated whether the stimulus was narrower (response = 1) or wider (response = 2). In the uncertainty condition, colour and shape trials were randomly intermixed. The subjects gave a single response on each trial: he or she pressed button 1 if the stimulus were judged bluer or narrower than the standard, button 2 if the stimulus were judged redder or wider. Note that the relationships between stimulus and response are the same in certainty and uncertainty conditions. We decided to employ this single-stimulus single-response procedure with two response alternatives, since it was best suited for the application in the MR scanner. Because of the spatial circumstances in the MR scanner and the technical requirements demanding rapid trial sequences, the subjects only responded with two fingers of one hand. The response interval (1 s) was adjusted to allow a speeded response.

In all conditions, a central white fixation point was displayed between stimulus presentations. After each response, feedback indicating whether the response was correct or incorrect was given via a brief (250 ms) colour change of the fixation point (green = correct, red = incorrect). The trial-to-trial interval was 2 s.

Before the main experiment, each subject was run in several sessions in the psychophysics laboratory. These sessions were part of the study by Vallines et al. [38] and accomplished two goals: (1) to select individual deviation values (between stimulus alternatives) by measuring the psychometric functions, relating deviation magnitude to d’, for each subject in order to adjust the difficulty level so that it was the same for all subjects; (2) to train the subjects in the tasks that they would perform in the MR scanner.

Procedure: The subjects lay supine within the MR scanner. A mirror was mounted above the head coil through which they looked out of the foot end of the scanner bore, where a rear-projection screen was placed on which the stimuli were presented with an LCD projector (D-ILA Projector, DLA-G10; JVC, Yokohama, Japan). The voltage-luminance function of the projector was calibrated with a spectral photometer. The stimuli were generated with a VSG graphics card (Cambridge Research Systems, Ltd., Rochester, UK), which was also used for response acquisition. The subjects responded as described above by button press on an optical response box (Cambridge Research Systems, Ltd., Rochester, UK). This response box is made entirely of plastic materials and a fibre-optic cable in order to avoid artefacts caused by current flows within the high magnetic field. It was placed at the subjects' right hand.

Measurements within the scanner were organised into six runs (two per experimental condition), each consisting of nine successive one-minute segments. Five of the segments were rest conditions in which the stimulus field was blank except for a fixation point at the centre. Alternating with the rest segments were judgement segments in which one stimulus was presented every two seconds. The experimental condition remained the same within each run and right before the beginning of a new run, the subject was told which condition would come next. The order of the different conditions was colour-certainty, shape-certainty, uncertainty, uncertainty, shape-certainty and colour-certainty (A-B-C-C-B-A).

MRI data acquisition: The MR scanner used for this experiment is a 1.5 Tesla whole body Siemens Vision Magnetom sited in the laboratory of Prof. Dr. Burckhard Terwey in the "Zentralkrankenhaus Sankt-Jürgen-Straße" in Bremen, Germany. fMRI data were acquired using a block design. Every six seconds (= time to repeat (TR)) one functional whole-brain T_2*-weighted gradient echo planar imaging (EPI) scan was carried out (time to echo (TE) = 60 ms; flip angle $\alpha = 90°$), each consisting of 32 contiguous slices (no gap) parallel to the anterior commissure-posterior commissure (AC-PC) plane with each slice being 64 x 64 voxels and a voxel size of 3 x 3 x 3 mm. Following the six experimental runs, an anatomical T_1-weighted scan (160 slices, each slice 512 x 512 voxels) was obtained in sagittal orientation, using a magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequence with TR = 9.7 ms, TE = 4 ms, inversion time = 300 ms and a voxel size of 1 x 0.5 x 0.5 mm.

Data analysis

Psychophysical data: Accuracy was measured by percentage of correct answers and d'. For computational purposes, stimuli which were bluer or narrower than the standard were arbitrarily designated noise and redder or wider stimuli were designated signal, and responses of 1 and 2 were treated as "no" and "yes", respectively [40]. Response times, measured from the onset of the stimulus to activation of the response button, were also recorded. On a few trials (less than 1 %), the subjects did not respond within the one-second time window allowed. Data from those trials were excluded from the calculations.

fMRI data: The functional imaging data were analysed using SPM99 (*S*tatistical *P*arametric *M*apping, 1999), a computer programme running under Matlab (see http://www.fil.ion.ucl.ac.uk/spm/ for further details). All images were realigned in order to eliminate motion artefacts and spatially normalised to the standard stereotactic space of Talairach and Tournoux [35] with a bilinear interpolation method. Smoothing was performed by a three-dimensional convolution of the functional images with an isotropic Gaussian kernel of 6 mm full width at half maximum, which accomplished the goals of increasing the signal to noise ratio and minimising the effects of individual differences in functional and gyral anatomy. Afterwards, an appropriate design matrix was specified for the pooled data of all subjects. Changes in the blood oxygenation level dependent signal (BOLD-signal) dependent on the different experimental conditions were assessed at each voxel by using a general linear model with a boxcar waveform convolved with the haemodynamic response function and by applying the theory of Gaussian fields [15]. To make statistical inferences about regionally specific effects (i.e., assign *p*-values), the estimates were compared using linear contrasts. *t*-values were assigned to every voxel and the resulting set of voxel values for each contrast constituted a statistical parametric map (SPM) of the *t*-statistic, SPM{t}, which was then thresholded at $p \geq 0.05$ (corrected for multiple comparisons). The extent threshold (*k*, minimum cluster size) was set at 10 voxels for contrasts against rest (experimental condition > rest), whereas no extent threshold was set for differential contrasts (between experimental conditions). No *a-priori* hypotheses were formulated concerning activations in certain parts of the brain.

Results

Psychophysical results: Figure 2 gives the percentages of correct answers for the different subjects and experimental conditions plotted against each other. In case of chance performance, the percentage would lie around 50 %, where the one-tailed confidence limit lies at 58 %. The diagonal line indicates the level of uniformity between the performance under the certainty and the uncertainty condition. *Table 1* presents individual d’ values and reaction times for the six subjects in the different experimental conditions. The different trials in the uncertainty condition were scored separately as colour- and shape-uncertainty trials. *Table 2* gives the magnitudes of the individual uncertainty effects as ratios of d’ in the uncertainty condition to d’ in the corresponding certainty condition. Smaller ratios indicate larger uncertainty effects. Column 1 gives the ratios for the colour task, column 2 for the shape task. Column 3 gives the root-mean-square (RMS) average of the ratios in the first two columns.

As can be seen in *Figure 2*, performances in the uncertainty condition are lower than the corresponding performances in the certainty condition. All but one of the data points lie below the diagonal, indicating reduced performance. An analysis of variance (ANOVA) on the d’ values in *Table 1* shows a main effect of certainty-uncertainty ($p < 0.01$). Consistent with the accuracy results, reaction times were longer in the uncertainty than in the certainty conditions ($p = 0.03$).

Although the stimulus differences to be discriminated were individually adjusted to make colour and shape discriminations equally accurate, the scores of three of the subjects are markedly lower on the colour task than their scores on the shape task. The lower performance occurs in both certainty and uncertainty conditions and, in the latter case, none of the proportion correct scores exceeds the 95 % confidence limit for chance performance. As measured by the ratios in *Table 2*, the uncertainty effects for these subjects in the colour task are much larger than the effects observed for these same subjects in the shape task and larger than any of the uncertainty effects observed for the other three subjects. While the uncertainty ratios for individual tasks in *Table 2* vary considerably from one observer to another, the RMS averages show greater agreement. The significance of the RMS averages is considered in the discussion section.

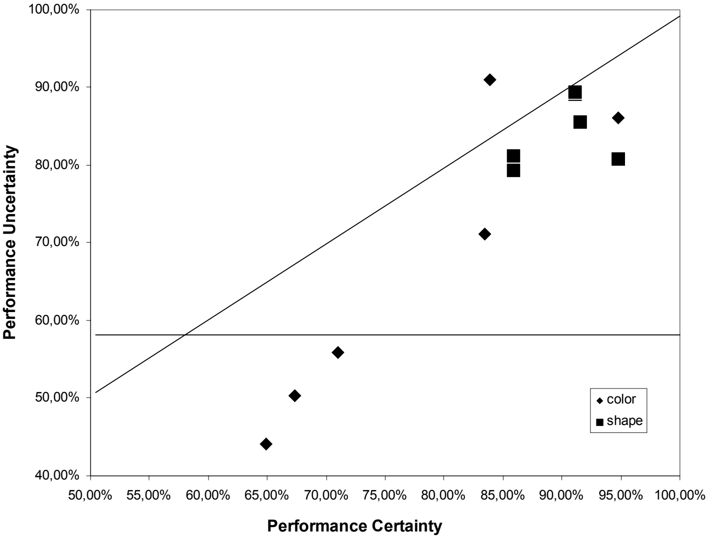

Figure 2: Percentages of correct answers for the different subjects (one subject per point) during the uncertainty condition plotted against those during the certainty conditions. The horizontal line indicates the one-tailed confidence limit of 58 %. The diagonal line indicates the level of uniformity between the performance under the certainty and the uncertainty condition.

Table 1: Individual d’ values and reaction times (RT; standard deviations (δ) given in brackets) for the different experimental conditions.

Subject	Colour				Shape			
	Certainty		Uncertainty		Certainty		Uncertainty	
	d’	RT (δ) [ms]	d’	RT (δ) [ms]	d’	RT (δ) [ms]	d’	RT (δ) [ms]
IV	0.7656	431 (132)	-0.3073	346 (140)	2.1603	331 (964)	1.7646	306 (142)
JM	1.1322	531 (162)	0.0925	672 (162)	2.8640	428 (124)	2.2600	462 (121)
MS	1.2247	583 (166)	0.4564	701 (153)	2.7964	358 (141)	2.4620	481 (162)
RW	3.3989	434 (122)	2.1963	654 (143)	2.2379	525 (129)	1.7328	551 (122)
SB	2.3441	572 (140)	1.6102	754 (141)	4.2661	487 (111)	2.2765	612 (139)
MJ	2.2931	478 (158)	2.7775	623 (157)	3.1979	410 (126)	2.5554	499 (158)

Table 2: Magnitudes of individual uncertainty effects as ratios of d’ in the uncertainty condition to d’ in the corresponding certainty condition (smaller ratio = larger uncertainty effect) and root-mean-square (RMS) averages of both ratios.

Subject	d’ Ratios (Uncertainty / Certainty)		RMS Average
	Colour	Shape	
IV	-0.4014	0.8168	0.6436
JM	0.0817	0.7891	0.5610
MS	0.3727	0.8804	0.6760
RW	0.6462	0.7743	0.7131
SB	0.6869	0.5336	0.6151
MJ	1.2112	0.7991	1.0261

Functional imaging results: We calculated three contrasts against rest (one for each experimental condition) and two differential contrasts for the pooled data of all subjects in order to find differences concerning the attended stimulus dimension: colour-certainty > shape-certainty and vice versa.

Since the subjects differ largely in the strength of their psychophysical uncertainty effect for the colour dimension and three of the subjects even drop down to chance level when performing colour discriminations under the uncertainty condition, we deemed it necessary to subdivide the subjects into two subgroups according to the strength of their uncertainty effect for the colour dimension. The "large effect group" contained subjects IV, JM and MS, whereas the "small effect group" consisted of subjects RW, SB and MJ. We calculated six different contrasts separately for these two subgroups: uncertainty > both certainty conditions taken together and vice versa (in order to find differences related to the amount of previous knowledge about the varied stimulus dimension and to the kind of attentional mechanisms involved) and separate contrasts between each certainty condition and the uncertainty condition (in order to find uncertainty effects specific to the stimulus dimension). By comparing the results of these contrasts of the two different subgroups to each other, information about several questions should be provided: Does the difference in the psychophysical uncertainty effect correspond to a similar difference in the functional imaging data? Did the subgroup with the small uncertainty effect simply perform colour and shape discriminations in parallel (plus some extra processing) during the uncertainty condition or did they cognitively restructure the task? Did the subgroup with the large uncertainty effect simply neglect processing colour information during the uncertainty condition or did they cognitively restructure the problem?

Contrasts against rest: Because of pronounced differences in stimulation between the rest and the experimental conditions, many activations are evident in the three contrasts against rest. These activations are distributed over all cortical lobes and both cerebral hemispheres.

In the frontal lobes, different regions in Brodmann Area (BA) 6 in the pre- and supplementary motor cortex (bilateral) show significant activations, as well as regions in BA 9 (bilateral), BA 10 (left), BA 32 (left), BA 44 (bilateral), BA 46 (right) and BA 47 (right). Significantly activated parietal areas are left BA 1 in the primary somatosensory cortex during the colour-certainty condition, right BA 7 in the posterior parietal cortex and different regions in BA 40 in both hemispheres. Two different areas on the right superior temporal gyrus showed significantly more activation during the colour-certainty condition, BA 22 and BA 38, where the latter was also more highly activated during the uncertainty condition. Furthermore, different extrastriate visual regions in BA 18 and BA 19 of both occipital lobes exhibited significantly more activation during one or more of the experimental conditions. In addition, BA 13 in the insular cortex of both hemispheres activated in a lateralised manner: on the left side during the colour-certainty and uncertainty conditions, on the right side during the shape-certainty condition.

Effects of the attended stimulus dimension: The direct comparisons between the two different certainty conditions reveal several areas that are selectively activated when subjects attend to a specific stimulus dimension. In the *colour-certainty* condition, two right prefrontal areas are more active when compared to the shape-certainty condition: an area at the border between BAs 10 and 46 and BA 32 on the anterior cingulate gyrus. These activations are also significant in the comparison between the colour-certainty and the rest condition.

In the reverse comparison, three areas in the left hemisphere are significantly more activated during the *shape-certainty* than during the colour-certainty condition: a prefrontal area at the border between BAs 10 and 11, BA 31 in the precuneus and BA 21 on the middle temporal gyrus. None of these activations are significant in the corresponding contrast between the shape-certainty and the rest condition.

Effects of stimulus uncertainty: The separate analysis of the contrasts concerning differences between certainty and uncertainty conditions yielded very different results for the two subgroups of subjects. The subgroup with the small uncertainty effect exhibited only very few differences in their cortical activity during certainty and uncertainty conditions. Right BA 9 was more active during uncertainty than during shape-certainty, left BA 9 was more active in the reverse contrast and left posterior parietal BA 7 was more active during uncertainty when compared to both certainty conditions taken together. No other significant differences were found in any of the six calculated contrasts.

A completely different pattern of results is provided by the results of the same contrasts calculated for the data of the subgroup with the large uncertainty effect. Many different cortical areas show more activity either during uncertainty or certainty conditions, while most of these differences are yielded by the comparisons between the shape-certainty and the uncertainty conditions. *Figure 3* displays cortical areas that were more active during stimulus uncertainty than during certainty. More activity during uncertainty was found in premotor BA 6 (bilateral), left prefrontal BA 46, left posterior parietal BAs 7 and 40 and left temporal BAs 21, 22 and 37. During either one or both of the certainty conditions, higher activity was exhibited in left frontal BAs 8 and 9, bilaterally in prefrontal BA 10, right prefrontal BA 11, left inferior temporal BA 21, left superior temporal BA 22 and left BA 40 on the supramarginal gyrus.

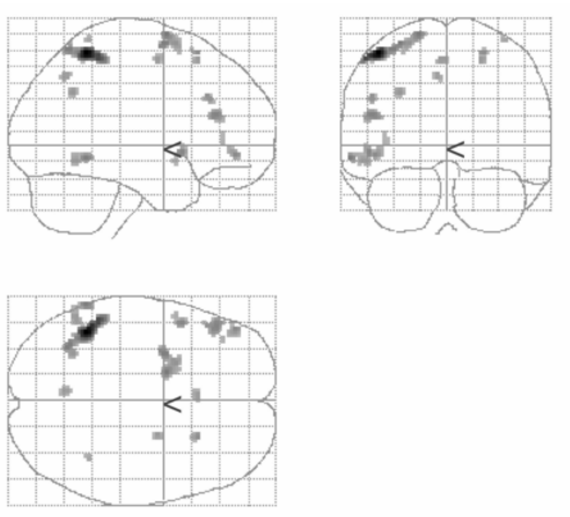

Figure 3: “Glass brains” illustrating brain areas that show higher activity during stimulus uncertainty when compared to both certainty conditions. (Data of the “large uncertainty effect” group; a statistical threshold of T = 4 was used for display purposes; left in the image corresponds to left in the brain.)

Discussion

Selective attention to different stimulus features: The present results indicate that cortical activity depends on the attended stimulus feature. In the two contrasts against rest between the conditions of colour- and shape-certainty and the rest condition, many more areas show activity in just one of the two certainty conditions than in both. In fact, among the many different areas in all four cortical lobes of both cerebral hemispheres that are activated in these contrasts, only some frontal areas (BA 6, 9, 44 and 47) and one occipital area on the fusiform gyrus show activity in both contrasts. However, in these contrasts against rest several effects contribute to the cortical activation (e.g., motor-, modality- and feature-specific effects). Hence, we focus on the two differential contrasts that make direct comparisons between the two certainty conditions, since here significant differences are most likely due to feature-specific effects. Five different cortical areas show presumably feature-specific effects in these contrasts, two colour-specific and three shape-specific.

Both of the two colour-specific areas show also significantly higher activity in the corresponding contrast against rest (colour-certainty > rest) and both of them lie in the right frontal lobe: one at the transition from BA 10 to BA 46 in the dorsolateral prefrontal cortex and the other on the anterior cingulate gyrus. Despite the fact that the cluster sizes of these two activations are very small in the differential contrast (2 and 4 voxels, respectively) and therefore any conclusions can only be tentative, they are nevertheless interesting, since these two areas have been shown earlier to be involved in different attentional processes. Of particular interest in the context of our results are two of these studies. Allison et al. [1] measured visually evoked potentials related to colour perception in dorsolateral prefrontal cortex and Banich et al. [2] found with fMRI the same area as that found here (within the anterior cingulate gyrus) to be selectively activated when subjects attended to the colour of a word instead of its meaning in a Stroop task.

The three cortical areas showing shape-selective activity lie in the left cerebral hemisphere: one in the medial part of the orbito-frontal cortex, one on the middle temporal gyrus and one on the precuneus. Activation in these first two areas agrees well with other studies since they are part of cortical regions involved in different aspects of shape perception. For example, lesion studies with monkeys (e.g., [29, 17, 33]) showed that the orbito-frontal cortex is important for selective attention to shape (and colour). Furthermore, the results of several functional imaging studies (e.g., [23, 24]) suggested that the lateral occipital complex, which extends up to the area on the middle temporal gyrus that is active in our study, is crucial for the perception of an object's shape.

The present results do not, on the other hand, yield a straightforward answer to the question for the locus of attention, i.e., early or late selection. We did not find any feature-specific attentional modulation in early visual areas. This lack of difference provides indirect support for the late selection theory. For colour, we only found selective activity in frontal areas that seem to be specialised in directing attention to colour but we failed to show attentional modulation in areas that are assumed to be specialized for colour processing itself (e.g., V4). On the other hand, we did find attentional modulation in an area that is specialised for shape perception (lateral occipital complex).

Differences between selective and divided attention: When the subjects' performances in the two certainty and the corresponding uncertainty conditions are compared, it is obvious that judgements are uniformly less accurate during uncertainty. This means that the sensitivity to near-threshold differences is much higher when subjects know in advance on which feature dimension a change will occur, so that they can direct their attention selectively to this feature, compared to when they have to divide up their attentional resources to different features of an object – an effect that has also been reported by Corbetta et al. [11, 12] and Thomas and Olzak [36] among others.

While the individual extents of the effect of stimulus uncertainty on performance vary from one subject to another, particularly in the colour task, the average effect closely agrees with the prediction of an ideal observer model that assumes stochastically independent processing of information on each dimension [36]. In this model the accuracy of each judgement process is putatively limited by Gaussian noise of internal and/or external origin. The noise arising for the judgement of one stimulus dimension is uncorrelated with the noise perturbing the other process. In the uncertainty condition, information from both dimensions is processed on each trial and the less ambiguous information is selected as the basis for the judgement response. Accuracy is necessarily reduced in the uncertainty condition because the judgement process is perturbed by noise from two sources, rather than from a single source as in each certainty condition. For various reasons (see [36]), the ideal observer may weight information from the two dimensions unequally, resulting in unequal uncertainty effects. However, the root-mean-square of the ratio measures for the two dimensions is independent of any such bias. *Table 3* gives these

RMS-averages, and their mean of 0.7058 is nearly identical with the model prediction of $2^{-0.5}$ (approximately 0.71).

This model assumes that observers carry out the same cognitive processes in the uncertainty condition as in the certainty conditions, except that both sets of processes are carried out in parallel. If this were the case, it might be expected that any area that shows activity during one or both of the certainty conditions would also show activity in the uncertainty condition. However, inspection of the contrasts against rest fails to support this conclusion. Although several areas accomplish this expectation, there are several areas that are either only active in one or both of the certainty conditions or only in the uncertainty condition. These results suggest that the subjects employ different cognitive processes in the uncertainty condition than those used in either of the certainty conditions. This would mean that observers do not simply perform both discriminations in parallel in the uncertainty condition, but rather restructure their cognitive approach. The cortical activity pattern during uncertainty would therefore not simply be the union of areas active during both certainty conditions, but would rather contain activity in entirely new areas as well as lack activity in other areas.

The differential contrasts, which make direct statistical comparisons between certainty and uncertainty conditions, provide pertinent information about the differences in neural activity between selective and divided attention. The results of these contrasts suggest a link between the behavioural and functional imaging data in that subjects differ in their cognitive strategies during stimulus uncertainty. Subjects exhibiting a relatively small psychophysical uncertainty effect seem to have carried out the same cognitive processes during the uncertainty condition as during the two certainty conditions, as indicated by the very few differences in cortical activity between these conditions.

In contrast to this, the subjects exhibiting a relatively large psychophysical uncertainty effect seem to have cognitively restructured the task during stimulus uncertainty, since their cortical activity differed largely between certainty and uncertainty conditions. Foci of higher cortical activity during the uncertainty condition mainly lie in frontal (BA 6), dorsolateral prefrontal (BA 46) and posterior parietal areas (BAs 7 and 40) that have been shown before to be essential for attentional and working memory processes (see [22, 13]). As many different studies have demonstrated, dorsolateral prefrontal and posterior parietal areas seem to be parts of a complex fronto-parietal attention network controlling attentional modulation of neural activity in other parts of the brain. It could be inferred that the higher degree of activation during the uncertainty condition in these areas goes back to the higher level of demand on attention and working memory during stimulus uncertainty. Furthermore, activity in the dorsolateral prefrontal cortex previously has been related to response conflict (e.g., [9]), which is also stronger during stimulus uncertainty than during certainty. Cortical areas exhibiting a differentiation in the opposite direction (higher activity during certainty than during uncertainty) were found mainly in orbitofrontal (BAs 10 and 11) and temporal areas (BAs 21, 22 and 37) related to shape perception and object recognition (see [19]). The fact that the differences in cortical activity are larger in number as well as in size between shape-certainty and uncertainty than between colour-certainty and uncertainty contradicts the hypothesis that these subjects simply neglected processing colour information during stimulus uncertainty. If this hypothesis were true, the opposite result would be expected: larger differences in cortical activity between colour-certainty and uncertainty than during shape-certainty and uncertainty.

Taken together, these results suggest that the subjects differ in their cognitive approaches during the condition of stimulus uncertainty, where they had to divide their attentional resources to monitor both stimulus dimensions concurrently. Where the “small uncertainty effect” group seemed to simultaneously carry out the same cognitive processes during uncertainty as during both certainty conditions, the “large uncertainty effect” group apparently restructured their cognitive approach during uncertainty. In the context of the psychophysical results of these subjects, it might be inferred that the cognitive processes underlying colour and shape discriminations reached a higher level of automation in the “small uncertainty effect” group and that it was therefore easier for these subjects to carry them out in parallel, without any cognitive restructuring of the task and with only a relatively small drop in performance. In contrast to this, the subjects exhibiting a relatively large uncertainty effect might have failed to automate the processes to the same extent, so that it was relatively harder for them to carry them out simultaneously. Because of the worse automation, they might have needed to put more effort in the discriminations and changed their cognitive approach during uncertainty, as suggested by the more pronounced differences in cortical activity between certainty and uncertainty conditions.

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A Neurocognitive Approach to Individual Differences in Reasoning

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Abstract

Recent investigations suggest that visuo-spatial processing is an essential component of reasoning. If so, then individuals with superior visuo-spatial skills should display enhanced performance in reasoning tasks and different patterns of reasoning-related brain activity than individuals with lower visuo-spatial abilities. We tested this hypothesis by using fMRI to examine how individual differences in visuo-spatial skill relate to reasoning performance and the underlying neuronal activity. The participants either solved spatial-relational reasoning problems or maintained the identical premises of the problems in working memory without making inferences. Visuo-spatial skill was subsequently assessed with a standardized neuropsychological test. In the absence of visual input (problems were presented in auditory format), activity was detected for both reasoning and working memory in a network comprising bilaterally the secondary visual cortex, the posterior cingulate cortex, and the medial anterior frontal cortex. The visuo-spatial skill index covaried positively with behavioural performance and negatively with activity of the precuneus for reasoning, but not for working memory. This pattern is consistent with a resource-based account of individual differences in cognitive abilities, and it confirms that visuo-spatial skills may determine how well individuals are able to reason.

Introduction

Reasoning is a fundamental aspect of human cognition. It underlies human intelligence, problem solving and decision-making, and it has shaped many aspects of our society including politics, law and science. While for this reason psychologists and philosophers have extensively studied the nature of human reasoning [8], relatively little is known about individual differences in this cognitive domain [31, 33].

The aim of the present investigation was to examine individual differences in reasoning from the perspective of cognitive neuroscience. Based on previous theories and findings, we were specifically interested in the relation between individual visuo-spatial skill and both reasoning performance and reasoning-related brain activation. Before describing an experiment in which we examined this question with functional magnetic resonance imaging (fMRI), we will further define the type of reasoning under study, and we will outline the theoretical basis of our approach. In the general discussion, we will link our results to a theory of individual differences in neuro-cognitive processing resources.

In the present study we focussed on relational reasoning with spatial content, which is common in our everyday lives, and is behaviourally well understood [8, 14]. This form of reasoning is required when we attempt to derive the relation between two objects on the basis of their relation to other objects. Consider the following problem:

> Peter is to the left of Paul.
> Mary is to the right of Paul.
> Which relation holds between Peter and Mary?

The first two sentences (called *premises*) of this problem describe a spatial layout, and a solution (called *conclusion*) can only be derived when jointly taking into account the information contained in both premises. Relational reasoning is thus a form of *deductive reasoning,* as it yields information that is true given the premises are also true.

The question of whether humans solve such problems by inherently linguistic or visuo-spatial processing has been the topic of a long-standing debate in cognitive psychology. On the one hand, proponents of theories based on formal rules claim that the human mind contains a set of *inference rules* that can be applied to linguistic representations of reasoning problems or their logical form [1, 27]. Reasoning is seen as the sequential construction of a chain of inferences that, in close similarity to linguistic processing, lead from the premises to the conclusion. On the other hand, theories based on mental models describe reasoning as the construction and manipulation of a visuo-spatial representation [12, 14]. This so-called *mental model* integrates the information described in the premises in a structurally isomorphic representation, and it is used to derive a conclusion and check it for consistency with the information contained in the premises. According to this account, the essential reasoning processes are inherently visuo-spatial, although basic linguistic processing is certainly needed to understand the premises and to imagine the state of the affairs.

Many behavioural investigations that have contrasted these two hypotheses have supported the mental models account. For example, it has often been demonstrated that reasoning problems consistent with several alternative mental models are more difficult to solve than problems that support only one solution [4, 7, 30, 36]. This fits the assumption that people actually construct and inspect all alternative models to solve the problem, while such a pattern should not emerge if people derived or evaluated a conclusion by a sequential chain of inferences. Model integration processes have also been demonstrated by showing that the premise presentation order may determine the order of the objects in the conclusion (*figural effect*; [11, 13, 19]), and that continuous premise orders are easier to solve than discontinuous orders (*continuity effect*; [19, 24]). Finally, dual-task-studies have demonstrated that reasoning performance deteriorates during the concurrent performance of simple visuo-spatial tasks, while it is not interfered with by verbal tasks [17, 20, 36].

In addition to these behavioural lines of evidence, the theory of mental models has recently been supported by the results of studies using functional neuroimaging methods [10, 21, 22]. The logic of these studies rests on the numerous findings that the encoding, maintenance, and manipulation of either verbal or visuo-spatial information in working memory engages neuronal structures that are also involved in either speech production and perception or visuo-spatial perception, respectively (overviews in [5, 32]). Thus, the repeated finding of activity in parieto-occipital cortices (and the lack of activity in left-hemisphere language regions) during relational reasoning supports the notion that at least this form of reasoning is carried out by the construction and manipulation of visuo-spatial mental models [10, 21, 22].

Based on this evidence, we tested in the present study whether individual differences in reasoning and reasoning-related neuronal activity can be accounted for by individual levels of visuo-spatial skill. We assumed that if visuo-spatial processing is indeed crucial to human reasoning, then individuals with superior visuo-spatial skills should perform better in reasoning tasks than individuals with lower visuo-spatial abilities. Moreover, we expected covariation of visuo-spatial skill with the activity level in brain areas devoted to visuo-spatial processing during reasoning, indicating a different taxation of the available processing resources.

In the study, fMRI was used to measure cortical activation while participants either solved relational reasoning problems or maintained the premises of the identical problems without making inferences as a working memory control task. All problems were presented acoustically in order to exclude the influence of reading processes or eye movements on visuo-spatial processing. After scanning, the individual level of visuo-spatial skill was assessed by means of a standardized neuropsychological test [35].

Methods

Participants: Twelve healthy male right-handed German native speakers (mean age 24.0 years, standard deviation 3.21 years) with normal or corrected-to-normal vision and normal audition participated in the experiment. All subjects gave their informed consent prior to the participation in the study, and all procedures complied with both University and Hospital ethical approval.

Materials: Twenty-four relational reasoning problems were constructed, using the following relations: left of, right of, overlaps from the left, overlaps from the right, meets from the left, meets from the right, inside, and outside (for a similar approach see [18, 21]). Subjects were required to evaluate the correctness of a conclusion presented after two premises. All problems described the spatial relation between coloured (“red”, “green”, “blue”, in German: “rot”, “grün”, “blau”) geometrical objects (“interval”, “bar”, and “rectangle”, in German: “Intervall”, “Band”, and “Rechteck”) in order to avoid effects of content or different ease of imagination for different objects. The three object terms were used as synonyms, and their position and colour association was fully permutated across the problems. An equal number of the problems were consistent with one, three, or five mental models, as successfully implemented in several previous studies [18, 25].

In the *working memory* control condition, the participants were presented with the identical premises of the reasoning problems. However, in place of the conclusions, one of the two premises was either repeated (valid) or presented with a different colour-object association for all three objects (invalid). The participants were instructed to judge whether the third sentence was an exact repetition of one of the premises, or modified in terms of its exact verbal content. Valid and invalid working memory problems employed the premises of invalid and valid reasoning tasks, respectively. Half of the problems repeated the first premise, and repetition of the first or the second premise was permutated across the problems consistent with a different number of mental models and the valid and invalid problems.

All sentences of the reasoning and working memory problems were recorded as audio files spoken in the same voice, edited for similar length (between 3.9 and 4.0 seconds), and normalized for loudness and peak gain.

Experimental procedures: In a study phase prior to instruction on the neuroimaging experiment and scanning, participants underwent a computerized training of the relational terms used in the problems. In order to reduce effects of novelty and strategy learning inside the scanner, participants then completed a training experiment using the identical conditions, problems, and time course as in the following neuroimaging experiment.

Inside the scanner (1.5 T Siemens VISION), the participants' head position was fixed in the head coil, and a mirror system was placed on the coil so that participants could see a projection screen mounted on the rear of the scanner bore. Visual stimuli were projected onto this screen using a video beamer. Reasoning and working memory problems were presented in auditory format via the headphones. The problems were presented in a blocked design with four separate runs containing six blocks each. The 24 blocks each contained one pair of problems, both of which belonged to one of the problem types (reasoning or working memory problems consistent with one, three or five mental models). The problem pairs were assigned to the four runs in random order for each participant, with the restriction that each run contained one pair of each problem type. Each block consisted of the presentation of six sentences (four seconds each) interleaved with silent breaks (six seconds each) during which scanning was performed. A rest interval of similar length (60 seconds) was included between two of the problem blocks. A white letter (drawn with a thin line of one pixel strength, visual angle two degrees) identifying the following problem pair as reasoning (S) or working memory (E) problem was displayed during the full course of the rest interval and the subsequent problem presentation. Participants responded to all problems by pressing two buttons of a MR-compatible response box with their right index and middle finger ("Yes"- and "No"-Responses, respectively) in the response interval after the presentation of each conclusion. Responses were recorded by the stimulus presentation software, and response times were automatically calculated from the end of the presentation of the conclusion. The presentation of each stimulus pair was synchronized with the TTL-pulse emitted by the scanner at the beginning of each functional measurement.

Functional images were collected with a gradient-recalled echo-planar imaging (EPI) sequence (30 parallel slices, TR 10.1 sec, TE 66 ms, FOV 256 mm x 256 mm, 2 mm x 2 mm in-plane resolution, 4 mm slice thickness). Seventy-four functional image volumes were collected in each of the stimulus runs. Two rest scans were collected in the beginning of each run in order for T1-effects to stabilize. These images were discarded from further analysis. In the end of the experiment, a functional EPI image with 40 slices and a sagittal T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) image of the entire brain (160 slices, TR 40 msec, TE 6 msec, FA 40°, FOV 256 mm x 256 mm, voxel size 1 mm x 1 mm x 1 mm) were acquired for purposes of co-registration and normalization during image preprocessing.

After the experimental session, participants were tested with the Block-Design Test (“Mosaiktest”) of the German equivalent to the Wechsler Adult Intelligence Scale (HAWIE-R, [35]).

Image processing and data analysis: All functional images were preprocessed and analyzed with the software SPM99 [37]. The functional images collected during one run were realigned and corrected for motion in the scanner. Translation and rotation corrections did not exceed 2.9 mm and 2.5 degrees for any run. Each subject’s anatomical image series and the mean functional images of all runs were then co-registered with the 40-slice EPI image volume collected in the end of the experiment. Parameters for spatial normalization were determined from each subject’s anatomical image volumes and applied to the respective functional image volumes. A new set of normalized functional images was created for which the original spatial resolution was interpolated to an isotropic voxel size of 3 mm^3. The realigned and normalized images were finally smoothed with a Gaussian kernel of 6 mm FWHM.

The hemodynamic response to the experimental cycle was modelled with a fixed-response box-car function convolved with the canonical hemodynamic response function. This function contained for each stimulus run the appropriately placed models of the hemodynamic response to the problems belonging to the six conditions (reasoning or working memory problems with one, three, or five possible mental models). Low frequency confounds were excluded from the model with a high-pass filter of twice an experimental run's length. The six sets of realignment parameters for each run were included in the model as covariates in order to account for undesired effects of head movement.

The parameter estimates derived from the function were used for statistical analysis of brain activation differences between the experimental conditions, using Statistic Parametric Maps (SPMs) and the framework of the General Linear Model (GLM) as implemented in SPM99. The following linear contrasts (subtractions) were specified: (a) reasoning versus rest, (b) working memory versus rest, (c) reasoning versus working memory and (d) working memory versus reasoning. The covariation of the brain activity during reasoning and working memory with the participants' visuo-spatial skills was examined with separate contrasts within the same model. For this purpose, the parts of the contrast vectors (a) – (d) that corresponded to one specific subject's images were multiplied with this subject's mean corrected block-design score (individual score – mean of all scores). Each of these new contrasts thus yielded the cortical areas that displayed a linear modulation of contrast-related activation by the subject's block-design score.

SPM(Z)s were thresholded at $p < 0.001$ uncorrected, and all inferences were performed at the cluster-level ($p < .05$ corrected for multiple comparisons across the whole brain, [9]). All coordinates used to describe the results correspond to the system originally introduced by Talairach and Tournoux [34]. For the behavioural data, all statistical analyses were performed at an alpha-level of .05 (two tailed).

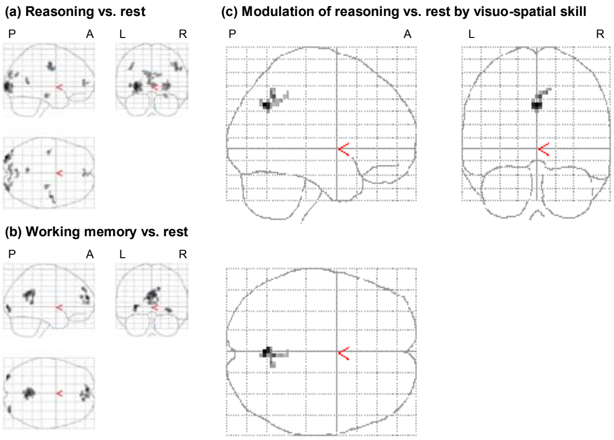
Results and Discussion

Behavioural data: The analysis of the performance measures showed that the reasoning problems were considerably more difficult than the working memory problems. The former were associated with a significantly lower mean percentage of correct responses (67.3 %, SD 13.4 % vs. 85.4 %, SD 15.8 %), Wilcoxon test, $z = 2.84$, $p < .01$, and with a significantly higher mean response latency (2474 ms, SD 650 ms vs. 2015 ms, SD 285 ms), Wilcoxon test, $z = 2.82$, $p < .01$. This pattern supports the notion that reasoning requires additional processes on top of maintenance in working memory.

The index of participants' visuo-spatial skills (block design score) was within the normal to superior range, mean value equivalent to an IQ of 114, standard deviation equivalent to 15 IQ-points, lowest value equivalent to an IQ of 103. Consistent with our hypothesis, the individual number of correct responses to the reasoning problems showed a significant positive correlation with the participants' block-design score, $r = 0.76$, $p < .01$. The mean response times to the reasoning problems showed only a non-significant negative correlation with this index, $r = -0.33$, $p = .29$. For the working memory problems, the corresponding correlations pointed in a similar direction, but both did not reach statistical significance, $r = 0.54$, $p = .07$ and $r = -0.47$, $p = .12$. This pattern suggests that participants with a high level of visuo-spatial skill were better at carrying out the cognitive operations specifically involved in reasoning, but not in the general encoding and maintenance of information in working memory.

Neuroimaging data: The neuro-cognitive processes active during reasoning and working memory were examined with the two contrasts reasoning versus rest and working memory versus rest. These contrasts revealed that despite the lack of task-related visual input, visuo-spatial processes were active during both experimental conditions. As displayed in *Figure 1* (left) and *Table 1*, reasoning was associated with activity in bilateral middle occipital gyri, bilateral posterior cingulate, bilateral medial frontal gyri, the precentral gyri of both hemispheres, and parts of the right parahippocampal gyrus. During the working memory condition, activation was found in a comparable network, which overlapped with that detected during reasoning in bilateral visual association cortex, bilateral posterior cingulate, and the bilateral medial frontal gyri. The occipital activation was more extensive for reasoning and also extended into the cuneus and precuneus. However, a subsequent conjunction analysis confirmed that activity was present in bilateral visual association cortex and posterior cingulate cortex during both conditions (for a detailed description see [28]).

The differences in neuronal activity during the two experimental conditions were examined with the contrasts reasoning versus working memory, and working memory versus reasoning. The results of this analysis are presented in *Table 2*. However, as they have been described and discussed in detail elsewhere [28], they will not be further considered here due to space considerations.



(a) Reasoning vs. rest

(b) Working memory vs. rest

(c) Modulation of reasoning vs. rest by visuo-spatial skill

Figure 1: SPM(Z)s for the contrasts (a) reasoning vs. rest, (b) working memory vs. rest and (c) the modulation of reasoning vs. rest by the subjects' mean corrected block-design score. SPMs were thresholded for height at Z = 3.09, and for spatial extent at p < .05 corrected for multiple comparisons across the whole brain. L = left hemisphere, R = right hemisphere, A = anterior end, P = posterior end.

The covariation of the task-related neuronal activity with the participants' level of visuo-spatial skill was examined with separate contrasts, as described in the section entitled "Methods". This analysis revealed that only the brain activation detected for the contrast *reasoning versus rest* was significantly modulated by the participants' visuo-spatial skill. *Figure 2* displays a cluster in the precuneus (peak coordinates x = 0, y = -62, z = 36, cluster size 33 voxels) that showed a negative covariation with the participants' block design score for this contrast. This indicates that that the higher the participant's visuo-spatial skill, the less activity elicited in that area during reasoning. We did not detect any such significant covariations for the contrasts corresponding to working memory versus rest, reasoning versus working memory, and working memory versus reasoning. These results suggest that reasoning, but not simple working memory, differentially taxes visuo-spatial processes in individuals with different levels of visuo-spatial skill.

General discussion

The present investigation examined individual differences in reasoning ability from the perspective of the underlying neuro-cognitive processes. As support for the hypothesized importance of visuo-spatial processing for reasoning, and consistent with previous studies [10, 21, 22], we found activation in visual association cortex during both relational reasoning and maintenance of the premises in working memory (for a detailed description and discussion of these results see [28]). The most important finding for the present study was that the individual reasoning performance covaried positively with an index of the participants' visuo-spatial skill, while the reasoning-related activation of the precuneus showed a negative covariation with this index. In other words, the higher a participant's visuo-spatial skill, the better his reasoning performance, and the less neuronal activation elicited in his precuneus by reasoning.

Table 1: Activation clusters detected for the contrasts reasoning versus rest and working memory versus rest. SPM(Z)s were thresholded for height at Z = 3.09 and for spatial extent at p < .05 corrected for multiple comparisons. Location, Z-score, and Talairach coordinates refer to the peak voxel of the cluster. L = Left, R = Right, B = Bilateral; ***p < .001, **p < .01, *p < .05, corrected for multiple comparisons across the whole brain.

Location		***Z* – score**	**Size**	**X**	**Y**	**Z**
Reasoning vs. rest						
L	Middle Occipital Gyrus	6.06	96 voxels***	-30	-93	2
R	Middle OccipitalGyrus	4.77	51 voxels***	33	-87	7
B	Cuneus	4.23	49 voxels***	-12	-86	26
L	Posterior Cingulate	4.53	18 voxels**	-6	-52	11
B	Precuneus	4.28	16 voxels*	-3	-73	23
L	Precentral Gyrus	4.77	43 voxels***	45	-10	39
R	Precentral Gyrus	4.40	17 voxels*	-39	-13	34
B	Medial Frontal Gyrus	4.02	25 voxels**	-6	53	8
R	Parahippocampal Gyrus	4.02	16 voxels*	27	-18	-14
Working memory vs. Rest						
L	Middle Occipital Gyrus	5.11	21 voxels*	-30	-90	5
R	Inferior Occipital Gyrus	4.18	21 voxels*	33	-88	-3
B	Posterior Cingulate Gyrus	4.69	126 voxels***	3	-54	22
B	Medial + Superior Frontal Gyrus	4.78	53 voxels***	-6	59	14
B	Medial Frontal Gyrus	4.06	35 voxels***	3	47	14

Table 2: Activation clusters detected for the contrasts reasoning versus working memory, and working memory versus reasoning. SPM(Z)s were treshholded for height at Z = 3.09, and for spatial extent at p < .05 corrected for multiple comparisons. Location, Z-score and Talairach coordinates refer to the peak voxel of the cluster. L = Left, R = Right, B = Bilateral; ***p < .001, **p < .01, *p < .05, corrected for multiple comparisons across the whole brain.

	Location	***Z* – score**	**Size**	**X**	**Y**	**Z**
Reasoning vs. working memory						
R	Anterior Cingulate Cortex	4.49	18 voxels*	9	14	38
L	Middle Frontal Gyrus	4.16	31 voxels***	-27	42	26
R	Middle Frontal Gyrus	4.14	54 voxels***	30	56	14
L	Insular Cortex	4.58	38 voxels***	-36	12	-1
R	Insular Cortex	4.49	31 voxels***	36	12	2
R	Posterior + Anterior Lobe	4.24	22 voxels*	18	-59	-15
Working memory vs. reasoning						
R	Inferior Parietal Gyrus	4.47	23 voxels**	36	-71	34
R	Precuneus	4.03	30 voxels**	15	-59	50
L	***Middle Temporal Gyrus***	4.67	23 voxels**	-42	-71	28

This pattern is in agreement with a recent account of individual differences in neuro-cognitive processing resources [26]. Resource models of neuro-cognitive processes posit that an increase in task difficulty should impose more demand on task-specific processing resources, and thus activate more strongly the neuronal structures carrying out the relevant cognitive processes. Such effects have already been demonstrated for various cognitive tasks, requiring sentence comprehension [15, 16], working memory [2, 29], or mental rotation [6]. However, resource models of cognitive processes also imply that a given task should elicit *less* activity in the relevant neuronal structures in individuals with a *high* level of skill, since less of the available individual processing resources are taxed. Precisely this relationship between skill level and neuronal activity was observed in a previous study of verbal and visuo-spatial sentence-picture verification [26], and in the present study of relational reasoning.

Viewed from this perspective, our results have two important implications. First, they confirm that our ability to reason depends crucially on visuo-spatial processing. That is to say, the observed visuo-spatial processes do not seem to be epiphenomena of other non-spatial reasoning operations. As an illustration, it may be argued that the correlation of behavioural reasoning performance with the block-design score merely reflects the common effect of general intelligence on both tasks. However, the covariation of visuo-spatial skill and reasoning-related activity of the precuneus, a structure with a well-established role in spatial cognition [3, 23], strongly supports that specifically visuo-spatial resources are taxed by reasoning. Second, our data support the notion that the individual ability to reason may be at least partially determined by the processing capacity of the neuronal structures carrying out elementary visuo-spatial processes.

However, the final acceptance of these two hypotheses must clearly await further investigation. Although the block-design test is obviously a more direct measure of elementary visuo-spatial skill than auditorily presented reasoning problems, correlational relationships never imply causality. Future studies should thus attempt to directly examine the dependence of reasoning on elementary visuo-spatial processing in patients with lesions in occipito-parietal structures, or by employing transcranial magnetic stimulation techniques (TMS). Moreover, the present study focussed on the relation between spatial-relational reasoning and visuo-spatial skill. It remains to be determined whether a similar pattern of results would emerge for explicitly non-spatial forms of reasoning, and whether other basic cognitive skills (e.g., verbal abilities) may also relate to reasoning performance and the underlying neuronal processes. Any of these proposed investigations would advance our understanding of how neuro-cognitive resources may determine an individual's ability to reason.

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IV.

Individual Differences in Language Functions

ERP Studies on the Role of Individual Differences in Working Memory Span for Language Comprehension

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Abstract

The role of working memory for comprehension and production of complex sentences has been highlighted in the past two decades. In particular, individual differences in the capacity to understand complex sentences, such as object relative clauses, have been attributed to the variable working memory capacity of different subjects. In this contribution, the neural correlates of working memory usage during sentence reading are illustrated by several event-related brain potential studies. These studies show that the increased working memory load imposed, for example, by object versus subject relative sentences, or by sentences starting with the temporal term "before" gives rise to a tonic negativity over the left fronto-temporal scalp. Moreover, at the points of working memory encoding and retrieval, phasic left temporal negativities are seen. These size of these effects is shown to vary as a function of individual verbal working memory span.

Electrophysiological studies thus reveal important information on the use of working memory during language comprehension.

Menschliche Stimme entströmte dem Schrein, männlich, weich und gewaltig auf einmal, vom Orchester begleitet, ein italienischer Bariton berühmten Namens, – und nun konnte durchaus von keiner Verkleinerung und Entfernung mehr die Rede sein: das herrliche Organ erscholl nach seinem vollen natürlichen Umfang und Kraftinhalt, und namentlich wenn man in eines der offenen Nebenzimmer trat und den Apparat nicht sah, so war es nicht anders, als stände dort im Salon *der Künstler in körperlicher Person, das Notenblatt in der Hand, und sänge.*

Introduction

Most readers will agree that the preceding sentence, taken from Thomas Mann's *Der Zauberberg* ("The Magic Mountain"), is difficult to understand, especially when it is heard rather than read. But just what factors make it so difficult to understand? Traditionally, linguists and psycholinguists have characterized sentences in terms of their syntactic complexity as revealed by the linguistic analysis. While it is intuitively obvious that syntactically more complex sentences tax the language processing system to a greater degree, it has been difficult to pinpoint exactly why this is the case. A rather recent development attributes the differences in processing difficulty to the differing demands that sentences pose on working memory [3, 8, 9, 24]. Perhaps even more interesting and related to the general spirit of the current volume are findings that suggest that individual differences in working memory capacity can shape a subject's ability to understand a complex sentence [8, 10].

In this contribution, after giving a brief introduction into the role of working memory during sentence comprehension, I will survey some of our own electrophysiological studies in this domain highlighting the effects of individual differences in working memory span.

Replacing the old concept of a unitary short-term memory store, working memory refers to a brain system that encompasses both, storage and computation of information. In his popular model Baddeley [1] considers working memory to be composed of a central executive system, supported by "slave systems" dedicated to specific types of information. Accumulating evidence implicates the lateral frontal cortex in working memory functions. Current models on its functional organization draw an anatomical distinction between the dorsolateral and the ventrolateral frontal cortical regions. They pursue two different lines of inquiry and differentiate either in terms of domain- or process-specificity [19, 20]. According to the principle of domain-specificity, the dorsolateral frontal regions subserve memory functions for spatial material while the ventrolateral regions deal with non-spatial representations [6]. The alternative model proposes that instead of the kind of information being processed, the type of processing accounts for the functional organization of the lateral frontal cortex [19, 20, 21]. The ventrolateral frontal lobe regions support a primary level of processing, responsible for the active organization of sequences of responses. Manipulation and monitoring of information that goes beyond this primary stage of processing is performed by regions of the dorsolateral cortex. In summary, it is widely accepted that working memory is a complex multicomponent cognitive structure. However, the exact components, functions and their relation to different brain regions remain to be specified.

Just and Carpenter's [6, 8] capacity constraint model of language processing [9] establishes an explicit link between working memory capacity and sentence comprehension. Working memory is viewed as a limited pool of cognitive resources, which are competed for by storage as well as processing functions. Crucially, working memory capacity constrains language comprehension in their model. Thus, the understanding of a sentence is influenced by an individual's working memory capacity as well as the demands that the comprehension task imposes on working memory resources. In other words, inter-individual variation in working memory capacity accounts for differences in language comprehension between high and low span readers [10]. On the other hand, a greater demand placed on working memory, for example by increasing the syntactic complexity of a sentence structure [9] or by superimposing an extrinsic memory load, interferes with sentence comprehension. Thus, if resource demand exceeds the individual supply, then sentence comprehension is predicted to deteriorate. Just and Carpenter have presented several pieces of evidence in support of their concept of a unitary verbal working memory by demonstrating interaction effects between syntactic complexity, individual working memory capacity and extrinsic working memory load. While this model has been challenged and refined recently [3, 24], it served as a stimulus and framework for the event-related brain potential (ERP) studies reported in this chapter.

ERPs as an on-line measure with a high temporal resolution may provide information on the use of working memory during language comprehension that goes beyond the standard comprehension scores used in working memory research. While a phasic left anterior negativity has been linked to retrieval of information from working memory [7, 11, 12], we will focus on more temporally extended effects over the left fronto-temporal scalp in this chapter [7, 11, 16]. In an early study King and Kutas [11] contrasted the ERPs evoked by reading subject- and object-relative clauses as given in (1a) and (1b):

(1a) The reporter who harshly attacked the senator admitted the error.
(1b) The reporter who the senator harshly attacked admitted the error.

Example (1a) contains a subject relative (SR) clause, i.e., a relative clause that uses the subject of the main clause also as the subject of the relative clause. Object relative clauses (OR, 1b), on the other hand, that use the subject of the main clause as their object. OR, are more difficult and time consuming to comprehend, because the role of the "filler" at the beginning of the object relative clause cannot immediately be defined. Rather, it has to be retained in working memory, waiting for its assignment at the location of the "gap" later on in the course of the sentence.

When clause level ERPs for the two conditions were compared, a left-preponderant relative frontal negativity for the OR sentences was observed during the early portion of the relative clause. As in the OR sentences the noun phrase of the relative clause (e.g., the senator) has to be maintained in working memory until the subject encounters the appropriate verb, while in the SR sentences the main clause subject can be assigned also as the subject of the relative clause, King and Kutas [11] interpreted the clause level negativity for the OR sentences in terms of the differing working memory loads of the two sentence classes. This interpretation gained further support by a comparison based on the splitting of their subjects into two groups, one having good comprehension scores for the relative clauses and the other having poor comprehension scores. The latter group showed a largely reduced clause level negativity. In a related ERP study using the same materials presented as connected speech, Muller, King and Kutas [17] could replicate these general effects with a pronounced negativity for the relative clauses of the OR sentences relative to the SR sentences. They also observed a larger OR/SR difference for the subjects with better comprehension scores.

In the King and Kutas [12] study the ERPs were also studied on the single word level. This comparison, however, is made somewhat difficult by the fact that in English the word order in OR and SR-type relative clauses differ. There are two positions in the relative clause (position 4 and 6, see (1a) and (1b)) at which adverbs and definite articles were contrasted. Only at position 6 (adverb in OR, article in SR) an N400-like activity was observed for the adverbs. The second difference between OR and SR sentences was seen at the verb of the main clause ("admitted" in examples 1a and 1b), where OR sentences were associated with a left anterior temporal negativity resembling the previously reported LAN effect [12].

The word order problems that are a feature of English materials can be overcome by turning to other languages. In German, for example, SR and OR can be differentiated by case-markings of the relative pronouns and definite articles, as illustrated in examples (2a) and (2b) that represent translations of (1a) and (1b):

(2a) SR: Der Reporter, der den Senator rüde angegriffen hatte, gab den Fehler zu.
(2b) OR: Der Reporter, den der Senator rüde angegriffen hatte, gab den Fehler zu.

Münte, Schwirtz, Wieringa, Matzke and Johannes [15] visually presented German sentences of the above structure to young subjects and could replicate the extended negativity for the OR clauses, albeit with a smaller amplitude than the King and Kutas [11] study. No reliable differences between SR and OR sentences were seen for the word level ERPs. A second group in the Münte et al. [15] study consisting of native speakers of English (mainly British military personnel stationed in Germany) viewing English sentences, however, did show the word-level differences of the King and Kutas study and the negativity for OR sentences for the early portion of the relative clause. This suggests that at least some of the word level effects in King and Kutas [11] can be attributed to the peculiarities of English word order.

In the Münte et al. [15] study, all nouns serving as subjects of the main clauses were of masculine gender to avoid a parsing ambiguity that can arise in the case of feminine gender nouns. Consider for example the following sentence:

(3) Die Reporterin, die$_{\text{[feminine, nom.? or acc.?]}}$ die$_{\text{[feminine, nom.? or acc.?]}}$ Senatorin$_{\text{[feminine, nom.? or acc.?]}}$ rüde angegriffen hatte, gab den Fehler zu.
The reporter$_{\textit{[feminine, sing.,]}}$*, who*$_{\textit{[feminine, nom.? or acc.?]}}$ *the*$_{\textit{[feminine, nom.? or acc.?]}}$ *senator*$_{\textit{[feminine, sing., nom.? or acc.?]}}$ *harshly attacked has, admitted the error.*

As accusative and nominative forms of the relative pronoun, definite article and relative clause nouns are identical for the feminine gender, it is impossible to unambiguously assign roles to the nouns in this sentence and pragmatic information must be used. If a feminine gender noun as the subject of the main clause is combined with a plural noun in the relative clause, the global parsing ambiguity of sentence (3) is reduced to a local ambiguity:

(4a) SR: Die Reporterin, die$_{\text{[feminine, nom.? or acc.?]}}$ die$_{\text{[feminine, nom.? or acc.?, plural, nom.? or acc.?]}}$ Senatoren$_{\text{[masculine, plural, nom.? or acc.?]}}$ rüde angegriffen hatte, gab den Fehler zu.
The reporter$_{\textit{[feminine, sing.,]}}$*, who the senators*$_{\textit{[plural, nom.? or acc.?]}}$ *harshly attacked has*$_{\textit{[sing.]}}$ *admitted the error.*

(4b) OR: Die Reporterin, die$_{\text{[feminine, nom.? or acc.?]}}$ die$_{\text{[feminine, nom.? or acc.?, plural, nom.? or acc.?]}}$ Senatoren$_{\text{[masculine, plural, nom.? or acc.?]}}$ rüde angegriffen haben, gab den Fehler zu.
The reporter$_{\textit{[feminine, sing.,]}}$*, who the senators*$_{\textit{[plural, nom.? or acc.?]}}$ *harshly attacked have*$_{\textit{[plural]}}$*, admitted the error.*

In this case the role assignment for the nouns can be carried out at the position of the auxiliary verb in the relative clause (hatte “has”, SR;

haben “have”, OR). This interesting feature of the German language has been exploited previously in ERP studies by Mecklinger, Schriefers, Steinhauer and Friederici [14] and Friederici, Steinhauer, Mecklinger and Meyer [5]. While these earlier experiments used right-branching relative clauses and focused on word level ERPs, we performed a study using center-embedded ambiguous and unambiguous SR and OR clauses in German as shown in example (4). The ERP analysis primarily focused on the across sentence averages. As in previous studies, subjects (n = 18) were classified according to their performance in the reading span task of Daneman and Carpenter [4]. The critical stimuli consisted of 200 German sentences containing relative clauses. Of each sentence four versions were generated:

(5a) masculine, SR
Der Agent, der die Spione enttarnt hat, kramte in den geheimen Akten.
The agent$_{\textit{[masculine]}}$ *who*$_{\textit{[nominative case, masculine]}}$ *the*$_{\textit{[plural amb.]}}$ *spys discovered has scanned the secret files.*

(5b) masculine, OR
Der Agent, den die Spione enttarnt haben, kramte in den geheimen Akten.
The agent$_{\textit{[masculine]}}$ *who*$_{\textit{[accusative case, masculine]}}$ *the spys*$_{\textit{[plural amb.]}}$ *discovered have scanned the secret files.*

(5c) feminine, SR
Die Agentin, die die Spione enttarnt hat, kramte in den geheimen Akten.
The agent$_{\textit{[feminine]}}$ *who*$_{\textit{[feminine amb.]}}$ *the spys*$_{\textit{[plural amb.]}}$ *discovered has*$_{\textit{[sing.]}}$ *scanned the secret files.*

(5d) feminine, OR
Die Agentin, die die Spione enttarnt haben, kramte in den geheimen Akten.
The agent$_{\textit{[feminine]}}$ *who*$_{\textit{[feminine amb.]}}$ *the spys discovered have*$_{\textit{[plural]}}$ *scanned the secret files.*

These sentences and 400 filler sentences of different length were presented word-by-word (duration 300 ms, onset asynchrony 500 ms) in yellow letters against a dark blue background in the middle of a computer-screen. After each sentence a short comprehension question requiring a yes/no button response was shown. Multichannel-ERPs (word and clause-level) were obtained. Waveforms were quantified by mean amplitude measures relative to a prestimulus baseline. Statistical analysis was performed by Analysis of Variance (ANOVA). Results for the reading span test ranged between 2.4 and 6.0 (mean 3.98, median 4.1). For the comprehension questions (feminine SR 87.2 % ± 12.2, OR 75.2 % ± 15.7, masculine SR 86.7 % ± 12.9, OR 83.0 % ± 13.0) main effects of sentence type (SR/OR, $F_{(1,17)} = 24.89$, $p < 0.0001$), gender of the main clause subject ($F_{(1.17)} = 6.65$, $p < 0.02$) as well as an interaction gender by type ($F_{(1,17)} = 12.01$, $p < 0.003$) were obtained. This suggests that participants used a subject first strategy in the ambiguous sentences with a feminine subject. *Figure 1* shows the grand average ERPs for some of the 29 scalp sites for the masculine and feminine sentences beginning with the onset of the relative pronoun. The masculine SR and OR sentences were differentiated at several points in the relative clause. The ERPs to the accusative relative pronoun “den” was associated with a more negative waveform starting about 300 ms after word-onset over frontal sites which was more prominent at right hemisphere sites (anterior set, 300 to 500 ms, main effect type $F_{(1,17)} = 1.8$, n.s., type by hemisphere $F_{(1,17)} = 9.05$, $p < 0.008$). Also, at the position of the auxiliary verb, SR sentences were associated with a positivity, the ERPs to the OR sentences stayed more negative. This effect was rather widespread and attained significance for both electrode sets (300 to 500 ms, anterior, $F_{(1,17)} = 4.69$, $p < 0.05$; posterior, $F_{(1,17)} = 8.43$, $p < 0.01$). In *Figure 2* the same comparison is shown for the sentences with a feminine subject. No systematic differences between the SR and OR conditions can be seen for the word positions up to the auxiliary. At the auxiliary the OR sentences, paralleling the effects in the masculine conditions, stayed more negative than the SR sentences. However, in the feminine sentences this effect seemed less widespread than in the masculine condition (300 to 500 ms, anterior $F_{(1,17)} = 1.98$, n.s.; posterior, $F_{(1,17)} = 8.20$, $p < 0.015$). No effect was seen for the main clause verb in the sentence level ERPs. Of particular relevance for our present purposes is the comparison of subjects with lower and higher scores of working memory span. Figure 2 shows that the more demanding feminine sentences led to comparable slow potential effects in low score and high score subjects, whereas the masculine sentences, in which syntactic roles could be unambiguously assigned early on, showed a differential effect. While in low score subjects no difference was seen for feminine and masculine sentences, masculine sentences in high score subjects were less negative than feminine sentences. This suggests that working memory resources of the low score subjects are taxed to their maximum by both, masculine and feminine sentences, while resources in the high score subjects exceed the demand posed by the masculine sentences.

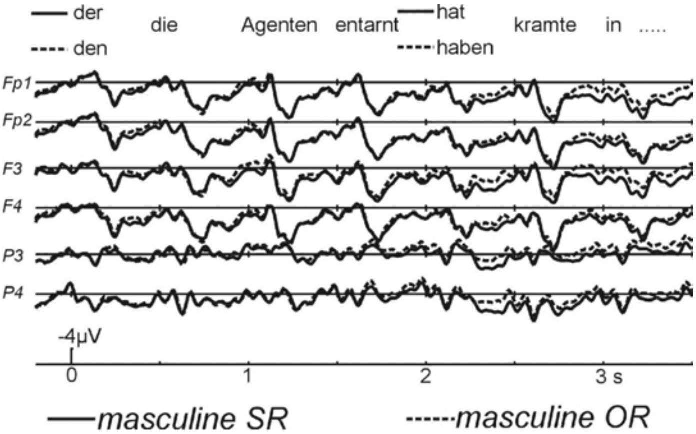

Figure 1: Across sentence grand average ERPs of “masculine” relative clauses. Object relative clauses are associated with a phasic negativity to the relative pronoun at frontopolar and frontal sites. At the auxiliary another phasic negativity is seen in for the object relative clauses probably associated with the retrieval of the filler from working memory. Unpublished data from Münte, King, Bartels and Kutas.

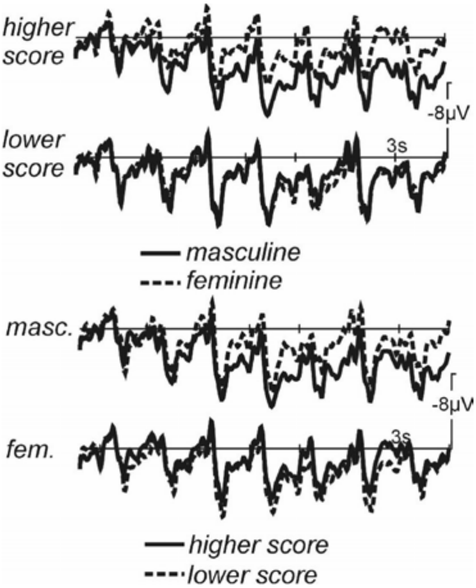

Figure 2: ERPs to masculine and feminine relative clauses (left frontal site). Subjects with low working memory scores do not show a differential effect for unambiguous masculine and ambiguous feminine relative clauses, whereas high score subjects show a relatively more negative waveform for the ambiguous sentences. Unpublished data from Münte, King, Bartels and Kutas.

As illustrated by the examples above and numerous additional studies in the literature, the SR/OR sentence has been the working horse of research into the individual differences of working memory in sentence comprehension. This type of material has certain problems, especially in the English language. We therefore have been looking at alternative paradigms that would allow such investigations without some of the drawbacks (e.g., word order variation in English) of SR/OR sentences [16]. For example, sentences starting with the temporal terms *before* or *after* afford the linguistic freedom to express a series of events in any order.

(6a) After the scientist submitted the paper, the journal changed its policy.

(6b) Before the scientist submitted the paper, the journal changed its policy.

In sentences starting with "After" the order of events in the sentence mimics the actual order in real time, while in sentences starting with "Before" this is not the case. Previous investigations, including acquisition studies in children ([22] and a study in Parkinson's patients [18] suggest that this linguistic freedom is not without cost, probably because sentences wherein events are presented in other than their actual order of occurrence tax working memory resources. We tested whether this indeed is the case by the recording of ERPs. Stimuli consisted of 120 critical and 480 filler sentences presented in random order, one word at a time (200 ms duration, 500 ms between word onsets) in yellow in the middle of a video monitor. The critical sentences had the following structure: Before/After the noun1 verb-ed the noun2, the noun3 verb-ed the noun4 ... *Before* and *after* versions of each sentence were shown to half the 24 right-handed English speaking volunteers (11 women, mean age 21.7 years). Each sentence was followed by a question that required a yes/no button press response. Subjects were grouped into high, medium, and low working memory span groups (each n = 8) according to their score on the Daneman and Carpenter test. Cross-sentence ERPs were obtained for 6144 ms epochs starting 300 ms before onset of the sentence and were quantified by mean amplitude measures for clause 1 (500 to 3000 ms) and clause 2 (3000 to 5500 ms) relative to baseline followed by ANOVA statistics.

Both sentence types consist of an initial subordinate clause and a subsequent main clause, each describing a distinct event that is neither logically nor causally related to the other (e.g., *Before/After the psychologist submitted the article, the journal changed its policy*). In other words, the event in each clause could easily be understood without reference to the other. However, our experience tells us that temporal conjunctions often draw attention to the sequence of events in a discourse [23]. *Before* and *after* highlight different points of the sequence: *after* signals that events will be expressed in their actual order of occurrence while *before* signals that events will be expressed in reverse order. Thus, it is conceivable that in a sentence beginning with *after*, the first clause can be integrated in a message level representation as soon as it ends. By contrast, in a sentence beginning with *before*, the first clause cannot be integrated in a message level representation until after the second clause. This clearly should place more demands on working memory. If this were true, the processing of both sentence types should be subject to individual differences in working memory capacity and processing speeds similar to the SR/OR sentences discussed above. Moreover, the greater WM load entailed in the processing of Before sentences should be reflected in greater negativity over left frontal scalp sites.

As *Figure 3* illustrates, *before* and *after* indeed are associated with very different brain potentials in that the response to *before* sentences is significantly more negative than that to *after* sentences beginning 300 msec after the presentation of the first word (main effect of sentence type, clause 1: $p < 0.005$, clause 2: $p < 0.003$). The left laterality of this effect is reflected in a sentence type by site by hemisphere interaction (clause 1: $p < 0.001$, clause 2: $p < 0.001$). The difference between the two sentence types is especially pronounced in the group of subjects with the highest working memory scores, while it is virtually absent in subjects with low scores. Working memory scores and the left frontal negativity, quantified as the mean difference between before and after sentences, were significantly correlated ($r = 0.783$, $p < 0.0001$). While in most previous studies of working memory load the order of lexical items, and, in some cases, structural complexity were confounded, this was not the case in the present study, as the critical sentences differed only in the initial lexical item. Thus, the prolonged ERP difference between *before* and *after* sentences cannot be attributed to differences in lexical characteristics, semantic features, or structural differences of the sentences. Rather, they differ in the long-term memory information they access and the ensuing utilization of working memory resources. The data specifically suggest that the WM resources of readers with low working memory spans are taxed even by *after* sentences, which elicit as much negativity as *before* sentences.

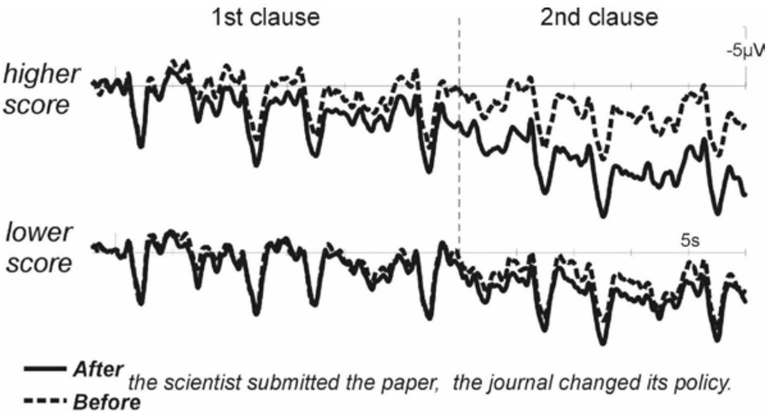

Figure 3: Grand average across sentence ERPs to sentences with initial temporal terms (left frontal sites). Only high score subjects show a differential effect for the two sentence classes: the more demanding sentences are associated with relatively more negative waveforms. The low working memory score subjects only show a rudimentary effect. Redrawn after data from Münte et al. [16].

Linguistic freedom, as exemplified by the before/after sentences above, is also supported by other language devices [13]. Owing to its relatively rich morphological system, German, for example, allows a relatively free word order, in other words, it permits a speaker to diverge from the standard SVO word order. This is exemplified by the following sentences:

(7a) Der begabte Sänger entdeckte den talentierten Gitarristen.
“The gifted singer (Masc. Nom.) discovered the talented guitar player (Masc. Acc.).”

(7b) Den begabten Sänger entdeckte der talentierte Gitarrist.
“The gifted singer (Masc. Acc.) discovered the talented guitar player (Masc. Nom.).”
>> meaning: The talented guitar player discovered the gifted singer.

(7c) Die begabte Sängerin entdeckte den talentierten Gitarristen.
“The gifted singer (Fem. Nom.? Acc.?) discovered the talented guitar player (Masc. Acc.)”.

(7d) Die begabte Sängerin entdeckte der talentierte Gitarrist.
“The gifted singer (Fem. Nom.? Acc.?) discovered the talented guitar player (Masc. Nom.).”
>> meaning: The talented guitar player discovered the gifted singer.

Sentences (7a) and (7c) are in standard word order, while (7b) and (7d) use a non-canonical, yet entirely grammatical word order. In (7a), the first noun-phrase is unambiguously nominative. Therefore, the syntactic and semantic role of the phrase can be assigned as it is read. In (7b), the reader first encounters an accusative noun-phrase. Here, role-assignment cannot be properly performed and the first noun-phrase has to be kept in working memory until subject and verb are encountered. Examples (7c) and (7d) represent an additional difficulty. As in the SR/OR study referred to above, the initial feminine noun phrases are compatible with either a “subject first” or an “object first” interpretation. Previous studies [2], however, indicate that a “subject first” reading will be preferred. Indeed, a survey of 200 sentences with initial feminine noun phrases derived from a major corpus of the German language (Cosmas, Institut für Deutsche Sprache Mannheim, 379 million words, http://corpora.ids-mannheim.de/~cosmas/) suggests that this is a useful heuristic as in 186 the ambiguous noun-phrase turned out to serve as the subject. Thus, in sentence (7c) the subject should experience no difficulty upon the encounter of the second noun phrase as this corroborates the initial interpretation. If the object interpretation becomes necessary as in sentence (7d), a reanalysis of the input would be required. The prediction for the ERPs with respect to the sentence material was that sentences with non-canonical word order should, due to a higher working memory load, give rise to a left fronto-central negativity at the beginning of the sentence (nominative article “der” vs. accusative article “den”) and in addition a left anterior negative shift in the across sentence averages. Canonical and non-canonical sentences with ambiguous feminine noun phrases in the first position should show no electrophysiological difference at first article position ("die" vs. "die") and over the subsequent words up to word position 8. There, a nominative ("der") article renders the preferred interpretation (subject first) impossible and a process of reanalysis should become necessary. Therefore, we expected a P600 for a nominative vs. the accusative article at word position 8. These predictions were confirmed in a group of 22 German-speaking students who viewed a set of 240 experimental sentences, 60 sentences of each type, on a video-monitor. To increase working memory load, an additional prepositional phrase after the verb (e.g., während der Weihnachtsfeier, *in the course of the christmas celebration,* nach der Prüfung, *after the examination*) was inserted in all sentences. *Figure 4* depicts the across sentence averages for sentences with initial masculine (unambiguous) and initial feminine (ambiguous) noun phrases. In keeping with the results from the SR/OR study reported above, initial accusative (i.e., direct object) masculine noun phrases elicited a ramp-like negativity over the frontal scalp compared to sentences starting with masculine nominative (i.e., subject) noun phrases (500 to 1500 ms, $F_{(1,21)} = 3.7$, $p = 0.068$; 1500 to 2500 ms, $F_{(1,21)} = 8.1$, $p < 0.01$; 2500 to 3500 ms, $F_{(1,21)} = 10.7$, $p < 0.004$). This effect is also similar to the one found with the before/after paradigm. As sentences with initial feminine noun phrases could not be differentiated until the disambiguating auxiliary verb, no difference was seen between subject first and object first sentences. The fact, that the overall negative level of these sentences resembled that of the masculine subject first sentences is in line with numerous studies indicating that German subjects adopt a default subject first interpretation. This is further corroborated by a posterior positivity, the P600, seen for non-canonical feminine sentences at the disambiguating verb (800 to 1000 ms relative to onset of auxiliary, $F_{(1,21)} = 9.8$, $p < 0.005$).

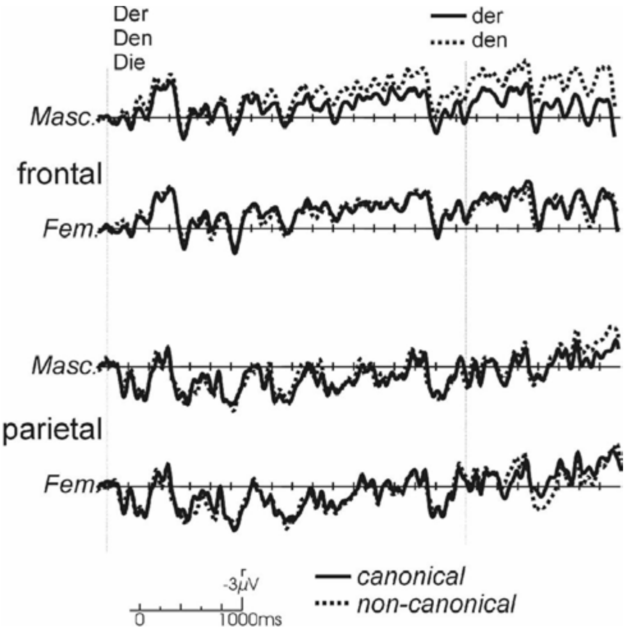

Figure 4: Grand average across sentence ERPs for canonical and non-canonical transitive sentences. Sentences with non-canonical (object-first) **word-order were associated with a relatively more negative waveform at frontal sites indexing the higher working memory demand of these sentences.

In conclusion, the present electrophysiological investigations underscore once again the role of working memory in language comprehension. In particular, effects of working memory usage could be demonstrated under circumstances, in which critical conditions differed only minimally (e.g., *Der* vs. *Den*, and *Before* vs. *After* as initial words of otherwise identical sentences). The data-sets reviewed in the present contribution converge in pinpointing the left lateral frontal region as supporting verbal working memory. However, they do not yet speak to the proposed role of different subdivisions of frontal cortex for maintenance of information and manipulation of information [19, 20]. As the topographical resolution of the ERP method is limited, the studies need to be complemented by functional imaging experiments.

With regard to the role of individual differences in verbal working memory, it could be clearly demonstrated that the development of the tonic left anterior negativity as a function of working memory usage is influenced by an individual's verbal memory span.

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Processing Inflectional Forms in a Morphologically Limited Language: Evidence from Mono- and Bilingual Speakers

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Abstract

This psycholinguistic experiment studied morphological processing in Swedish and compared the results of Swedish monolinguals to those of Finnish-Swedish early bilinguals. The aim was to replicate an earlier finding by Portin and Laine [19]: they found that in visual lexical decision, Swedish monolinguals processed tri-morphemic Swedish nouns as full entities (as indicated by equally fast reaction times on the tri-morphemic nouns and uninflected control nouns), while Finnish-Swedish bilinguals decomposed the stem from the inflectional affixes during the process (as suggested by slower reaction times on the tri-morphemic nouns than on the uninflected control nouns). The present experiment, which employed a more up-to-date and far larger lexical corpus than the one used by Portin and Laine, revealed a processing cost (longer reaction times) on tri-morphemic inflected nouns for both mono- and bilinguals, suggesting that both groups employed the decomposition route with the tri-morphemic inflected Swedish nouns. Thus in contrast to previous findings in Swedish, even the monolingual language-users may resort to morphological decomposition in this morphologically limited language. It is concluded that the structure of the language and the frequency range employed may be important determining the processing route used.

Introduction

A central issue in research on lexical processing is the way morphologically complex word forms such as PLAY+ER+S are represented and accessed in the mental lexicon. A number of theoretical models have been put forth, ranging from full-form representations for all possible morphological variants [4] to morpheme-based representations where all meaning-bearing constituents (e.g., PLAY, -ER, -S) are stored separately [21]. Many current models on morphological processing can be characterized as hybrids, i.e., they combine features of full form storage and morphological decomposition [e.g., 6, 16, 20].

Does the overall structure of the language we speak affect the way we process multi-morphemic words in that language? It seems evident that in morphologically rich languages like Finnish or Turkish, which entail myriads of possible inflectional forms, morphological decomposition must take place [7]. Indeed, experimental evidence from Finnish has consistently indicated a processing cost for inflected nouns when pitted against otherwise matched uninflected nouns in visual lexical decision [6, 9, 10, 13, 16], eye movement recording during reading [8], and aphasic reading performance [11, 12]. On the other hand, evidence for morphological decomposition appears less consistent in morphologically limited languages. For example, visual lexical decision results obtained in normal monolingual Swedish speakers have failed to show differences between inflected vs. uninflected word forms [1, 19]. This has been interpreted as evidence for storage of morphologically complex words as full entities when their rates in a language are limited. An exception to this would be bilingual speakers: Portin and Laine [19] reported a significant processing cost for Finnish-Swedish bilinguals when they made lexical decisions for inflected vs. uninflected Swedish nouns. A possible explanation for this could be a spill-over of morphological decomposition strategy from the other language (Finnish) and/or less practice in a language.

In the present experiment, we set out to test the assumption based on Portin and Laine [19] that in a morphologically limited language like

Swedish, monolingual but not bilingual speakers utilize full form representations when recognizing inflected forms. We were prompted to perform this replication attempt due to the relative lack of previous relevant experiments, and also because we recently got access to an extensive Swedish lexical data base (the unpublished Göteborgs-Posten lexical database consisting of 24.2 million word tokens) which allows a good control over various frequency factors known to affect word recognition. Following Portin and Laine [19], both mono- and bilingual (Finnish-Swedish) speakers of Swedish were subjected to a visual lexical decision experiment.

Method

Materials: Two 20-item word lists were collected for the lexical decision experiment from the Göteborgs-Posten lexical database using a computerized search program [14]. One of the lists included only uninflected Swedish nouns and the other list only inflected tri-morphemic Swedish nouns with a stem, the definite and the genitive case ending (e.g., *pojke+n+s* = "boy" + definite marker + genitive marker: "the boy's"). The word lists were matched for a number of factors, which can affect word recognition: lemma frequency, surface frequency, bi-gram frequency, word length in letters and morphological family size (i.e., the number of derivations and compounds incorporating the stem). The characteristics of the two target word lists are presented in *Table 1* (see the Appendix for the word lists). The two lists were also subjected to abstractness/concreteness ratings by six native speakers (different from those participating in the experiment), who estimated the abstractness/concreteness levels of each word form using a 5-point scale. No significant difference emerged from this comparison. Finally, to prevent any effects that might be caused by the excellent Finnish knowledge of the bilingual group, no orthographically close Finnish cognates were selected into the word lists (our criterion for "non-cognates" was that the word forms had to differ from their Finnish translation equivalents by at least two letters).

Table 1: Properties of target words

Word Category	WL	SF	LF	BiF	FS
Uninflected	6.5	8.9	166	783	245
Inflected	6.5	8.2	174	780	301

Mean Values of Word Length (WL) in letters, Surface Frequency (SF), Lemma Frequency (LF), Bigram Frequency (BiF) and Family Size (FS) for the word groups. Surface and Lemma Frequency are reported as frequencies per million.

In sum, the experiment included two 20-word sets of nouns, yielding altogether 40 target words. 193 filler words (133 Swedish nouns in nominative singular form and 60 nouns in inflected, definitive singular form) were also included.

In addition to the target words and fillers, 233 non-words (50 % of the total number of items) were included in the experiment. They were constructed by changing one to three letters of real Swedish words, so that the phonotactic rules of Swedish were not violated. Hundred of these items also had endings similar to the affixes of real words (e.g., the non-word "*kjalens*" could be seen as a non-word stem "*kjale*" + definitive marker "*-n*" + genitive marker "*-s*"). The "inflected" non-words included either definitive or both definite and genitive endings.

Participants: Two groups of university students (from the University of Stockholm, Sweden, and the only Swedish-speaking university in Finland, Åbo Akademi University) participated in the experiment after giving their written informed consent. None of them reported of reading difficulties, and everyone had normal or corrected-to-normal vision. The first group consisted of 18 participants who were all early Swedish monolinguals (14 females, 4 males), and the second group consisted of 20 early Finnish-Swedish bilinguals (11 females, 9 males). The monolinguals had learned only the Swedish language before school-age (i.e., before the age of seven). The bilinguals, on the other hand, could speak both Finnish and Swedish already at that age. The monolingual group consisted mostly of students having either various Indo-European languages or simultaneous interpreting as their major. Seven of the bilingual participants were also students majoring in philology while the others were students of various subjects. The age range of the monolingual group was 24 to 39 years (mean, 29.8; SD, 4.99) while that of the bilingual group varied between 19 and 34 years (mean, 23.7; SD, 3.65). The difference in age was significant between groups ($t(36) = 4.37$, $p <. 001$). In the Swedish translation of Edinburgh Inventory [17], 14 of the monolinguals reported being completely or mostly right-handed and four reported being left-handed. The bilingual group, in turn, consisted of 17 right-handers, two left-handers and one ambidextrous participant.

The language background of both groups was investigated by a questionnaire. The participants estimated their language skills by using a 4-point scale (1 = deficient, 2 = satisfactory, 3 = good, 4 = excellent). There was no difference between the groups in their Swedish skill estimates (mean for monolinguals, 3.82; mean for bilinguals, 3.80; $t(36) = .144$, $p = .87$). The difference in the two groups' Finnish skills was naturally enough highly significant, since the monolingual participants could practically speak no Finnish (mean for monolinguals, 0.11; mean for bilinguals, 3.60; $t(36) = -26.9$, $p < .001$). In bilinguals the skill estimates for the two languages were approximately similar (mean for Swedish, 3.8; mean for Finnish, 3.6; $t(19) = -1.80$, $p = .09$), and therefore it can be concluded that this group consisted of fairly balanced bilinguals.

To further estimate the participants' language skills, a digit reading task with 20 items was included. Chincotta et al. [5] found that digit reading times in bilinguals were faster in their dominant language when effects of different word length of digit names in the two languages were controlled for. Here the participants verbalized numeric signs into Swedish from 1 to 20 presented in random order. The reading time of each participant was measured with a stopwatch. The average reading time for the monolingual participants was 7.5 seconds (SD, 1.9) and for the bilinguals 11.2 seconds (SD, 3.1). The difference was highly significant ($t(36) = -4.51$, $p < .001$) which could be attributed to the effects of language background (bilinguals tend to be slower than monolinguals in language tasks) and study orientation.

The monolingual group consisted to a large degree of students of simultaneous interpreting which requires excellent verbal ability and concentration. This could provide them a further advantage over the bilingual participants, who represented a more heterogeneous group of university students.

Procedure: The task instructions told the participant to decide as quickly and accurately as possible whether the letter string on the screen was a real Swedish word or not and respond by pressing the corresponding button with their dominant hand. After each response they were to press a third button by their non-dominant hand to make the next stimulus appear. An asterisk appeared always 500 milliseconds before each stimulus to alert the participant of the forthcoming item. The experiment was run by a specially made computer program (SuperLab Experimental Laboratory Software, Version 2.0, Cedrus Corporation), which recorded the participants' reaction times in milliseconds (the time from the appearance of the letter string to the pressing of the reaction time key) and the correctness of their responses. The task was presented in two blocks. Every participant performed both of the blocks, with a 5-minute break in between. The presentation order of the blocks was counterbalanced and the order of the stimuli within each block was randomized for each participant. Before the experiment proper, participants had a practice session of 30 items to familiarize themselves with the task. Participants were tested individually in a quiet room and the experiment took about 50 minutes. All communication during the experiment was in Swedish.

Results

Prior to the data analyses, the incorrect responses and response latencies longer than three standard deviations above individual mean value were discarded. None of the participants exceeded the preset error rate criterion of 15 %. The error rates of the monolingual participants varied between 1.1 % and 10.3 % (mean, 4.84; SD, 2.69) and those of the bilinguals between 1.1 % and 10.5 % (mean, 4.94; SD, 3.11). The groups did not differ significantly from each other as regards to overall error rates (*t*(36) = -.113, *p* = .91). No target item was excluded from the analysis as all of them were classified correctly by over half of the participants. The average by-participant reaction times and error percentages per condition can be found in *Table 2*.

Due to the significant age difference between the two participant groups, we performed correlational analyses, which showed that in these groups of relatively young subjects, age exerted no effect on reaction time (RT). Therefore age was not included in subsequent analyses.

Table 2: Average lexical decision latencies and error rates for targets in the monolingual vs. the bilingual group

Monolinguals Word type	RT in msec (SD)	Mean error rate (SD)
Uninflected	654 (90)	1.3 (2.8)
Inflected	694 (95)	3.1 (3.8)
Bilinguals Word type	RT in msec (SD)	Mean error rate (SD)
Uninflected	703 (120)	2.0 (2.5)
Inflected	760 (139)	6.3 (7.6)

Two-way mixed-model analyses of variance (language group x morphological structure) were performed for reaction times and errors. As regards RTs, the ANOVA yielded significant main effects for morphological structure both in the by-participant and in the by-item analysis (F1(1,36) = 24.5, *p* < .001; F2(1,76) = 15.9, *p* < .001), indicating that the processing of the inflected items was overall slower than that of the uninflected items. The main effect of language group did not reach significance in the by-participant analysis (F1(1,36) = 2.69, *p* = .11) but it did in the by-item analysis (F(1,76) = 22.1, *p* < .001), suggesting that the bilinguals tended to be slower than the monolinguals. The interaction term was not significant either in the by-participant or in the by-item analysis (F1(1,36) < 1; F2(1,76) =

1.06, p = .31), confirming that the difference in the processing of uninflected vs. inflected items was similar in the two groups.

With regard to error rates, a significant main effect for morphological structure was observed both in the by-participant and in the by-item analysis (F1(1,36) = 9.82, p = .003; F2(1,76) = 4.83, p = .03). This effect stems from the fact that the error rates for the inflected items were higher than those for the uninflected items. The main effect for language group was significant neither in the by-participant nor in the by-item analysis (F1(1,36) = 2.81, p = .10; F2(1,76) = 3.23, p = .08), confirming that the error rates did not differ between mono- and bilinguals. The interaction term was not significant in the by-participant or in the by-item analysis (F1(1,36) = 2.53, p = .12; F2(1,76) = 1.44, p = .24). This suggests that the two participant groups evidenced similar patterns of errors.

Discussion

The aim of this study was to investigate the recognition of morphologically complex words in speakers of a morphologically limited language, Swedish, and to try to replicate the earlier studies performed with this language [1, 19] with better-controlled stimulus material. Moreover, we wanted to see if mono- and bilingual speakers of Swedish employ different processing strategies when recognizing inflected words, as was suggested by Portin and Laine [19]. On the basis of their study, we expected to find a processing cost for inflected, tri-morphemic nouns in bilinguals but not in monolinguals. However, what we observed in our experiment were significantly longer processing times for inflected items not only in bilinguals but also in monolinguals. These effects were not products of a speed/ accuracy trade-off confound since the inflected items elicited both longer RTs and higher error rates than the uninflected targets. The results indicated that both participant groups, even the monolinguals, processed morphologically complex nouns via the decomposition route, not via full-form representations. Although this finding is in line with the Portin and Laine study as regards bilinguals, it contradicts the results obtained earlier with Swedish monolinguals [1, 19]. The present results indicate that monolingual Swedish speakers do not always employ full-form processing with inflected items as was assumed before.

A possible explanation for the discrepancies between the present study and that of Portin and Laine [19] can be the fact that different corpora were used to search and match the target stimuli. Portin and Laine [19] collected their stimulus words from a 1960's newspaper corpus of only one million word tokens [3] while the 1990's newspaper corpus that did not become available until for the present study is far larger with over 24 million tokens. A reinvestigation of the stimulus characteristics in Portin and Laine [19] using the latter corpus did, indeed, indicate two potential sources of confound. In their stimulus sets, average lemma frequency and bi-gram frequency of the inflected items is significantly greater than those of their uninflected items. If these inflected words had been in reality processed via the decomposition route, the higher lemma frequency of these items could have speeded up stem recognition, and this advantage, along with the higher bi-gram frequency which may boost early orthographic processing, could have attenuated the difference between the item types in individuals with more efficient language processing systems, i.e., monolinguals. In fact, a closer look at their results shows a non-significant 21-millisecond RT difference in the expected direction.

With regard to the processing of inflected word forms in Swedish, it is worth noting that we do not claim that morphological decomposition would necessarily be common: our inflected stimuli (similarly to those of Portin and Laine [19]) were somewhat exceptional as they were tri-morphemic. We only argue that in contrast to previous findings [1, 19], it is indeed possible to obtain evidence for morphological decomposition in this language. Besides morphemic complexity, the surface frequency of an inflectional word form must also affect the way it is stored and accessed. Pinker [18] argued that high frequency regular forms may be coded into the long-term memory as whole units since that spares processing time. A recent lexical decision study in Finnish [15] suggests that in a morphologically rich language full-form representations start to develop in monolinguals only at relatively high frequencies (perhaps with surface frequency at around 20 per million). The case with morphologically more limited languages is not yet clear, although on the basis of studies in English it has been proposed that inflected words with a surface frequency of over 6 per million start having full-form representations [2]. In the present study, the inflected Swedish words had a surface frequency of about 10 per million, and these words seemed to be processed via the decomposition route. The fact that our inflected items were tri-morphemic, however, may make these results incomparable to those obtained in studies with bi-morphemic inflected words. The average surface frequency of the tri-morphemic inflected words used by Portin and Laine [19] was as low as 4 per million according to the 24-million word token database, but as noted earlier, there were confounding factors which could have attenuated morphological decomposition effects. At some point of the frequency continuum, Swedish speakers presumably start developing full-form representations for inflected nouns. It is probable that this point is lower for Swedish than for the morphologically rich Finnish because of the fewer inflected word forms possible in Swedish.

On the assumption that a similar processing cost in the processing of inflected words reflects a similar access procedure (i.e., the use of morphological decomposition), our results indicate that as far as a morphologically limited language like Swedish is concerned, mono- and bilinguals may differ only in terms of overall speed of lexical processing. However, things may be different in morphologically richer languages: the recent lexical decision results from the Finnish language reported by Lehtonen and Laine [15] reveal a differential pattern of morphological processing between mono- and bilinguals. As noted above, Lehtonen and Laine [15] found that although morphological decomposition is the common strategy in the recognition of inflected Finnish nouns, monolinguals can develop full-form representations for highly frequent inflectional forms. Finnish-Swedish bilinguals, in contrast, did not show evidence for full-form storage of inflected words even at the highest frequency range. Again, subjective frequency of occurrence, which is lower for bilinguals, may explain these effects. One lesson to be learnt here is that the similarity between a monolingual and bilingual speaker may vary depending on the language under scrutiny.

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Appendix

Uninflected targets

BRANSCH ("(branch of) trade")
BRODER ("brother")
CIGARETT ("cigarette")
ENTRÉ ("entrance")
FLYKTING ("refugee")
FÖRÄLDER ("parent")
INDIVID ("individual")
KAMRAT ("friend")
KRONA ("crown")
KVART ("quarter")
MODERAT ("supporter of the Moderate Party")
NÄMND ("committee")
PATIENT ("patient")
RESURS ("resource")
SKOLA ("school")
SOLDAT ("soldier")
STRÄCKA ("stretch")
STUDENT ("student")
TRAKT ("region")
ÄRENDE ("errand")

Inflected targets

ARMÉNS ("the army's")
BANKENS ("the bank's")
BOKENS ("the book's")
FACKETS ("the box's"/"the profession's")
FOLKETS ("the people's")
JULENS ("the Christmas'")
JURYNS ("the jury's")
LÄNETS ("the county's")
MAKENS ("the spouse's")
MAKTENS ("the power's")
MATCHENS ("the game's")
MUSEETS ("the museum's")
ORTENS ("the neighbourhood's")
PARETS ("the pair's")
POJKENS ("the boy's")
SJÄLENS ("the soul's")
SONENS ("the son's")
SORTENS ("the type's")
VÅRENS ("the spring's")
ÖDETS ("the fate's")

Individual Differences in Affective and Non-Affective Processing of Neutral and Negative Words: ERPs Reveal the Role of Dissociative Style

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Abstract

Studying a non-clinical sample, it was hypothesized that high-dissociative participants would show enhanced attentional abilities both towards relevant and irrelevant stimulus features. In the experiment, affectively negative and neutral words were classified on their affective valence and the presence of the letter A. The high dissociators showed evidence of enhanced attention to both valence and the letter A in a letter detection task. It is concluded that dissociative style does not correspond to a damaged or disturbed function but to an enhanced ability to direct and divide attention.

Dissociation is a disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment [1]. The most widely known psychiatric disorders that have dissociation as a core feature are Post-Traumatic Stress Disorder (PTSD) and Dissociative Identity Disorder (DID). Dissociative experiences are a part of everyday life, however, and frequently occur outside any traumatic context [10]. For example, car drivers may become so engrossed in daydreaming, a conversation with a passenger, or other mentation, that the mental processes associated with driving are evidently dissociated from consciousness, yet the road is successfully navigated. To determine to what extent individuals have a general tendency for dissociative experiences, the Dis-Q [12] was used.

Laboratory studies of dissociative processes have largely focused on memory processes in patient groups that are characterized by (presumably pathological) dissociation [2, 3, 4, 7, 8]. Unexpectedly, because dissociation was assumed to induce amnesia for the traumatic events, high-dissociative patients, at least under some circumstances, showed superior (i.e., “hypermnesic”) memory performance in a number of laboratory studies for both emotionally neutral and presumably trauma-related words. The extreme level of forgetting that is suggested by the term “amnesia” was not obtained in any condition. This led to the hypothesis that dissociative patients may not be very well able to forget traumatic events, but instead use their high attentional abilities to divert attention from re-experiencing these events [4].

The hypothesis that motivated this study was that high dissociative persons are characterized by increased attentional abilities, compared to low dissociative persons. Similar to a person with good eyesight, for instance, there may be no trade-off, but the perception of both central and peripheral details may be improved. In this experiment, attention was focussed by the instruction on one of two stimulus dimensions of visually presented words. With affective classification participants had to indicate if they thought the meaning of the presented word was negative or neutral. In the other task participants had to perform a visual search [6]. They were instructed to detect the letter A in the word presented.

Event-related brain potentials (ERPs) were recorded simultaneously with reaction time (RT) and error measures, to assess the influence of dissociative style on attentional processing. One component of the ERP in particular, the Late Positive Potential (LPP), is sensitive to both affective and non-affective processing [9], the amplitude of the LPP reflecting the allocation of attention and its onset latency reflecting temporal aspects of stimulus processing.

It was expected that in the affective evaluation task (i) threat words would elicit faster responses than neutral words), (ii) threat words would elicit larger LPP amplitudes than neutral words and (iii) these effects would be larger for high than for low dissociators. For the letter detection task, it was expected that (i) words containing the letter A would elicit faster responses than words not containing the letter A, (ii) words containing the letter A would elicit larger LPP amplitudes than words not containing the letter A and (iii) these effects would be larger for high than for low dissociators, (iv) the irrelevant stimulus feature (affective valence) would attract attention, particularly of the high dissociators, and would aid the direction of attention to the relevant feature. To our knowledge, no consistent effects of valence on ERPs have been found when words are used as stimulus material and when attention is not directed to the meaning of the words. We speculated that, with a distinction based on individual differences, we would find an effect of stimulus valence for the high dissociators in the letter detection task.

Approximately 120 students had previously filled out the Dis-Q in unrelated experiments and had consented to be contacted for participation in a following experiment. Eventually, 16 students with low (Dis-Q 1.32 ± 0.13; mean age 22.6 yrs ± 5.5, three reported to be left handed, six male) and 16 with high (Dis-Q 2.19 ± 0.37; mean age 23.4 yrs ± 3.72, two reported to be left-handed, seven male) The experimenter was unaware of the Dis-Q score of the participant. All participants had normal or corrected-to-normal vision, indicated not to be dyslexic, to have no history of mental or sustained physical illness and had Dutch as their first language. Written informed consent was obtained from all participants.

The stimuli consisted of 304 Dutch words. Half of the words were neutral words, the other half were threat words, selected from a pool of words validated in a perceptual clarification task (Ter Laak, 1992, unpublished Master's thesis), in which these words were recognized most consistently and rapidly as neutral and threat words under conditions of minimal stimulus visibility. This resulted in a collection of neutral and threat words that were relatively highly frequent and very representative for each category. Half of the words contained the letter A, the other half did not. Words were selected that varied in length between five and ten letters. Neutral and threat words were matched on word length, word type (verbs, adjectives and nouns) and frequency of usage. A subset of 45 neutral and 45 threat words was randomly selected and ordered for the affective evaluation task. Another subset of 45 neutral and 45 threat words was randomly selected and ordered for the letter detection task. Approximately half of the neutral and half of the threat words contained the letter A. Each stimulus consisted of a single word that appeared in white lowercase letters against a black background in the center of a 17’’ monitor positioned at 80 cm from the participants’ eyes. Words were presented for 1s, with an interstimulus interval randomly varying between 2 and 3 s. Each word subtended a vertical angle of 1.43° and a horizontal visual angle varying between 4.55° and 8.58°. A small fixation cross was continuously present, except during presentation of the stimulus. Stimulus presentation and response registration was performed with in-house software of the Department of Psychonomics, University of Amsterdam that was run on a Pentium personal computer. Participants were tested individually in a dimly lit, sound-attenuated room. They were comfortably seated in an easy chair, and two response buttons were both positioned either on the left or the right armrest, dependent of the participant’s handedness. In these tasks the participants were instructed to look at the fixation cross continuously and to respond as quickly and accurately as possible. After filling out an informed consent and some personal details, participants were seated in a chair. Subsequently, the electrode cap, EOG, ground and reference electrodes were attached. The order of the two tasks was counterbalanced across participants within each participant group. During all task blocks, participants had to respond in a forced choice fashion by pushing a button with either the index or middle finger of the preferred hand. In the letter detection task, participants had to decide if the letter A was present in the presented word or not. The button that could be pushed by the index finger was labelled “wel A” (“with A”), the button that could be pushed by the middle finger was labelled “geen A” (“without A”). In the affective evaluation task, participants had to decide whether the presented word was affectively neutral or negative. One button was labelled “neutral” (neutral), the other was labelled “negatief” (negative). Response button was counterbalanced across participants within each group. EEG was continuously recorded from 58 tin electrodes embedded in an elasticised cap (Electro-cap international). EEG recordings were referenced to a left mastoid electrode. Horizontal eye movements were measured by deriving the Electrooculogram (EOG) from two electrodes placed at the outer canthi of the participants’ eyes. Vertical eye movements and eye blinks were detected by deriving an EOG from two electrodes placed approximately one centimetre above and below the participants’ right eye. Impedance of all channels was kept below 10 kOhm. Signals were amplified with a band-pass of 0.16 to 100 Hz and digitised and stored at 250 Hz. During off-line analysis, data were segmented into epochs of 300 ms before to 1744 ms after stimulus onset and subsequently scanned for A/D saturation and flat lines. Ocular artifacts were controlled according to [13]. All epochs containing artifacts (change in amplitude of more than 100 μV per 5 consecutive samples) or electrical drifts (change in amplitude of more than 200 μV per epoch) in one or more channels were omitted from further analysis. A 100 ms pre-stimulus interval was used as a baseline. The grand average ERPs were smoothed using a 5-point binomially weighted filter.

No effects of stimulus type on RT were found in the affective evaluation task. In the letter detection task, participants responded faster to words with the letter A ($\underline{M}$ = 625 ms, $\underline{SD}$ = 73) than to words without the letter A ($\underline{M}$ = 657 ms, $\underline{SD}$ = 84, $\underline{F}(1,30) = 15.63$, $\underline{p} < 0.001$, see Figure 2, lower panel). This probably arises from the fact that on average the search can be ended earlier when the letter is present than when it is not [6]. In addition, letter detection responses were faster to threat words ($\underline{M}$ = 637 ms, $\underline{SD}$ = 83) than to neutral words ($\underline{M}$ = 644 ms, $\underline{SD}$ = 75), which resulted in a marginally significant main effect of valence ($\underline{F}(1,30) = 3.19$, $\underline{p} = 0.084$). The effect of A on RT was larger for high dissociators (words containing the letter A: M = 627 ms, SD = 66; words not containing the letter A: M = 672 ms, SD = 81) than for low dissociators (words containing the letter A: M = 623 ms, SD = 80; words not containing the letter A: M = 641 ms, SD = 88), although the interaction between group and A was not significant ($F(1,30) = 2.68$, NS). Separate analyses of RT for the two groups, however, showed that the high dissociators were mainly responsible for the effect of A (high dissociators: $F(1,15) = 14.98$, $p < 0.005$; low dissociators: $F(1,15) = 2.80$, NS). The detection of the letter A was facilitated by a negative valence, only for the high dissociators (interaction between group, valence and A: $F(1,30) = 5.31$, $p < 0.05$; valence x A interaction for low dissociators: $F(1,15) = < 1$; for high dissociators: $F(1,15) = 5.73$, $p < 0.05$). Whereas the detection of A by the high dissociators was aided most by the threat words ($F(1,15) = 13.95$, $p < 0.005$), the effect of A was also significant for the neutral words ($F(1,15) = 8.77$, $p = 0.01$). No further main or interaction effects were significant in the analysis of letter detection.

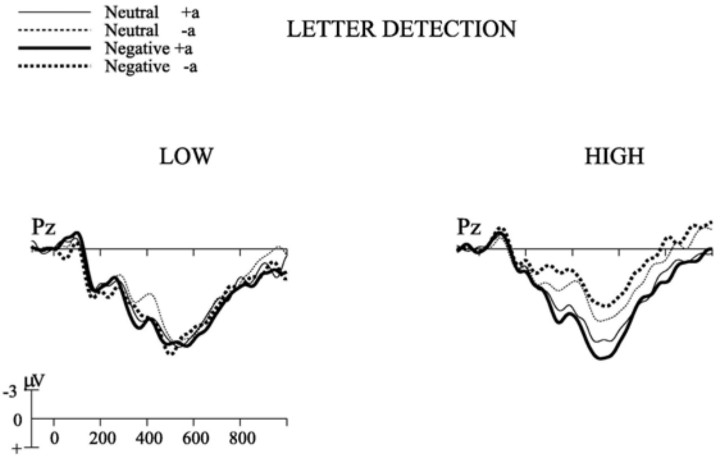

Figure 1: Grand average ERP waveforms at Pz for low (left panel) and high (right panel) dissociators during the letter detection task. Depicted are ERPs to neutral words containing the letter A, neutral words not containing the letter A, negative words containing the letter A and negative words not containing the letter A.

During affective evaluation, negative stimuli elicited a larger LPP than neutral stimuli. This effect tended to start earlier for high than low dissociators, which was reflected in a group x valence interaction ($F(1,30) = 4.79$, $p < 0.05$) 200 to 300 ms post-stimulus. Separate post-hoc analyses for the low and high group revealed that for low dissociators there was no effect of valence ($F(1,15) < 1$), whereas for the high dissociators the effect was fully significant ($F(1,15) = 14.56$, $p < 0.005$). During letter detection, words containing the letter A elicited a more positive amplitude than words not containing the letter A 400 to 600 ms post stimulus ($F(1,30) = 7.36$, $p < 0.05$). The effect of A was larger for the high than the low group, which was reflected in a group x A interaction ($F(1,30) = 5.94$, $p < 0.05$). Post-hoc tests confirmed this (low group: ($F(1,15) < 1$, NS); high group: ($F(1,15) = 9.06$, $p < 0.01$). The enhancement of the effect of A by valence for the high, but not the low, group now resulted in a significant group x valence x A interaction ($F(1,30) = 6.94$, $p < 0.05$). This observation was again confirmed by post-hoc tests (valence x A for the low group: $F(1,15) < 1$, NS, for the high group: $F(1,15) = 8.62$, $p < 0.01$). Further tests revealed that, for the high group, the effect of A was larger for negative words ($F(1,15) = 11.22$ $p < 0.005$) than for neutral words ($F(1,15) = 4.76$, $p < 0.05$), but that it was still present for neutral words.

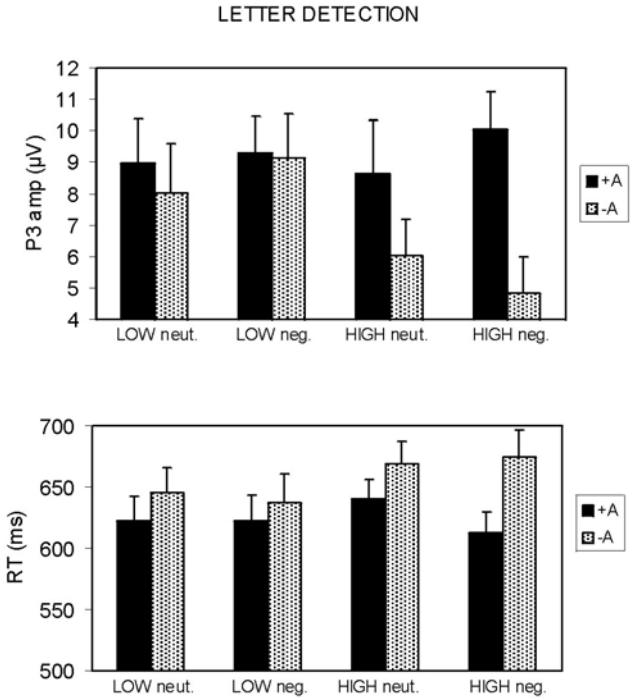

Figure 2: Behavioural data. *Upper panel:* Mean reaction times in milliseconds of hits for low and high dissociators of neutral and negative words with or without the letter A during letter detection. *Lower panel:* amplitude at Pz in µV of ERPs to neutral words containing the letter A, neutral words not containing the letter A, negative words containing the letter A and negative words not containing the letter A.

Particularly the high-dissociative participants responded faster to words containing the relevant feature A than to words not containing the A. The accompanying ERP positivity was robust for almost the entire recording epoch for the high dissociators, reflecting increased focused attention to the relevant stimulus feature, whereas it was virtually absent for the low dissociators. In addition, letter detection was enhanced by the presence of negative valence for the high group: detection of the relevant feature (A) was facilitated by negative relative to neutral words, which was accompanied by an enhanced ERP amplitude. The affective value of the word, thus, helped only the high dissociators to focus attention on the relevant stimulus feature, even when they were not instructed to do anything with word valence. These effects are very reminiscent of a study by [11]. In an emotional cueing paradigm, targets that were validly cued by negative words elicited faster responses than those validly cued by neutral words. Conversely, when serving as an invalid cue negative words tended to slow down the response, although this effect was not significant. Stormark et al. [11] interpreted this effect in terms of negative words eliciting focused attention at the cued location. Contrary to our results, however, there was no cueing effect for neutral words, which may be due to the fact that Stormark et al. [11] did not distinguish between participants with different information processing characteristics. In our experiment, even when the words were neutral, the high dissociators were better at detecting the letter A than the low dissociators.

Attention to the irrelevant feature facilitated detection of the relevant feature in high dissociators, which was accompanied by an increase in ERP amplitude of the relevant feature (words with A). Though unexpected, these results seem to strengthen the hypothesis of enhanced attentional capabilities in high dissociators relative to low dissociators. High dissociators seem to have a higher ability to direct attention towards stimulus features to which they should respond (i.e., focused attention) and simultaneously a higher ability to attend to irrelevant features (i.e., divided attention).

Enhanced focused attention of high dissociators is found both for non-affective features, such as the letter A, and for affective features, such as threat word valence, and, thus, does not appear to be driven by emotional influences. In addition, when attending to non-affective stimulus features, the high dissociators' attention is drawn to the valence resulting in faster A detection. Enhanced divided attention, thus, appears to be affect-specific, apparently supporting the notion that dissociation may be related to emotion, and possibly even to trauma. The idea that these abilities then serve to avoid re-experiencing this painful emotion [3] is contradicted by the increased, instead of reduced, attention to negative valence [4].

In sum, our results argue in favour of a relative independence of dissociation and emotional processes. From a clinical perspective, it cannot be excluded that traumatic experience contributes to dissociative tendencies, but this independence, and the large genetic influence [5] support the notion that dissociative pathology probably develops on top of pre-existing dissociative tendencies. This view would be compatible with the finding of increased memory performance in high dissociators under some conditions [2, 4, 7, 8]. Dissociative patients would then be characterized by an inability to forget a traumatic experience and the employment of an alternative information processing strategy (i.e., dividing attention and dual tasking) to do their best to avoid the negative affect associated with the trauma. This leads to the conclusion, which of course requires further investigation, that dissociative disorders may not be related to a damaged or disturbed function, but actually to an enhanced ability, which can also be found in non-pathological individuals. More importantly, the individual difference of dissociative style may also serve to improve our insights in fundamental information processing mechanisms, such as those involved in attention.

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V.

Effect of Aging on Brain Activity

The Aging Homunculus: The Decline of Selective Attention and Executive Control Processes with Normal Aging

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Abstract

The present chapter starts with a brief overview of age-related changes in selective attention functions as manifested in performance measures and in scalp-recorded components of the event-related potential (ERP). Although the capacity aspect of attention is more compromised than the selectivity aspect of attention, it is concluded from both data sets that old and young subjects do not seem to differ substantially in the quality of attentional operations. We then focus on some general theoretical constructs that have been proposed to account for cognitive decline with old age in general, and on the major anatomical and physiological characteristic of the aging brain.

The final conclusion is that progress in cognitive aging research can benefit most from an integrative approach that cuts through various theoretical concepts and levels of analysis such as the behavioural (psychometric and experimental) computational and neurobiological level.

Attention and aging

A dominant view in the aging literature is that with advancing age subjects tend to become progressively slower and also more variable in their cognitive performance across a wide spectrum of cognitive tasks. This variability exists for differences within as well as between subjects. Selective attention has often been used as a central explanatory concept to account for these findings. The major findings derived from two different approaches in the field of attention research are briefly summarised below.

Performance studies

In the last three decades numerous studies have focused on age-related changes in attention from a purely behavioural perspective [17, 18]. The general conclusion that emerges from these studies is that elderly subjects are less able to ignore irrelevant information and to divide attention between several simultaneous inputs or tasks. A second important finding from the same studies is that age-related deficits in performance seem to become more pronounced as task complexity increases. This holds especially for the divided attention functions, as manifested in dual-task and search task performance. For instance, in visual and memory search tasks the typical increase in RT with an increase of display set or memory set is much larger in old than in young subjects. In contrast, age-related decline in focused attention tasks seems to be relatively spared. The latter findings however do not necessarily mean that division of attention is a function that is specifically compromised in old age. It could also reflect that in general divided attention tasks are more complex (i.e., involve more processing operations) than focused attention tasks.

ERP studies

In several respects event-related potentials of the brain (ERPs) can be useful in detecting age-related deficits in attentional processes. First, ERP components can help in localizing the specific processes that are involved in the selection of information and that may become compromised with advanced age. For instance, if pre-attentive processes are more resistant to effects of old age, sensory ERP components that occur relatively early in the processing stream should be less affected in old subjects than components that reflect attention-demanding processes. Second, in focused attention tasks ERPs elicited by irrelevant events provide more direct information with respect to age-related differences in the ability to ignore irrelevant information than behavioural measures. Third, in divided attention tasks late endogenous components of the ERP such as P3 and Slow Waves allow a more direct "on-line" investigation of age-related deficits in attentional capacity than is permitted by behavioural measures.

In old subjects early selection processes, as reflected in their selection potentials, have a somewhat slower onset than in young subjects, especially in conditions when selection is based upon complex discrimination of stimulus features ([14], see also *Table 1*). Furthermore, the pattern emerging from ERPs that were recorded in visual and memory search studies (reflecting divided attention) is that search-related negativities in the ERPs are smaller and of longer duration in old than in young subjects over the central and anterior scalp sites. These effects could indicate that controlled search is less intense or takes more time per search operation in old than in young subjects.

In sum, these ERP studies confirmed the general pattern derived from performance studies, namely that old and young subjects do not differ substantially in the quality or architecture of attentional operations.

General slowing and task complexity

Since the age-related decline in selective attention is more pronounced for complex than simple tasks, it has been suggested that this decline is not necessarily limited to selective attention tasks but could reflect some general or more fundamental deficit. On a quantitative level this type of deficit is typically manifested in complexity or global slowing functions. General slowing implies that performance of old subjects is always a constant proportion (e.g., 30 %) slower regardless of the nature of the specific cognitive task operation. Various meta-analytic studies have indeed demonstrated that the relation between response speed between young and subjects can be modelled satisfactorily with simple linear or non-linear functions [7, 21]. An obvious advantage of these slowing models is their theoretical parsimony. However, general slowing as such is a descriptive phenomenon that needs to be explained on a more theoretical level. A number of attempts that have been made to account for age-related slowing of

Table 1: Summary of results of ERP studies that reported age-related changes in focused attention (a-c) and divided attention (d-e) paradigms Listed are changes in amplitude/latency of ERP components in old relative to young subjects. LRP = lateralised readiness potential. Nd = negative difference wave. P3 = late positive response. Search negativity: subtraction ERPs in low load from ERPs in high load conditions (from [14]).

PARADIGM	STIMULI	AGE-RELATED ERP RESULT
(a) sustained set (same stimulus feature selected in a block of trials)	auditory: change in pitch auditory: change in duration	no age effects larger and more prolonged Nd at frontal sites, smaller frontal slow wave negativity and P3 to targets
	visual: orientation/location	later onset selection negativity. reduction of selection negativity at fronto-central site
	visual: multiple non-spatial features	later onset selection potentials. smaller P3 to targets
(b) spatial cueing (trial by trial cueing of stimulus feature)	central cue (visual)	delayed contralateral negative shifts to central cues in cue-target interval at anterior sites
(c) flanker interference	letters (small visual angle between target/flanker)	larger positive 'dips' in early LRP, later onset LRP
(d) memory search	visual: letters	smaller increase P3 latency with increasing load. smaller P3 to targets. anterior sites: smaller and longer duration search-related negativity. posterior sites: tendency towards larger search-related negativities.
(e) visual search	visual: letters	central-parietal sites: smaller and more sustained search-related negativity.
	visual: letters (high visual-spatial load)	enhanced central-parietal negativity

cognitive functions are briefly summarized below. Some of these theories can also been seen as first attempts to integrate psychological principles with properties of the brain.

Neural noise

A first example of a mechanism that may account for general slowing of cognitive functions is that of neural noise [34]. According to neural noise theory the aging brain is characterized by less separation between signal and noise, less distinct neural representations and loss of information due to a decreased connectivity of neurons. The neural noise principle is also a central element in the information-loss model of Myerson [21].

Loss of connectivity

Cerella proposed that the aging human brain can be conceptualised as a network in which links become gradually disconnected due to degeneration of axonal connections [8]. Network degradation affects performance in complex tasks more strongly than in simple tasks, because complex tasks involve more processing steps and/or longer neural pathways. In this network he distinguished between a computational core in which 50 % of the links were lost and a perceptual-motor shell in which only 20 % of the connections were lost. This type of network was able to predict effectively the proportional loss in transmission time (response speed), which is characteristic for the general slowing principle discussed earlier.

Processing Resources

Another influential theoretical construct that was offered in particular to account for the larger age related decline in performance in complex than simple tasks is the concept of a limited supply of capacity or processing resources [30]. The resource concept has been often criticized because of its circularity and lack of constraints [22]. More recently however there have been attempts to "flesh out" the resource concept and bring it down to more elementary components. In the framework proposed by Salthouse resources were already conceptualised in three different ways, namely in terms of speed (cycle time of a central processor), capacity (working memory) and energy (attention or arousal). The latter conceptualisation of resources is perhaps more useful than the older unitary definition of capacity as proposed by Kahneman [12] because it is (a) much more differentiated and (b) defined in more specific and operational terms. It is important to realize however that these three forms of "resources" are conceptually and empirically interdependent. This interdependency was also recognized by Salthouse [31], who suggested that processing speed probably represented the most fundamental "resource" underlying a great variety of cognitive tasks, including tasks that make demands on working memory. This is because due to a built-in time pressure of many working memory tasks, products of early processing may have decayed and lost in time when later processing is completed. Likewise, working memory and selective attention are strongly interdependent because (a) working memory maintains representations that are crucial for selecting task relevant stimuli or actions and (b) selective attention limits the content or representations in working memory. Recently attempts have been made to define resource components more precisely by using formal models [19, 24]. In some of these models a speed account of capacity limitation in old age seemed to fit well with empirical data obtained in memory updating tasks with varying memory load.

Executive control

Another theoretical concept in cognitive aging research that has become increasingly popular in recent years is that of executive control. Executive control is closely related to Baddeley's conceptualisation of working memory which major functions where the integration of information and control of action [3]. It is a concept that is specifically relevant for attention researchers because it provides a framework for the control of attention in situations when subjects must divide attention between two inputs, or dynamically switch attention between two tasks or stimulus features. Executive control is, like resources, a somewhat vague concept but in fact encompasses a broad range of cognitive functions such as (a) inhibiting distracting, overlearned or pre-potent responses, (b) monitoring ongoing or past performance and (c) planning of future goals. It has also been proposed that executive functions depend on the integrity of the prefrontal cortex [35]. This hypothesis is supported by empirical findings showing that old subjects have a specific difficulty with performing tasks which are supposed to tap frontal lobe functions such as the Wisconsin card sorting test, stopping tasks and interference sensitive tasks [9, 15].

Aging and the brain

In the last two decades studies of changes in the human brain that occur during normal aging, have provided important neural underpinnings of the theoretical constructs that were discussed above. The principal findings will be briefly summarized in the following sections.

Structural changes

Post mortem studies as well as in vivo MRI studies have established structural changes that occur in normal aging in both white and grey matter [26]. Normal aging is associated with reduction in weight and volume of the brain (median correlation with age is r = -60 for volume corrected for cranial size). Other major findings are: cerebrovascular pathology (leading to decreased blood supply), shrinkage of neurons, loss of dendrites in dendritic trees, and reduction of whiter matter (myelin). Especially loss of white matter due to demyelination could be important as a neural basis for the general age-related slowing discussed earlier, because it is presumed to have its major impact on connectivity and transmission of information between different cortical areas. An additional important finding is that different cortical areas show a different vulnerability for effects of age. More specific, it has been hypothesized that the gradient of vulnerability follows the rule of "last in first out". Last in refers to areas in the brain such as prefrontal cortex and posterior parietal cortex. These areas have presumably developed relatively late from a phylogenetical and ontogenetical perspective as compared to primary sensory and motor areas which matured relatively early and are largely spared in old age (see also *Figure 1*). In sum, the prefrontal cortex appears to be the area in the brain, which is most strongly affected by structural changes in grey and white matter as described above [27, 33].

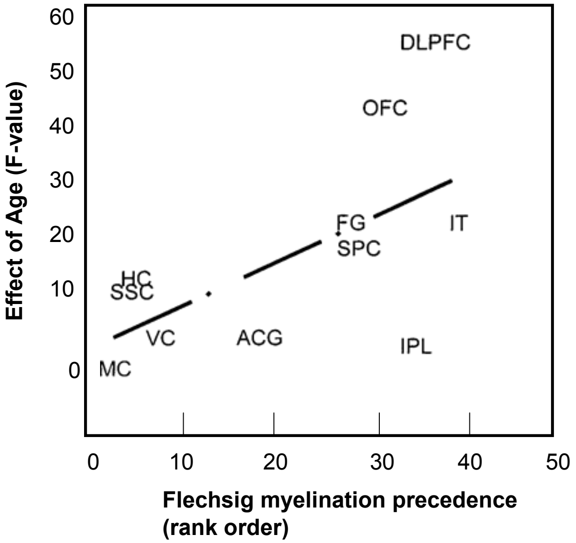

Figure 1: Myelogenesis (horizontal axis) plotted against vulnerability of 11 cortical regions (magnitude of age effects expressed in F-ratio) measured by Raz (27). Greater rank corresponds to later myelination. Greater F value indicates stronger association between age and regional volume (corrected for gender and body height). DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex, IT = inferior temporal, IPL = inferior parietal lobule, SPC = superior parietal cortex, ACG = anterior cingulate gyrus, MC = motor cortex, VC = visual cortex, HC = hippocampus, SSC = somatosensory cortex, FG = fusiform gyrus (adapted from [26]).

Functional (physiological) changes

Neuroimaging techniques such as PET and fMRI hold a considerable promise for clarifying the physiological processes and networks in the brain that are responsible for the changes in cognitive functions as manifested in performance and ERP measures. It should be realized however that age-related differences in the vasculature of the brain could imply that the relationship between the hemodynamic response and neural activity is not fully equivalent in old and young age groups [29]. Keeping this reservation in mind, available studies reveal that older persons utilize different functional networks than younger persons even when they perform the same task, perhaps to compensate for reductions in efficiency in other brain areas [10]. For instance, recent PET/fMRI studies [6] showed that in particular old subjects that performed well in cognitive tasks showed less asymmetry in the prefrontal cortex than young subjects and low performing old adults. This is consistent with the idea that high performing older subjects compensate for decline in performance by recruiting special neural mechanisms. Another fMRI study [28] demonstrated that retrieval mediated reduction of activity in dorsolateral prefrontal cortex accounted for the decrement in working memory performance (storing letters, objects or locations in memory) with normal aging. Finally, evidence has been found of age-related decrease in dorsolateral and parietal areas in the colour-word Stroop task, which areas were assumed to be involved in attentional control. The same study also reported an increase of activity in the ventral visual areas which probably reflected decreased inhibition of task irrelevant information [20].

Attention and Brain functions

The knowledge of neural systems and mechanisms in the brains that are responsible for the decline in attentional functions in old age is still far from complete. A currently accepted view is that there are two major networks that are associated with two functionally distinct forms of attention [25]. First, an attentional network in the posterior brain is believed to be responsible for orientation and shifting of spatial attention to perceptual events. This system includes not only the posterior parietal cortex but also subcortical structures such as thalamus (in particular the pulvinar) and superior colliculus. Second, an anterior attention system that comprises the various subdivisions in frontal cortex is believed to be responsible for control of action, working memory and division of attention among various competing inputs. As noted earlier, both the posterior parietal cortex and prefrontal cortex are structures that show a relatively late myelination and greater vulnerability to aging (*Figure 1*) which could imply that the related attention systems are also compromised in old age.

Neuromodulation of synaptic transmission

Another factor which has recently received much attention is the age-related decline in neurotransmitter systems such as the cholinergic and dopaminergic systems. Depletion of dopamine resulting from a loss of neurons in substantia nigra has been reported to occur in Parkinson disease. However, dopamine transmitter content and binding mechanisms in various brain regions have also been shown to decline during normal aging in humans [13] and in monkeys [1]. Earlier studies focused mainly on dopamine mechanism in nigrostriate regions (where a reduction of around 10 % per decade starting around 20 years have been reported). More recent findings using PET in normal subjects suggest that there is also loss of D2-receptors (and to a lesser extent also of D1 receptors) in areas outside the striatum like the anterior cingulate gyrus (13 % per decade) and frontal cortex (11 % per decade). There also appears to be an association between various psychometric indices of working memory and processing speed, and estimated density of D2 receptors in frontal cortex [2]. Thus, in addition to structural changes, attenuated effects of dopamine could also contribute to age-related prefrontal dysfunction described earlier.

The modulatory effects of dopamine may vary strongly depending on the cortical region or receptor site. Nevertheless it has been proposed that a general feature of dopamine is to alter the signal-to-noise ratio of neural information, for instance by increasing the differentiation between background or baseline firing rates and those that are evoked by afferent stimulation [16]. In prefrontal cortex, dopamine could modulate the responsivity of input units, updating of context information and reward conditioning [5].

Computational modelling

Computational modelling has proven to be a useful technique in cognitive aging research to provide converging evidence about basic theoretical principles and mechanisms underlying decline in speed and working memory, in addition to empirical findings. Two varieties of computational modelling may be discerned, namely (a) application of formal mathematical models or models derived from the computer metaphor and (b) simulation of networks within a connectionist framework. The first approach has been fruitful in unravelling the specific subcomponents of resources, working memory and age related slowing [19, 24, see also above]. The second approach has been successfully applied in modelling the regulating effects of catecholamines on executive prefrontal functions. In neural networks these effects can be simulated by adjusting the Gain (G) parameter of the activation function in feed-forward, back-propagation networks [5, 16, 32] Using this approach Li et al. [16] reported that the reduced responsivity due to dopamine attenuation leads to less differentiation between internal neural representations and increased neural noise. Another theory [5] focused more strongly on the interaction between the dopaminergic system and dorsolateral prefrontal cortex, in the regulation and active maintenance of context information in working memory. This was assumed to favour processing in task-relevant pathways over other competing pathways. In the elderly attenuation of this interaction could lead to weakened task representations and increased conflict between relevant and irrelevant stimuli and associated responses [4]. Others [11] have developed a computational model that assumes that the ERN (error-related negativity) is elicited whenever a negative reinforcement signal is conveyed to the anterior cingulate cortex via the mesencephalic dopamine system (the ERN is a ERP component that is elicited by the perception of an error or some form of conflict that predisposes to errors). It has recently been shown that the ERN is specifically reduced in old age, and that this reduction effect could be simulated by manipulating a single parameter that corresponded with a weakened phasic activity of the mesencephalic dopamine system [23]. Taken together, these findings suggested that dopaminergic signals that are associated with error processing and reward based learning are weakened in old subjects and that the anterior cingulate is involved in regulating these effects.

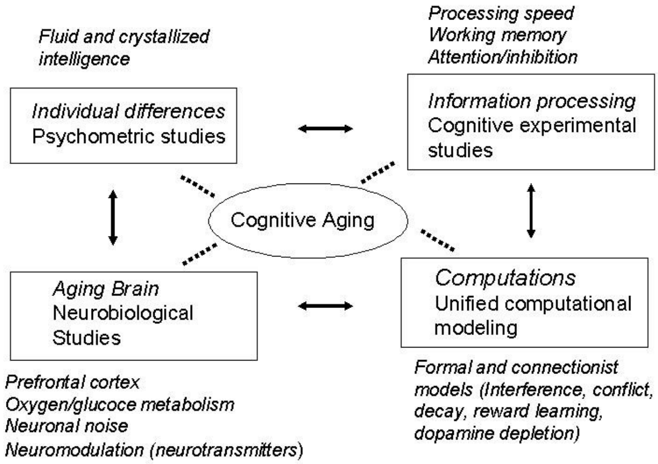

Figure 2: Schematical view of the cross level approach in cognitive aging research. Shown are the various levels of analysis (boxes), their interconnections and some issues addressed in each of these analyses (adapted from [16]).

Towards a multilevel approach in cognitive aging research

In recent years considerable progress has been made in understanding the role of structural and functional changes in the brain and how these changes relate to the decline of cognitive functions in normal aging. An exciting aspect of these developments is that they offer the possibility of integrating findings from different levels or domains of investigation (see also *Figure 2*). For instance, dopamine depletion (at the cellular level) together with glucose and oxygen metabolism (at a more molar level) now provide the neurophysiological analogues of important metaphors of processing resources such as working memory, speed and energy. In addition, dopamine findings provide a model for how neuromodulation could affect signal representations and control processes in prefrontal cortex. From a different angle, computational modelling has also lead to more precise insights into the computational principles underlying age-related increase in neural noise or decrease in resource components and selective attention. Finally, the neuroimaging approach offers the possibility of localizing regions and networks in the brain that are associated with functions that are specifically compromised in old age, such as working memory and executive functions.

A challenge for the future is the integration of the various conceptual frameworks that have been applied in the past to account for age-related changes in cognitive functioning, such as general slowing, selective attention, working memory, neural noise and processing resources. It is important to distinguish however between the use of these concepts at a purely descriptive level and at a more explanatory level. For instance, generalized slowing provides a good account of RT data in great number of studies, but is a purely descriptive phenomenon. Alternatively, loss of connectivity, increased neural noise, reduction of capacity and executive control are theoretical concepts that are often used to explain observed behavioural findings. As noted before these concepts (and their neural substitutes) may not be completely independent but could represent different formulations of the same underlying neurocognitive principles or mechanisms. Especially theoretical perspectives emphasizing the role of executive control processes are promising from an integration point of view, not only because they can account for a wide spectrum of behavioural indices, but also because of interesting parallels between age-related deficits in executive processes and the prefrontal structures in the brain [35].

This raises a second central problem that remains to be solved in future research, namely the relative contribution of local versus global factors in age-related decline in neurocognitive functions. According to the local or specific view elderly subjects show a greater loss or slowing in their performance in tasks that involve higher executive functions, because brain aging takes the heaviest toll from the prefrontal areas and the dense dopaminergic pathways projecting to these areas. A deficit in executive functioning could also be expressed as a generalized cognitive impairment, with a greater impact on complex than simple tasks. In contrast with the local view the "global loss" hypothesis states that decrements in cognitive performance is global and quantitative and not different for different cognitive or neural domains. The neural correlates of global loss could be global reduction in blood flow, neurotransmitters functioning and diffuse and random loss of connectivity in the brain. An important element of this hypothesis is the correspondence principle: the quality or structure of cognitive processes remains unchanged with age [21]. According to the global loss hypothesis greater decrements in performance in complex than simple cognitive tasks could result from the fact that these tasks depend on networks that occupy a larger amount of "neural space" than simple tasks. This may hold in particular for task operations that rely on the anterior executive system, such as working memory and task switching. Notice also that the frontal system occupies a widely distributed network in the brain consisting of many reciprocal connections not only with adjacent areas but also with more distant areas in the brain stem, limbic areas and posterior cortex. Thus, from the global perspective complex cognitive functions are more compromised in old age, not because they depend on a specific and more vulnerable brain areas, but because they recruit larger networks with more dense and longer intra- and intercortical fibres than simple functions. Future neuroimaging studies should thus focus also on the possible role of task-related global changes in the brain that result form diffuse neural loss or global reduction in blood flow. These changes may be easily overlooked in subtractions between hemodynamic responses elicited in a baseline condition and a condition of interest.

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ERP Correlates of Individual Differences in Neuropsychological Function

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Abstract

The aim of the present study was to explore the relation between ERP measures (MMN, P3a and P3b) and performance on psychometric tests (CVLT and PASAT) in a large sample of normal subjects (n = 88), and to discuss how ERP measures can be included in the neuropsychological evaluation of individual patients. Univariate analysis revealed no significant correlations between any ERP measure and the psychometric measures, neither in the group as a whole nor in subgroups classified according to performance level on the two tests. A multidimensional ERP measure from one patient was found to be highly deviant from the measures among normal subjects. Together with information from the psychometric tests, brain dysfunction was strongly indicated in this patient.

Introduction

Measurements of cognitive evoked potentials (ERPs) have been widely applied in studies of individual differences and clinical problems since the P300 or P3 was first described by Sutton and collaborators [14]. P3 is the ERP component most frequently focused on, but other components like the mismatch-negativity (MMN) has been applied to various clinical conditions [6].

The ERP components are highly relevant for understanding the processes underlying behaviour in an ongoing task. MMN has been used as an indicator of the functional state of the cortex and the early stage of automatic information processing, whereas the P3 is regarded as an indicator of selective attention and memory updating. In more recent literature, P3 is separated into a P3a component related to novelty detection and a P3b component related to processing of task relevant stimuli (see paper by Polich, this volume).

Several studies have associated shorter ERP latencies with superior cognitive performance. Polich and collaborators [8] have related the variability in P3- latency to cognitive measures of perception and attention, and Paller et al. [7] have found increased amplitudes in a late positive ERP-component to be associated with superior memory performance. In clinical studies, ERP measures have been shown to correlate with performance on tests of memory function [13] and problem solving abilities [12], as well as a general impairment of neuropsychological function [10].

There are few studies relating ERP measures to performance on psychometric tests in larger samples of normal persons. Some studies (see [2]) focus on the relation of P3-latency to intelligence on the assumption that ERP-latency measures some basic speed factor of the central nervous system. This view of P3 or MMN latency is less consistent with current theories, in which these ERP components are regarded as reflecting specific cognitive processes. It thus seems more reasonable to explore relations between specific measures from the cognitive and electrophysiological domains.

The aim of the present report was to explore relations between ERP-measures and results on selected tests of memory function, and to discuss how ERP measures can be included in the neuropsychological evaluation of individual patients. Firstly, we selected a measure of verbal learning from the California Verbal Learning Test (CVLT) [3] and a measure of working memory and processing speed from the Paced Auditory Serial-Addition Task (PASAT) [5]. We then asked if these measures were differentially correlated with the ERP components MMN, P3a and P3b in the group as a whole, as well as in groups with different levels of performance on the neuropsychological tests. Since ERP and psychometric test have widely divergent methodological limitations and sources of error variance, we tried to correct for some of the error variance by a procedure correcting for absolute differences in ERP-amplitudes between subjects.

Secondly, we included a multidimensional measure of the ERP components, and asked if simultaneous evaluation of ERP components could differentiate between normal controls and a patient with brain dysfunction.

Methods

Subjects: Eighty-eight normal volunteers from a multi-centre Norwegian study were included in the present study. The subjects reported normal hearing and no history of serious brain injury, substance abuse, psychiatric or neurological disease, or learning problems leading to remedial teaching programs. The female/male ratio was 58/30 and the mean age was 29 years (range = 20 to 55 years). The mean education level was 14.5 years (range = 10 to 19 years), and the mean verbal IQ was 113.4 (range = 88 to 137).

ERP measures: The ERP paradigms were administered in a fixed sequence, starting with a resting EEG, followed by a mismatch negativity paradigm, a P3 oddball paradigm, a dichotic processing negativity (PN) paradigm and further visual paradigms. In the present report, only results from the MMN and the P300 oddball paradigms will be presented. Band pass filter setting was 0.05 to 70 Hz with a sampling rate of 500 points per second. Electrode placement followed the standard 10-20 system with the addition of bilateral mastoid electrodes, of which M1 served as reference.

In the Oddball paradigm, continuous EEG was segmented into epochs of -100 to 1000 ms relative to stimulus onset and low pass filtered (15 Hz, -24 dB/octave). Correction for eye movement was performed according to the procedure of Semlitch et al. [11], and epochs with amplitudes above +/- 100 µV were rejected before averaging.

In the MMN paradigm, continuous EEG was segmented into epochs of -50 to 250 ms relative stimulus onset and band pass filtered (.5 to 12 Hz, -24 dB/octave). Epochs with amplitudes larger than +/- 150 μV (EEG or EOG channels) were rejected from averaging.

MMN paradigm: Stimuli were composite tones with a 500 Hz fundamental frequency and harmonics at 1000 Hz (-3 dB) and 1500 Hz (-6 dB). The frequent stimulus had 75 ms duration while the infrequent deviant stimulus had a duration of 25 ms and occurred in 10 % of the trials. The paradigm was chosen based on recommendations from Tervaniemi et al. [15]. A total of 2000 stimuli were presented at 250 ms intervals with 60 dB intensity while the subjects read a selection of their own choice.

Oddball paradigm: The same composite tones were presented in this paradigm as well. In addition, a distractor sound with white noise was included which was spectrally band pass filtered (24 dB/octave) with an interval of 250 to 3000 Hz. A total of 360 stimuli were presented at 1000 ms intervals. Targets (14 %) were 25 ms duration, 80 dB tones, standards (72 %) were 75 ms duration, 80 dB tones, and distractors (14 %) were 100 ms duration, 95 dB filtered noise. The instruction was to press a button as soon as the short tone occurred, and reaction time was recorded.

Measures of verbal learning and attention: CVLT is a test of verbal learning and memory. In the first five trials, the subjects were asked to recall a list of sixteen words immediately after its presentation. The verbal learning measure used in the present report was the total number of words recalled across these five trials.

PASAT is a serial addition task that is speed-dependent and probably more closely related to efficiency of working memory function than the CVLT learning measure. The numbers were presented every third second. The subject was instructed to add pairs of numbers such that each number was added to the one that immediately preceded it.

Data reduction and statistical methods

ERP analysis: Using signal averaging, ERP waveforms were computed separately for each lead and for each category of stimulus. P3b and P3a were measured in ordinary waveforms to target and distractor stimuli, respectively. Difference waveforms, deviant stimulus minus frequent stimulus, were used to determine the MMN. MMN amplitude was defined as the maximum negative amplitude in the time window 100 to 250 msec. The P3a amplitude was the maximum positive amplitude in the time window 200 to 350 msec. P3b amplitude was the maximum positive amplitude in the time window 250 to 500 msec. Peak latencies were measured at Fz for the MMN, at Cz for the P3a and at Pz for the P3b.

Statistical evaluations: Matlab 6.5 was used to analyse and visualize the data. We computed the univariate correlation between the CVLT learning and PASAT scores and the ERP measurements (amplitude and latency for the MMN, P3a and P3b components). The subjects were then allocated to three subgroups according to performance level on the neuropsychological tests. We defined low level as performance below the 25 percentile on both tests and high level as performance above the 75 percentile on both tests. The relation between amplitude and latency within each ERP component was visualized for all subjects, and the correlations between ERP measures and neuropsychological test measures within each subgroup were calculated. In a subgroup of 32 subjects we scaled the amplitude variable for MMN, P3a and P3b according to the N1 component (set to 1.0/100 %) to obtain a measure that was individually adjusted and correlated the results with the CVLT learning score.

Finally, we used a multi-dimensional method, estimating the Mahalanobis distance, r (e.g., [4]) between each normal subject ($x_{i)}$ and the class-mean (μ) in order to establish a threshold value for later detection of “outliers” that might represent abnormal ERPs in patients. More specifically, we computed and plotted r_i for each subject i, where $r_i^2 = [x_i - \mu]' \Sigma^{-1} [x_i - \mu]$, x_i is the vector of 4 ERP measures in subject i, an Σ^{-1} is the inverse covariance matrix computed from the full (88x4) data-matrix of control subjects. Two sets of ERP measures were selected. First we selected measures from the early ERP component MMN (MMN amplitude and MMN latency) and the P3b (P3b amplitude and latency) component known to be related to processing of task relevant stimuli.

Results

The distribution of subjects on the CVLT learning score, the PASAT score and the ERP scores (MMN, P3a and P3b amplitude and latency) were generally normally distributed with the exception of PASAT, on which most persons performed close to the ceiling.

The correlations between the neuropsychological and ERP measures were far from statistically significant (*Table 1*).

Table 1: Univariate correlations between measures of ERP and test performance

	MMNamp	MMNlat	P3a amp	P3a lat	P3b amp	P3b lat
CVLT	r = 0.01 p = 0.94	r = 0.10 p = 0.35	r = 0.13 p = 0.24	r = 0.04 p = 0.69	r = 0.17 p = 0.11	r = 0.16 p = 0.14
PASAT	r = 0.14 p = 0.19	r = 0.06 p = 0.55	r = 0.02 p = 0.86	r = 0.02 p = 0.87	r = 0.11 p = 0.33	r = 0.11 p = 0.31

When the ERP measures were scaled according to N1 in a subset of the subjects (N = 32), there was still no significant correlation between any ERP measure and the CVLT learning score.

Figure 1 shows the Mahalanobis distances for each normal control subject to group mean, calculated from the P3b and MMN measures. Notice that each ERP feature was close to a Gaussian distribution. A patient denoted 900 (plotted in bold) was included. He was 31 years old when an accident led to a C3/C4 lesion. Problems with respiration resulted in a sinus-arrest and a pacemaker was implanted. Afterwards he recovered well, and no signs of brain damage were revealed on the neurological and neuroimaging examinations. One year after the accident he reported impaired short-term memory function, and he was referred to a neuropsychological evaluation.

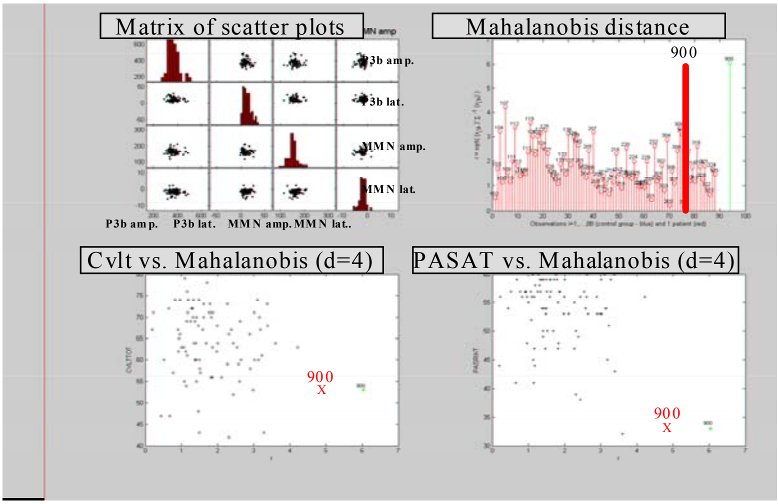

Figure 1: Measures of Mahalanobis distances for P3b and MNN. A patient is denoted 900.

In *Figure 1* it can be seen that all but one control subject obtained a *r* less than 4, while the patient had a distance above 6. The two bottom figures depict the ERP Mahalanobis distances versus the CVLT and PASAT test measures. To the right we include the patient (in bold). Although some of the control subjects showed as low performance as the patient on the neuropsychological tests, the Mahalanobis ERP distance for the patient was still far outside the distribution of the normal control subjects.

Discussion

In the present report we explored the relation between two neuropsychological test measures and ERP components measuring different stages in sensory and cognitive information processing. The test results were not systematically related to MMN, P3a and P3b, neither when analysed separately nor when the subjects were divided into subgroups with different levels of test performance. Our study thus indicated that ERP measures and neuropsychological test performance represent two independent measures of brain function. An attempt to reduce error variance related to non-cognitive factors influencing ERP amplitudes by a scaling procedure did not result in stronger relationships. We can still not conclude that there is no relationship, considering that several studies have shown neuropsychological test measures and ERP components to be more closely related in patients (e.g., [8]), and that both measures are influenced by age (e.g., [1, 16] and Reinvang et al., this volume). A general problem in studies of normal volunteers is the restricted variance in performance resulting from the fact that subjects are generally recruited from highly functioning subpopulations. The findings should therefore be followed up in clinical studies and in groups with a wider age and performance range.

In a clinical neuropsychological setting we use a multi-dimensional evaluation of findings. The question is how to incorporate ERP measures in such an evaluation, taking into account that there is common variance as well as variance representing specific processing components in these measures. We have presented an approach to take account of more than one ERP component. The scalar Mahalanobis distance in a 4-dimensional feature space was found to be distributed rather homogeneously in the normal control subjects. The results from one patient showed a deviant ERP distance measure. We propose that the combined information from neuropsychological test results and the ERP measure strongly indicated brain dysfunction in this patient. The findings also underscore that the relative independence of ERP and neuropsychological measures can be exploited in order to optimise combined information from both sources. More patients should be included to evaluate the clinical utility of this approach. Furthermore, there might be other discriminating features in the underlying continuous EEG that should be used as part of the neuropsychological evaluation of individual patients.

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Effects of Aging on Sensory-Motor Processing

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Abstract

In this article, results from an original event-related potential (ERP) study are presented. The aim was to analyse different stages of central processing mechanisms during a sensorimotor task and to evaluate their contribution to aging-related behavioural slowing. ERPs were recorded from two groups of subjects, young (22.5 years) and old (58.3 years), who performed a four-choice-reaction task. Major results demonstrated that reaction times increased with increasing age. This behavioural slowing was not accompanied by significant delays in central processes of perception (as reflected by latencies of early ERP components), and sensorimotor integration, response selection and initiation (as reflected by the onset of the lateralised readiness potential). Instead, the age-related behavioural slowing was accompanied by significant alterations of the central processing mechanisms of motor response execution.

Introduction

It is nowadays well recognized that aging is accompanied by changes in the speed and/or mode of information processing in the brain. Increased age is consistently associated with slower performance in a wide range of speeded tasks [23]. To explore the origin(s) of behavioural slowing with age, a major question addressed is whether *particular processes* (sensory, sensorimotor, motor or cognitive) are impaired in the aging brain, or more general and *unspecific alterations* such as neural loss, decline in inhibitory functioning, reduction of processing resources or changed neural connectivity and neurotransmission produce behavioural decrements as a result of multiple distributed deteriorations [11, 14, 22].

Speed-dependent variables have been recorded in tasks with varying complexity and specificity to clarify which levels of information processing become deficient with aging [23]. However, these variables reflect performance at the behavioural level and, being an integral output measure, cannot efficiently evaluate the timing of centrally activated perceptual, motor or cognitive processes, and their respective contribution to response speed. More recently, functional imaging has substantially advanced current knowledge on the aging brain. Differences in spatial activations have been identified between young and old subjects suggesting functional dedifferentiation or altered inter-area connectivity with age [4, 22]. However, the fine temporal dynamics of neural processes underlying aging-related decline is not well known.

Psychophysiological research may substantially aid to resolving this issue. Amplitude and latency values of event-related brain potentials (ERPs) are well documented to correlate with central mechanisms of information processing and may specifically reflect early or late processing stages (rev. [21]). Hence, the combined analysis of behavioural speed as reflected by reaction time (RT) and measures of central information processing as reflected by ERP components may be employed in an attempt to identify processing stages associated with performance deficits [11, 19, 23]. In this contribution, results from an original ERP study are presented. The aim was to analyse different stages of central processing mechanisms during a choice-reaction sensorimotor task in order to evaluate their contribution to aging-related behavioural slowing.

Methods

A total of 25 subjects were studied. They were divided into two age groups: young (n = 13, 6 female, mean age 22.5 years, SE = 1.5), and old (n = 12, 6 female, mean age 58.3 years, SE = 2.1). All subjects were healthy, without history of neurological, psychiatric, chronic somatic or hearing problems in the past. They were drug-free during the experimental sessions, with normal or corrected to normal vision.

A four-choice reaction task (4-CRT) was used, in which four stimulus types represented by the letters A, E, I, and O were delivered randomly with equal probability of 25 %. A total of 200 stimuli were presented in each experimental series, with n = 50 for each stimulus type. The task was to respond to each stimulus type with a predefined finger: The letter A had to be responded with the left middle finger (stimulus-response type 1, SR1), the letter E – with the left index finger (SR2), the letter I – with the right index finger (SR3) and the letter O – with the right middle finger (SR4). Responses were made by producing a flexion with each of the four fingers in force-measuring devices.

Subjects performed the 4-CRT in two modalities – auditory and visual. Auditory stimuli (duration 300 ms, intensity 67 dB SPL) were delivered via headphones binaurally. Visual stimuli with the same duration were shown in the middle of a monitor (visual angles 1° horizontal/1.5° vertical, 50 cd/m^2) situated 1.5 m in front of the subject. Interstimulus intervals varied between 1440 and 2160 ms (mean 1800 ms). When the response was slower than 700 ms a feedback tone was delivered. This tone had to be avoided.

Data were recorded in three consecutive experimental days. Sequences of auditory and visual blocks were counterbalanced across subjects. EEG was recorded from 64 channels with Cz being the recording reference. In parallel, muscle activity (electromyogram, EMG) was recorded from the forearms, and mechanograms were recorded from the responding finger. The EEG traces were scanned for gross electrooculogram (EOG) and EMG artifacts. Contaminated trials were discarded along with records exceeding ±50 μV. Slight horizontal and vertical eye movements preserved in the accepted epochs were corrected by means of a linear regression method for EOG correction [9]. Individual averages for each stimulus type in each recording session were produced, with the number of sweeps being between 30 and 45. For quantification and topography assessment, data were transformed to current source density (CSD) [17]. The SCD transform produces reference-free signals, whose local cortical generation can be reliably considered [17]. Additionally, CSD leads to a spatial enhancement of the recorded EEG activity [2, 3]. Two types of spatially enhanced averages were computed, stimulus-locked (event-related potential, ERP) and response-locked (response-related potential, RRP). They were used to enable a better distinction of the bioelectrical correlates of stimulus evaluation and response execution.

Aging-related response slowing

RT and error rate measures were subjected to ANOVA with a between-subjects factor Age (young vs. old), and within-subjects variables Modality (auditory vs. visual), Day (first vs. second vs. third) and Stimulus-Response (SR) type (SR1 vs. SR2 vs. SR3 vs. SR´ß4).

Figure 1 shows that RT was overall slower in the old than in the young adults (F(1/25) = 22.17, $p < 0.001$, mean 475 vs. 537 ms). This was observed for each stimulus-response type as verified by the non-significant Age x SR interaction, although the effect of the SR type was significant (F(3/75) = 22.5, $p < 0.001$). Age-dependent RT slowing was found for both the visual and auditory stimuli. Yet, responses of old adults tended to be delayed more after visual than auditory stimuli (Age x Modality, F(1/25) = 4.2, $p = 0.052$). In contrast to RT, the total number of errors did not depend on age.

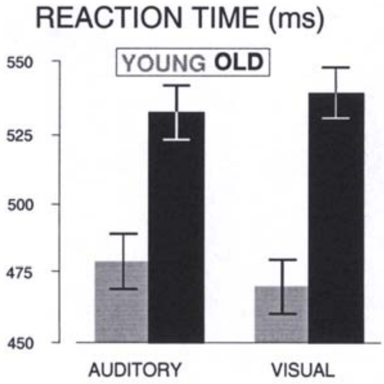

Figure 1: Group mean reaction time (RT) and SE of young and old adults in auditory and visual four-choice reaction task.

The observation that behavioural slowing reflected by RT was found for both modalities (auditory and visual) indicates that a more general, modality-independent deficit may produce delayed responses in the old subjects. An additional larger deterioration of visual-motor processing with age can also be suggested from the more pronounced slowing in the visual modality. Interestingly, in a simple reaction task using the same stimuli, RT delay in the old adults was not significant, indicating that choice reactions were especially vulnerable to aging alterations.

Central processing stages: parameters

Figure 2 illustrates electrophysiological parameters analysed in this study to describe consecutive stages of central information processing.

Perception: The first is the stage of sensory stimulus evaluation (*Figure 2a*). At that stage stimulus sensory characteristics are processed and stimulus recognition occurs. Early stages of stimulus evaluation are reflected by the P1 and N1 components of the stimulus-locked averaged potential[7, 21]. By measuring latencies and amplitudes of these components it is possible to examine differences in the speed and mode of early perceptual mechanisms between young and old adults [1, 8, 10, 12, 18, 19, etc.]. Late stages of stimulus relevance and context evaluation are thought to generate late endogenous ERP components, such as P300[20], which, in this task, coincide with motor-related potentials. Thus, to describe age-related differences in perception, amplitude and latency of P1 and N1 ERP components were measured and analysed (*Figure 2a*).

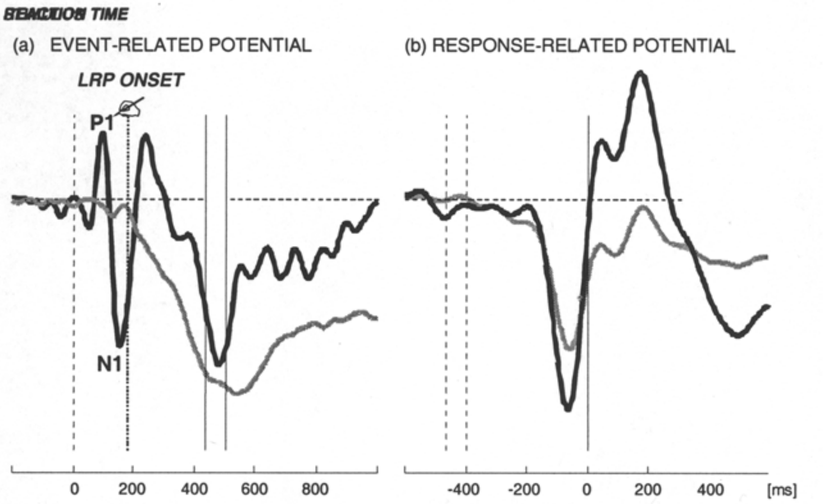

Figure 2: Schematic illustration of analyzed parameters in (a) stimulus-locked averages (event-related potentials, ERPs) and (b) response-locked averages (response-related potentials, RRPs). Dense lines show original signal averages, light lines show Lateralised Readiness Potentials (LRPs, i.e., difference waves computed by subtracting ERP (RRP) recorded at the ipsilateral motor cortex from ERP (RRP) recorded at the contralateral motor cortex). Indices of perception (P1, N1), sensorimotor integration (LRP onset), and motor activity (motor-related potential) are also shown.

Sensorimotor integration: Upon need of responding to an external stimulus, response-related mechanisms are switched on immediately after or even in parallel with stimulus identification. One parameter that has been recognized to reflect the initiation of motor-related processes is the Lateralised Readiness Potential, LRP [5]. Motor response execution activates specific regions of the primary sensorimotor cortex contralateral to the responding effector (or hand), and such activation cannot be observed at the ipsilateral motor cortex. As shown in Figure 2a, if the difference between contra- and ipsilateral ERPs (e.g., the LRP) is measured at motor cortical locations, the start of this difference would reflect the time when the effective movement is initiated. In the present study, the onset of the LRP was analysed to see if RT slowing might originate from slowing of central response initiation. Because SR type had a significant effect on RT, LRP was not calculated in the classical way [5] but was computed as a C3-C4 difference for right-hand, and as a C4-C3 difference for left-hand responses. LRP onset was measured as the time when a significant divergence between ERPs at C3 and C4 was detected.

The correct motor response can be initiated after stimulus is identified, stimulus information is matched to the associated motor program, and motor selection is made. Altogether, these processes can be regarded as reflecting sensorimotor integration. The time when the adequate motor response begins (LRP onset) would reflect the speed of sensorimotor integration mechanisms.

Motor processing: Figure 2a shows that stimulus-locked averaging cannot extract motor-related potentials because of the varying response latencies. To extract motor-related activity it is necessary to make response-locked averaging. As demonstrated in Figure 2b, this procedure emphasizes and enhances motor-related components. On the contrary, stimulus-locked components are smeared in the RRPs. To compare motor-related processes between young and old adults, RRPs were analysed at relevant locations at the contralateral motor cortices.

Measurable parameters were statistically assessed by means of a repeated measures analysis of variance. The exact analysis designs are explained for each parameter. For repeated-measures variables with more than two levels, the Greenhouse-Geisser correction procedure was employed, with original degrees of freedom (*df*) and corrected confidence probabilities (*p*) being reported.

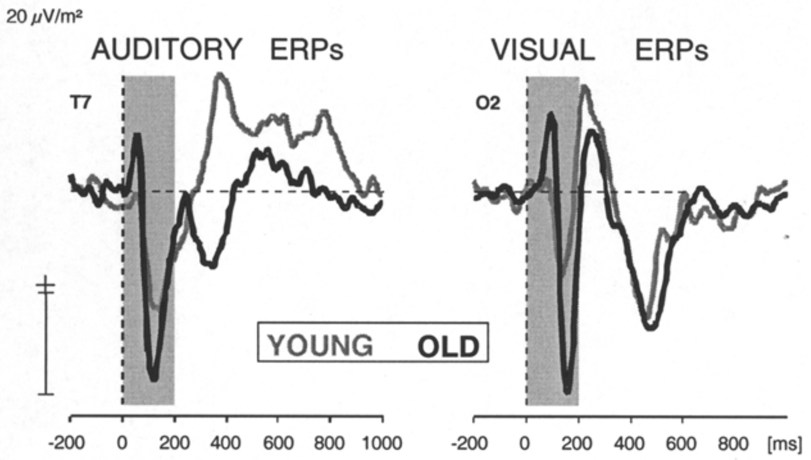

Figure 3: Grand average auditory and visual ERPs at modality-specific electrodes of young and old adults. Shaded areas indicate the latency range of analysed components, P1 and N1.

Figure 3 shows early components of spatially enhanced ERPs at modality-specific sensory areas – temporal for the auditory and occipital for the visual ERPs. Auditory P1 and N1 components manifested the expected topographical distribution at bilateral temporal and vertex locations, with larger N1 amplitudes found for the left hemisphere. Visual P1 and N1 components displayed bilateral scalp distribution over the occipital cortex. Therefore, statistical analysis was performed separately for auditory and visual ERPs from the temporal and occipital locations, respectively, where the early components were mostly expressed. The repeated-measures ANOVA design was Age x Day x SR type.

As illustrated in Figure 3, comparing early ERP components (P1, N1, shaded areas) between young and old adults at modality-specific locations revealed prominent aging-dependent differences: (1) The amplitude of each of the early ERP components was larger in the old adults. A significant main effect of age was found for P1 amplitude (auditory ($F(1/25) = 5.01$, $p < 0.05$) and visual ($F(1/25) = 5.92$, $p < 0.05$). Age-related amplitude enhancements of N1 tended to depend on SR type and Day. (2) Since slowing in perception may precede and cause follow-up delays of subsequent processes, a question of interest was whether perceptual processes as reflected by early components latencies slowed down with aging. In line with previous studies (rev. [1]), P1 and N1 latencies of auditory ERPs did not differ between the two age groups ($F(1/25) < 0.9$, $p > 0.3$). Yet, P1 latency to visual stimuli was significantly longer ($F(1/25) = 12.36$, $p < 0.005$) in old (mean 87 ms, SE = 2.8) relative to young adults (mean 72 ms, SE = 2.7). The same trend was detected for visual N1 component ($F(1/25) = 3.0$, $0.05 < p < 0.1$; mean 152 ms, SE = 5.3 for old adults; mean 140 ms, SE = 5.1 for young adults).

Thus, it can be concluded that: (1) In a 4-CRT task, aging is accompanied by delays in perceptual processes only in the visual, but not in the auditory modality, and (2) a modality-unspecific augmentation of early stimulus evaluation mechanisms occurs in the old adults as indexed by larger P1 amplitudes [11]. However, despite the lack of perceptual slowing in the auditory modality, RT to auditory stimuli were longer in the old adults. Also, a 15-ms perceptual slowing in the visual modality, though significant, was much less than the aging-related RT slowing to visual stimuli. Thus, the general pattern of these results indicates that sensorimotor response delays with age cannot be explained with deficits in early perceptual mechanisms.

Sensorimotor integration

In *Figure 4*, stimulus-triggered LRPs of young and old adults are shown. Importantly, despite the pronounced LRP augmentation with age, no significant differences in LRP onset were detected between young and old adults for either modality ($F(1/25) = 2.1$, $p = 0.15$; group mean 237 ms, SE = 5.0, for young, and 247 ms, SE = 4.8, for old adults). No significant interactions of the Age factor with other variables were found for LRP onset.

This indicates that sensorimotor integration in a choice-reaction task is not delayed significantly with aging, and old adults appear virtually capable of initiating the effector mechanisms of adequate response production as fast as young adults. Given the aging-related delay in early visual perception (see above), it is notable that some compensation occurs in the old subjects to speed up motor response initiation. This finding is of special interest with regard to recently reported compensatory networks in the elderly identified by means of brain imaging techniques [4, 22]. The present results from the visual modality indicate that in a sensorimotor choice reaction task, subtle perceptual delays in old adults may be compensated before response initiation.

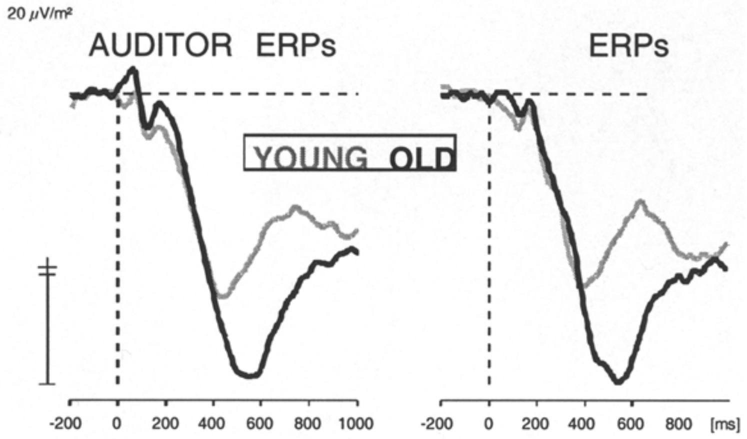

Figure 4: Grand average LRPs of young and old adults in auditory and visual choice reaction tasks. LRPs of four stimulus-response types are averaged.

Motor-related processes

Figure 5 illustrates RRPs synchronized with the response and shows that RRPs of old adults substantially differ from those of young adults by being larger in magnitude and longer in duration. The topographical distribution of RRPs (not shown) was similar for the two age groups and was characterized by larger amplitudes over the motor cortex contralateral to the responding hand. Statistical evaluation

(Age x Day x SR type) of peak RRP latency (largest negative component at contralateral motor cortex) did not reveal differences between young and old subjects. However, peak amplitudes were larger for old than young adults ($F(1/25) = 5.51$, $p < 0.05$). Likewise, analysis of area measures of RRP activity between 200 ms before and after the response showed significantly larger values for the groups of old subjects ($F(1/25) = 4.6$, $p < 0.05$), which obviously resulted not only from larger peak amplitudes but mainly from longer duration of the motor-related potential. These aging differences in the motor-related activity at contralateral electrodes can be associated with the prominent effects of age on stimulus-locked LRP magnitude and timing, as shown in *Figure 4*.

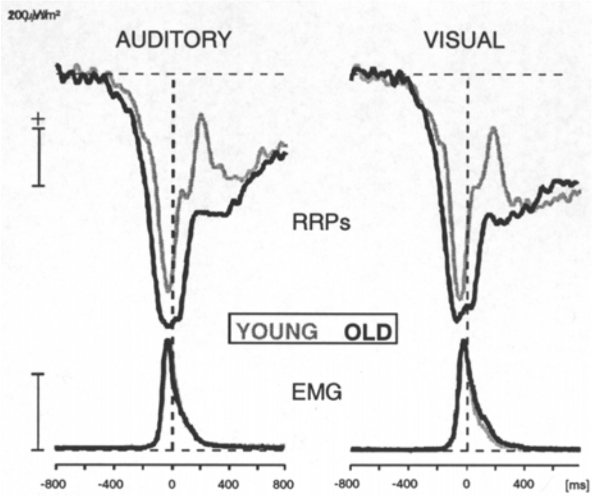

Figure 5: Grand average auditory and visual RRPs at the contralateral motor cortex of young and old adults (upper panel). Grand average EMG from responding effectors of young and old adults (lower panel).

These results indicate that after response initiation in the contralateral motor cortex, it takes longer for the central motor processes to support response execution in the old subjects. Exactly the same RRP enhancement and prolongation was observed for the two modalities (auditory and visual – *Figure 5*), indicating a modality-independent alteration of motor processing in a 4-CRT as a function of age.

Figure 5 additionally shows EMG activity recorded from the responding muscles. It is noteworthy that EMGs did not differ between young and old adults. Also, the mechanograms were very similar for the two groups. Thus, differences in the activation of motor cortical areas may not have resulted from differences in the force, strength, acceleration, or other characteristics of the movement itself.

The interpretation of these RRP findings is that old adults need stronger and longer activation of the contralateral motor cortex to trigger and promote response execution. This electrophysiological result is consistent with MRI findings, according to which additional activation of the contralateral sensorimotor cortex is recruited by elderly adults even for the performance of a simple motor task [15]. While higher thresholds of cortical motoneurons may be suggested to lead to the observed over-activation, the reasons for altered thresholds may stem from a general decline in cortico-striatal neurotransmission (e.g., [24]), or from a functional dysregulation of executive control mechanisms involved in choice response selection and execution [6, 13]. With respect to behavioural slowing with aging in a choice reaction task, response delay is caused obviously by the additional time needed by old subjects to develop an extra activation of the contralateral motor cortex.

Conclusions

(1) In a four-choice reaction task, behavioural responses (RT) are delayed with increasing age in adults.
(2) This behavioural slowing cannot be explained with delays in central processes of perception (as reflected by early ERP component latencies), and sensorimotor integration, response selection and initiation (as reflected by the onset of the lateralised readiness potential).

(3) The age-related behavioural slowing is accompanied by and probably due to a delay in the central processing mechanisms of motor response execution.

Acknowledgment

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Age-related Differences in Executive Control: Introducing the Canavan Conditional Associative Learning Task (C-CALT)

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Abstract

In this study we present preliminary results about the normalisation and validation of the Spanish version of the Canavan Conditional Associative Learning Task (C-CALT [1]). This test consists of two parts: one verbal part involving colour-words associations, and one non-verbal one involving colour-image associations. Earlier studies showed that performance in conditional associative learning tasks depends mostly on executive functioning [5, 6], and declines with normal ageing [1].

The purpose of this study was to explore the association between normal ageing and performance in the C-CALT and several other tests of executive function (i.e., Trail Making Test, FAS, etc). A sample of 80 healthy volunteers without any neurological or psychiatric condition was divided into four age groups: 16 to 24, 25 to 44, 45 to 64, and 65+ years-old. IQ scores were prorated using six of Wechsler's Adult Intelligence subscales (WAIS-R Comprehension, Vocabulary, Similarities, Digit Symbol, Block Design and Object Assembly) [10].

The results showed reliable internal consistency for both the C-CALT verbal and non-verbal halves, and a significant relationship between these and TMT and FAS scores. Age-related differences in cognitive performance were found between young (16 to 24) and middle-aged (25 to 44) adults compared to adults over 45 years-old. These results

suggest that while most non-executive cognitive functions remain largely preserved through age, an age-related decline in executive functioning seems to appear towards the third quarter of a life-span.

Introduction

The definition of *executive functioning* still remains a controversial issue. Traditionally executive functioning has been considered related to processes such as working memory and selective attention. It has also been linked to functions such as *inhibition*, *planning*, *monitoring* and *control* [9]. This author refers to executive control as those kind of cognitive processes necessary to perform novel tasks, set goals and plans, choosing between alternative courses of action, and estimating the probability of success of different actions before they occur, so as to maximise behavioural outcomes. According to Rabitt [9], one critical characteristic that distinguishes *executive* from *non-executive* functions is the ability to detect and correct mistakes, and flexibly adapt one's own behaviour on the basis of environmental feedback. However, much remains to be known about a possible taxonomy of executive control processes [8].

In recent years, different authors have consistently reported the existence of age-related changes in executive functioning [4, 9]. However, it remains controversial whether executive functioning should be regarded as a pure construct, or if it denotes a mixture of different and independent skills, each with its own pattern of age-related decline.

For instance, it has been pointed out that age-related decline in cognitive performance could be attributed to a general decrease in processing speed rather than to a specific decay in executive control processes. One pending issue is that most neuropsychological tests were not designed to tease apart the contribution from basic motor or perceptual processes from those genuinely related to the executive control of cognition [9].

The present Conditional Associative Learning Task was originally designed by Canavan et al. [1] after an earlier proposal that conditional associative learning tasks could be associated to executive functioning [5]. In this kind of tasks, subjects have to learn arbitrary associations between pairs of stimuli and so need constant feedback in order to establish these associations. This type of associative learning task has been shown to be similarly compromised in neurological patients with damage to the frontal cortex and the hippocampus [5, 7]. After these early studies, a new conditional associative learning task was proposed that minimised the motor demands made upon the patients [1]. This new task required the ability of learning arbitrary associations between a number of target items and colour plates, based on the contextual feedback provided by the experimenter. The ability to flexibly modify or discard the incorrect associations, and adaptively refresh or update the correct ones is supposed to hinge upon executive control processes.

The two main aims of the present study were: (1) to evaluate age-related changes in executive functioning in a sample of healthy volunteers, and (2) to analyse the relationship between the C-CALT and other tests of cognitive functioning such as the Trail Making Test, FAS and some WAIS subscales [2]. In order to achieve these objectives, we tested the following two hypotheses: (1) C-CALT scores will be specifically sensitive to age-related cognitive decline, and (2) C-CALT scores will be related to other tests of executive functioning.

Method

Subjects: 80 volunteers (37 men, 43 women) were distributed in four age groups: Group 1 ranged from 16 to 24 years-old (N = 15; mean = 19.9; Sd = 2.3); Group 2 ranged from 25 to 44 years-old (N = 32; mean = 32.8; Sd = 6.8); Group 3 ranged from 45 to 64 years-old (N = 20; mean = 53.9; Sd = 6.0); and Group 4 included people older than 65 years-old (N = 13; mean = 68.1; Sd = 2.5) (see *Table 1*). This sample was selected according to the 2002 Spanish census distribution. The exclusion criteria for this sample were (a) any perceptive or motor disease, (b) any history of neurological or psychiatric disease,

(c) alcohol consumption (d) and consumption of drugs with nervous system effects.

Materials: The main tool was a version of the task developed by Canavan et al. [1], the Canavan Conditional Associative Learning Task (C-CALT). The task consists of two parts. In the verbal part target stimuli are written abstract words. In the non-verbal part target stimuli are visual abstract patterns (see *Figure 1*). There are six verbal targets and six visual targets. In both the verbal and visual parts, each of the six targets are to be paired with six different colours, based on a set of predetermined but arbitrary associations initially unknown to the subject. The correct associations are to be determined based just on the feedback delivered by the examiner. The task develops as follows: A list of six targets and coloured plates are presented to the subject. Then the subject picks up the card and physically matches one of these target cards with one colour plate. Then the examiner gives feedback as to whether the pairing is "correct" or "incorrect". The subject must keep trying different target-colour associations until the correct one is found. Once the subject has correctly paired the first target stimulus with its associated colour plate, the next colour plate is showed, and the whole process starts again. This matching process restates until the six colour plates have been correctly associated with their corresponding targets. Subjects are told to remember these associations in order to complete another three blocks of trials. Each block contains the same target stimuli but re-arranged in a different order. Colour plates are also presented in a different order. The examiner must score the number of perseverative errors made by the subjects while attempting to complete a set of six target-colour associations. A perseverative error is defined as any incorrect association made after having had prior feedback about the correct association. A high score of perseverative errors has been shown to be a sensitive index of executive dysfunction [4]. Importantly, the C-CALT does not make any time requirements to complete the target-colour associations. Henceforth, it can be assumed that C-CALT performance is not influenced by processing speed, a complex function known to decline with age.

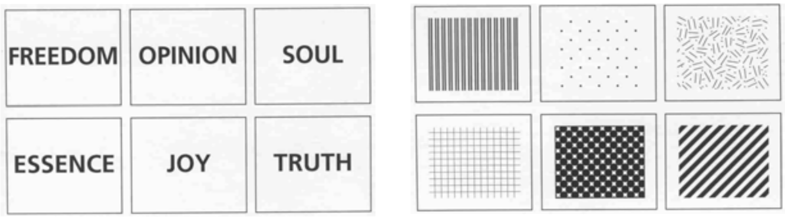

Figure 1: Examples of written words (left) and visual patterns (right) of the Canavan Conditional Associative Learning Task (C-CALT).

The following neuropsychological tests were also included in our battery:

- 6 WAIS subscales (Wechsler Adult Intelligence Scale-Revised, Comprehension, Vocabulary, Similarities, Digit symbol, Block design and Object assembly).
- TMT (*Trail Making Test*); the TMT – part A has been regarded as an index of perceptual and motor processing speed; the TMT – part B consists of a divided attention task which demands executive control.
- FAS (also known as *Controlled Oral Word Association Test*); a task that measures verbal association fluency, and is considered as related to other executive functions.

The order of administration of the tests was counterbalanced. The time for each testing session was about two hours, with a 15 minutes break between tasks.

Independent variables. We looked for differences between four age groups, as described before.

Dependent variables. Indexes of executive functioning were derived from the following test scores:

- TMT: the time taken to complete both part A and part B was scored, and then the time difference between part B minus part A (in seconds) was computed as an index of executive functioning.

- FAS: the number of words starting by “f”, “a”, and “s” produced during 1 minute for each letter in turn.
- WAIS subscales: two variables were scored, one for the visuo-constructive subscales, and the other one for the verbal subscales. Both subscales used their respective standardized scoring system (scores were not age-corrected).
- C-CALT: the number of perseverative errors for the verbal and non-verbal parts were scored and used as separate variables.

Results

Overall means and standard deviations for each of the four age groups across the main dependent variables are reported in *Table 1*. The results of simple effects showing the significance of the post-hoc pairwise comparisons between groups are presented in *Table 2*. *Figure 2* shows the pattern of performance (in Z scores) for each dependent variable across the four age groups.

TMT: There was a main Group effect for the TMT-A scores [F(3,76) = 13.9; $p < 0.0001$]. The post-hoc tests of simple effects (with the Bonferroni correction) showed significant differences between groups 1 and 3 ($p < 0.001$), groups 1 and 4 ($p < 0.001$), between groups 2 and 3 (p 0.005), and between groups 2 and 4 ($p < 0.001$). These results suggest that age groups differed in perceptual and motor processing speed. Therefore, this variable was used as a covariate in all of the subsequent ANOVAs in order to correct for the influence of processing speed and distil the genuine age differences in executive functioning.

Uncorrected TMT B-A scores showed a main Group effect [F(3,76) = 8.6; $p < 0.0001$], and post-hoc tests of simple effects showed that there were also differences between groups 1 and 3 ($p < 0.005$), and between groups 1 and 4 ($p < 0.005$), being the best performance for group 1 (age 16 to 24). Corrected TMT B-A scores showed a main Group effect [F(3,76) = 5.4; $p < 0.002$], and post-hoc tests of simple effects showed that there were also differences between groups 1 and

2 versus group 3 ($p < 0.005$), being the worse performance for group 3 (age 45 to 64).

FAS: There was a main Group effect for uncorrected FAS scores [F(3,76) = 8.7; $p < 0.0001$], reflecting significant differences between groups 2 and 3 ($p < 0.001$) and between groups 2 and 4 ($p < 0.001$). There were no differences between groups 3 and 4. For corrected FAS scores, there was a main group effect [F(3,76) = 4.9; $p < 0.004$], but differences appeared only between age groups 2 and 3. In all cases, the highest scores were obtained by age group 2 (age 25 to 44). When TMT-A scores were used as covariates in the ANOVA, they manage to explain just over 30% of FAS scores ($R^2 = 0.31$).

WAIS subscales: Uncorrected WAIS Verbal scores showed no differences between groups. Uncorrected WAIS Visuo-constructive scores showed a main Group effect [F(3,76) = 6.7; $p < 0.0001$], and post-hoc tests of simple effects showed that there were also differences between groups 1 and 2 versus group 3 ($p < 0.05$), and between groups 1 and 2 versus group 4 ($p < 0.01$), being the worse performance for group 4 (age 45 to 64). However, corrected WAIS Visuo-constructive scores did not yield significant group differences [F(3,76) = 1.5; $p = 0.23$]. When TMT-A scores were used as covariates in the ANOVA, they managed to explain about 30% of WAIS Visuo-constructive scores ($R^2 = 0.30$).

C-CALT: Uncorrected C-CALT Verbal scores showed a main Group effect [F(3,76) = 11.7; $p < 0.0001$], and post-hoc tests of simple effects showed differences between groups 1 and 2 versus groups 3 and 4 ($p < 0.01$; see *Table 2*). Uncorrected C-CALT Non-Verbal scores showed a main group effect [F(3,76) = 11.7; $p < 0.0001$], and post-hoc tests of simple effects showed that there were also differences between groups 1 versus group 3 ($p < 0.01$), and between group 2 versus groups 3 and 4 ($p < 0.01$), being the worse performance for group 3 (age 45 to 64; see *Table 1* and *Figure 2*). This overall pattern of group differences still held even when C-CALT scores were corrected for TMT-A performance. This was in spite of a significant contribution of TMT-A scores to the group differences in C-CALT Non-verbal – but not Verbal – scores. Indeed, when TMT-A scores were used as covariates in the ANOVA, they manage to explain about 37% of C-CALT Non-Verbal scores ($R^2 = 0.37$). Pearson correlation coefficient between the Verbal and Non-verbal parts of C-CALT was R = 0.73 (p 0.001).

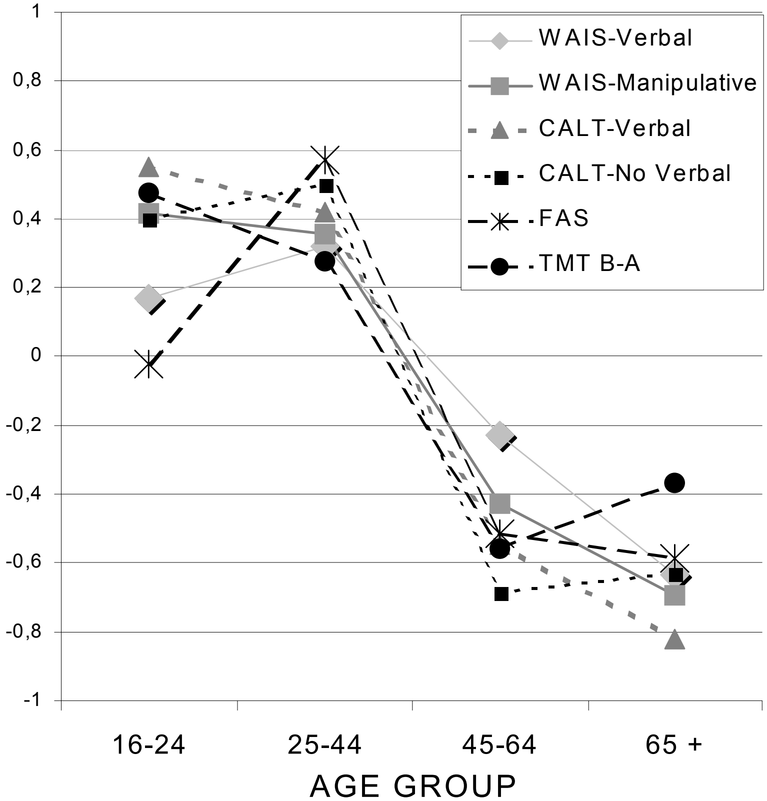

Figure 2: Profiles of Z scores across age groups for each dependent variable.

Table 1: Means (and SDs) for all dependent variables across the 4 age groups

	C-CALT Perseverations		FAS	TMT B-A	WAIS	WAIS
	Verbal	Non-verbal			Vis-Cons.	Verbal
Group 1 *(n=15, 16 to 24)*	9.6 (7.6)	6.9 (9.2)	40.4 (12.2)	35.2 (14.3)	12.6 (3.0)	13.2 (1.6)
Group 2 *(n=32, 25 to 44)*	11.2 (7.5)	5.6 (5.4)	48.0 (12.6)	43.2 (28.5)	12.4 (2.5)	13.6 (1.3)
Group 3 *(n=20, 45 to 64)*	22.7 (12.9)	20.9 (14.5)	34.0 (10.2)	76.9 (59.2)	10.2 (2.7)	12.3 (2.6)
Group 4 *(n=13, 65+)*	25.9 (12.9)	20.2 (15.5)	33.1 (8.7)	69.2 (31.3)	9.5 (1.9)	11.5 (3.0)

Table 2: Summary of significant group differences for each dependent variable

	C-CALT Perseverations						FAS			TMT B-A			WAIS			WAIS		
	Verbal			Non- verbal									Vis-Cons			Verbal		
Groups → ↓	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**
Group 1 *(n=15, 16 to 24)*		■	■		■						□	□		□	■			
Group 2 *(n=32, 25 to 44)*		■	■		■	■		■	■					□	■			
Group 3 *(n=20, 45 to 64)*																		

Key for statistically significant group comparisons (with Bonferroni correction):

■ $p < 0.01$ □ $p < 0.05$

Discussion

It has been frequently reported that normal ageing is accompanied by a decline in cognitive functioning [4, 9]. However, it remains controversial whether this decline can be genuinely attributed to a specific decay in executive functioning, or it depends on a more general decrement in the speed of perceptual and motor processes. The main aim of this study was to employ a newly developed test of executive functioning, the Canavan Conditional Associative Learning Task (C-CALT), to describe the specific contribution from executive control functioning to the cognitive decline related to ageing. The C-CALT, together with a representative battery of more traditional “frontal-lobe” tests, were administered to a sample of normal volunteers ranging from 16 to 75 years of age, and distributed into four age groups (see *Table 1*). In order to estimate the contribution of general perceptual and motor processes, and to isolate them from genuine executive functions, TMT-A scores were taken as indexes of perceptual and motor processes, and introduced them as covariates in the main ANOVAs for the other dependent variables.

TMT-A scores reflected the expected age-related decline in processing speed of basic perceptual and motor functions, and the same happened for all the other uncorrected measures (*Figure 2*). However, a different and more interesting pattern of results appeared when TMT B-A, FAS, WAIS-R and C-CALT scores were corrected using TMT-A scores as a covariate. In fact, results from these covariance analyses suggested that TMT-A scores were able to explain about 30% of the variability in FAS and WAIS visuo-constructive test scores, and up to 37% of the non-verbal C-CALT scores. In spite of this large contribution from TMT-A scores to the variability in most of the other dependent variables, some age-related group differences also prevailed after this correction.

For instance, for corrected FAS performance age-related group differences reached significance only between groups 2 and 3, which suggests that the older age group did not present any really significant decline in verbal fluency, independent from a decline in more basic perceptual and motor processes. Likewise, an age-related decline in WAIS performance was found only for the uncorrected visuo-constructive WAIS subscales. Interestingly enough, corrected WAIS visuo-constructive scores did not yield any age-related group differences, suggesting that the former might be due to a general slowness in perceptual and motor processing speed. This is particularly important since group differences were found only in the visuo-constructive

– but not the verbal – subscales, which also place a strong time pressure on the subject, thus favouring an interpretation of the referred age-related effects in terms of perceptual and motor processing speed.

In marked contrast, verbal and non-verbal C-CALT scores yielded significant age-related group differences, even after introducing TMT-A scores as a covariate in the analyses. Age-related C-CALT differences reached significance even though TMT-A scores explained up to 37% of the variability in the non-verbal C-CALT scores. This result suggest a contribution from factors other than general perceptual and motor processing in C-CALT performance, which makes it a potentially valuable and sensitive index of executive functioning, beyond those used in conventional neuropsychological assessment procedures. Likewise, C-CALT scores provide some other relevant information worth mentioning. Firstly, there is a significant relationship between the C-CALT's verbal and non-verbal halves (correlation of R = 0.73). This high correlation suggests that, unlike many other indexes of executive functioning, age-related variability in C-CALT performance is not highly influenced by the subject's linguistic ability. Secondly, both the verbal and non-verbal C-CALT perseveration score yielded differences between young (16 to 44 years-old) and older adults (+45 years-old), thus suggesting a significant age-related decline in C-CALT performance. Although *Figure 2* shows a similar pattern of results for all the uncorrected measures, most of these measures cannot be taken as direct indexes of executive functioning, independent from general perceptual or motor processing. Therefore, C-CALT scores might help us to isolate a genuine age-related decline in executive functioning independent from a deficit in more general perceptual-motor skills.

These results showed reliable internal consistency for both the C-CALT verbal and non-verbal halves, and a significant relationship between these and TMT and FAS scores. Age-related differences in cognitive performance were found between young (16 to 24) and middle aged (25 to 44) adults compared to adults over 45 years old. These results suggest that while most non-executive cognitive functions might remain largely preserved through age, an age-related decline in genuine executive functioning seems to appear towards the third quarter of a life-span. Future research should address how these different functions interact with each other, and which other factors are involved that could explain the lower executive performance towards the third quarter of a life-span.

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ERP (P3) and Aging – the Role of Attention

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Abstract

The present study examines a group of healthy persons (N = 89) in the age range of 20 to 70 years with ERP measures of automatic and controlled attention (P3a and P3b) in an oddball task. Results indicate a significant effect of age on P3b, but not on P3a latency. Amplitudes are affected by age for both P3a and P3b. While the finding on most electrodes is an amplitude reduction, there is a significant increase in amplitude measured frontally for P3b. The results are consistent with a model of reduction in specificity of cerebral activation in aging, combined with a compensatory increase in frontal activation when a demanding task is presented.

Introduction

Attention is one of the central areas of research in cognitive neuroscience, and the currently held view identifies a specific cerebral attention system with several subsystems [11].

In research with event related potentials (ERP) a set of paradigms have been developed to measure different aspects of attention [7]. These include paradigms involving involuntary (automatic) attention, as well as focused and sustained selective attention. The majority of studies involve the oddball paradigm, in which the main ERP-indicator of supra-modal focused attention (P300) has been identified. The oddball task is a continuous performance task (CPT, see [12]) in which the person monitors a series of stimuli and reacts to the presence of a target while ignoring distractor stimuli. The P3a component is elicited by stimuli deviating from the task context, and is known to be sensitive to frontal lobe injuries, whereas the P3b component is elicited by stimuli identified as targets, and is sensitive to temporo-parietal as well as hippocampal injuries [10, 15]. Although observed waveforms usually reflect some degree of component overlap, recent studies have described paradigms that successfully discriminate between P3a and P3b components of the P300 complex in the visual and the auditory modality [3; 10]. Both P3a and P3b are regarded as reflecting essentially supra-modal underlying attention mechanisms.

Neuroimaging and ERP studies have been mainly concerned with identifying basic cognitive mechanisms, whereas studies relating the functioning of these mechanisms to individual variations in performance are only in their beginning. In clinical neuropsychology and differential psychology the study of individual differences and the variation in underlying mechanisms is a central theme. The study of attention has played a varying role in these fields, the problem being that attention is a concept used without a very clear conceptual or empirical basis. Studies seeking to operationalise the elusive concept of speed of processing have therefore looked to ERPs as an attractive option [4]. In the literature on cognitive aging [13] variation in speed of performing cognitive tasks is seen as accounting for a large proportion of age related variance.

The present report focuses on the effect of aging on P3a and P3b, here conceived as physiological measures of attention. Previous studies reviewed by Polich [8] have not differentiated between P3a and P3b, and the paradigms used indicate that they probably measure mainly P3b. These studies have shown a consistent increase in latency with increasing age, whereas the findings on amplitude are less consistent. However Anderer et al. [1] find that P3b amplitude is attenuated parietally by 0.15 μV per year leading to a more equipotential distribution of amplitude in the frontal-posterior axis with increasing age. Recent studies attempting to differentiate the age effects on P3a and P3b have not been conclusive, but Friedman et al. [5] report that the novelty P3 shows similar scalp distribution as the target P3b for the elderly, and Friedman et al. [6] report a frontal scalp focus in older persons. Walhovd and Fjell [16] report that P3 amplitude to target and distractor stimuli are highly correlated and show similar relations to aging. Unknown factors that may contribute to the findings are task variables as modality and difficulty, as well as subject variables including age range, gender and general cognitive level of participants.

Methods

Participants: They were 89 healthy persons who volunteered to undergo a set of ERP and neuropsychological studies as part of a project with the aim of gathering a data base on normal cognitive functioning. Only persons with no previous history of remedial education, and without a record of neurological or psychiatric disorders requiring treatment, were included. Participants signed a statement of informed consent, and the project was approved by the Regional Committee on Medical Research Ethics. Further characteristics of the group are shown in *Table 1*.

Table 1: Participant characteristics (N = 89), FSIQ = Full scale IQ, WASI = Wechsler Abbreviated Scale of Intelligence

	Gr. 1 Age 20 to 34 (n = 49)	**Gr. 2 Age 35 to 49 (n = 20)**	**Gr. 3 Age 50 to 69 (n = 20)**	**p**	
Gender (m/f)	23 / 26	10 / 10	9 / 11	n.s.	
Age (yrs)	25.8 ±3.7	42.2 ±4.8	61.1 ±5.1	***	*1≠2≠3*
Education (yrs)	14.2 ±1.7	15.7 ±2.7	16.0 ±2.3	**	*1≠2,3*
FSIQ (WASI)	115.5 ±7.7	115.0 ±7.2	112.5 ±9.5	n.s.	

n.s. = non significant; ** $p < 0.01$; *** $p < 0.001$

Stimuli: Three basic stimuli were used to construct an auditory duration discrimination task. The stimuli serving as targets and standards were two spectrally composite tones of 25 ms and 75 ms duration respectively, both with a 500 Hz fundamental frequency and harmonics at 1,000 Hz and 1,500 Hz as described by Sinkonen and Tervaniemi [14]. We added a distractor sound made with white noise which was spectrally band pass filtered (24 dB/octave) with an interval of 250 to 3000 Hz. All stimuli were windowed with a 5 ms rise/fall time. They were presented in a quasi random series of 360 stimuli with the restriction that a target was never followed by another target, and that no target occurred among the initial 10 stimuli. Targets (14 %) were 25 ms duration, 80 dB tones, standards (72 %) were 75 ms duration, 80 dB tones, and distractors (14 %) were 100 ms duration, 95 dB filtered noise. The stimuli were presented binaurally through calibrated earphones. Button press to targets were recorded.

EEG/ERP recording: Data were recorded online as a continuous EEG-file with event markers. Band pass filter settings were 0.05 to 70 Hz with a sampling rate of 500 points per second. Electrode placements followed the standard 10-20 with M1 as reference. A pair of electrodes placed above and below the left eye served as control for eye movements, and ground was placed on the forehead. The present report only includes midline electrodes, at which sites the P3a and P3b waveforms have maximum amplitudes, and which are suitable for analysing topographical differences in the anterior-posterior axis.

The continuous EEG record was segmented into sweeps of -100 to 1,000 ms relative to stimulus onset, baseline corrected and low pass filtered (15 Hz, 24 dB per decade attenuation). Correction for eye movement was performed, and epochs with amplitudes above ±100 µV were rejected before averaging.

ERP analysis: Grand average waveforms for target and distractor stimuli are shown for midline electrodes in *Figure 1*. Peak maximum amplitude around 300 ms was seen on the Cz electrode for distractors (P3a), and at around 370 ms on the Pz electrode for targets (P3b).

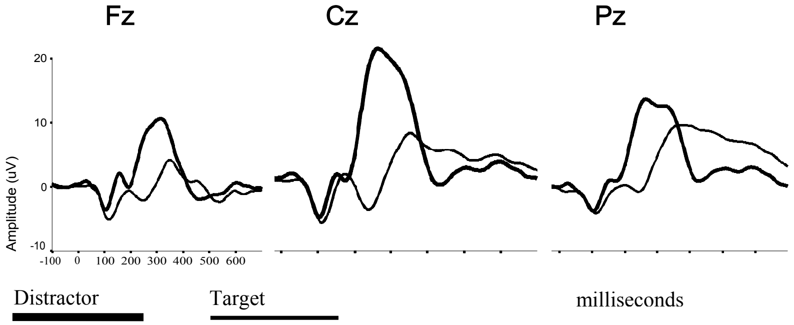

Figure 1: Average waveform for target and distractor stimuli

Based on the grand average waveforms, time windows were defined for localizing peaks in individual subjects. We measured the peak latencies in milliseconds and the corresponding amplitudes on the three midline electrodes (Fz, Cz, Pz) for each participant. P3a latency was defined as the time point of maximum amplitude in the time range 250 to 400 ms for the distractor stimulus. P3b latency was defined as the time point of maximum amplitude in the time range 300 to 500 ms for the target stimulus.

Results

The button press reaction in the ERP task was performed with an accuracy (hit rate) of 95 % and the false alarm rate was below 3 %. Values for P3a and P3b measures are given in *Table 2*.

Table 2: ERP results across age groups

	Gr. 1 Age 20 to 34 (n = 49)	**Gr. 2 Age 35 to 49 (n = 20)**	**Gr. 3 Age 50 to 69 (n = 20)**	**p**	
P3b Latencies					
Fz	361.3 ±37.7	369.8 ±48.4	437.0 ±55.7	***	*1,2≠3*
Cz	370.9 ±40.9	369.3 ±55.3	443.4 ±63.6	***	*1,2≠3*
Pz	378.8 ±37.2	382.0 ±58.1	426.0 ±53.8	***	*1,2≠3*
P3b Amplitudes					
Fz	2.4 ±4.6	6.4 ±4.2	6.6 ±4.7	***	*1≠2,3*
Cz	6.6 ±6.1	6.9 ±5.2	5.5 ±6.4	n.s.	
Pz	10.8 ±7.1	9.3 ±4.6	8.1 ±5.0	n.s.	
P3a Latencies					
Fz	301.0 ±28.6	288.1 ±37.0	295.8 ±37.2	n.s.	
Cz	276.7 ±31.1	281.4 ±30.6	287.3 ±27.8	n.s.	
Pz	284.5 ±37.6	284.1 ±31.2	286.7 ±28.0	n.s.	
P3a Amplitudes					
Fz	11.5 ±6.4	12.2 ±6.2	9.8 ±4.3	n.s.	
Cz	21.5 ±9.3	17.7 ±5.7	11.8 ±6.2	***	*1≠3*
Pz	15.8 ±7.5	12.1 ±5.1	8.3 ±5.4	***	*1≠3*

n.s. = non significant; *** $p < 0.001$

Significant age effects are found for P3b latency measured at Pz, Cz, and Fz. Pairwise comparisons indicate that the age > 50 group accounts for the significant latency increase. In young subjects latency at Fz leads Pz by 17 milliseconds, whereas in old subjects the tendency is for Fz to show longer latencies. For P3a latency there is no significant age effect, and the topographic distribution is similar across age groups.

For amplitudes there are significant age effects for both P3b and P3a amplitudes. The amplitude measured frontally increases with age for P3b, and the increase is significant already in the age > 35 group. The trend for decreasing amplitude at Pz, where P3b is typically measured, is not significant. P3a amplitude shows a gradual decline with age at the central (Cz) and posterior (Pz) electrode, whereas the amplitude at Fz seems to remain stable. These patterns on individual electrodes is tested more systematically by submitting the ERP data to a factor analysis and testing the variation on factor loadings with age (*Table 3*), and relation to age (*Table 4*).

Table 3: Principal component analysis of EPR measures with unrotated (g) and varimax rotated (F1-4, h^2) solutions

	g	**F1**	**F2**	**F3**	**F4**	h^2
P3b Latencies						
Cz	-.44	.95	.03	-.05	-.04	.91
Fz	-.38	.93	.03	-.09	.10	.89
Pz	-.44	**.92**	-.03	-.04	-.11	.87
P3a Latencies						
Cz	-.43	.07	.96	.00	-.04	.93
Pz	-.43	.05	.92	-.01	-.09	.85
Fz	-.36	-.08	**.82**	-.15	.04	.70
P3a Amplitudes						
Cz	.49	-.13	-.20	.91	.24	.93
Fz	.37	.06	.09	.88	.00	.85
Pz	.83	-.19	-.13	.85	.31	.79
P3b Amplitudes						
Cz	.70	-.01	-.11	.25	.92	.94
Pz	.68	-.07	-.12	.24	.83	.87
Fz	.75	.28	.10	-.00	**.77**	.78
Eigenvalues	3.7	2.7	2.5	2.5	2.3	
% variance	31.2	22.5	21.1	20.6	19.4	$\Sigma = 83.5$

Table 4: ERP-components across age groups

	Gr. 1 Age 20 to 34 (n = 49)	Gr. 2 Age 35 to 49 (n = 20)	Gr. 3 Age 50 to 69 (n = 20)	p	
F1	-0.3 ±0.7	-0.2 ±1.0	1.0 ±1.1	***	*1,2≠3*
F2	-0.0 ±1.0	-0.0 ±1.0	0.1 ±1.0	n.s.	
F3	0.3 ±1.1	-0.1 ±0.8	-0.6 ±0.8	**	*1≠3*
F4	-0.1 ±1.1	0.1 ±0.8	0.2 ±0.9	n.s.	

n.s. = non significant; *** $p < 0.001$; ** $p < 0.01$

The results bring out that there is a general factor shared by amplitudes on P3b and the posterior electrode for P3a, but which only explains about one third of the variance in the ERP data. Relating the rotated factor scores (F1 to F4) to age (*Table 4*) confirms the pattern shown in analysis of individual variables. Factor 1 (P3b latency), and factor 3 (P3a amplitude) show significant age effects.

Discussion

The general goal was to study P3a and P3b as measures of attention components and relate the results to aging. For this purpose we extended a paradigm previously shown to be optimal for eliciting an early attention related ERP component (mismatch negativity) by adding a distractor stimulus. The participants had to perform a relatively demanding duration discrimination task while ignoring the distractor, which deviated from the target in both duration, frequency spectrum and intensity. The paradigm therefore satisfies the general conditions specified by Comerchero and Polich [3] for eliciting P3a and P3b. The waveforms elicited by target and distractor stimuli show latencies and topographic distributions previously described as typical for P3a and P3b (see [10] and we therefore conclude that the waveform elicited by the distractor stimulus is a P3a while the target waveform is a P3b.

The participants in this study were a well characterized group of high functioning persons with above average IQ and education level. The older participants tended to have a somewhat higher level of education than the youngest group, but several of the young participants were students who had not completed their education. The samples were otherwise well matched for intellectual function and gender distribution.

The present results are consistent with previous findings in reporting a significant increase in P3b latency with increasing age [8]. This relationship was not found for P3a latency, in contradiction to the results of Walhovd and Fjell [16] who found similar age-latency correlations for both target and distractor P3s. We also confirm that aging leads to a more equipotential topographic distribution of amplitudes along the anterior-posterior axis, but the manner in which this pattern comes about is distinctly different for P3a and for P3b amplitude. For P3a there is a reduction with age of almost 50 % in central (Cz) amplitude, while the Fz amplitude is stable. For P3b there is a significant increase in frontal (Fz) amplitude combined with a weak trend for reduction in posterior amplitude (Pz), where the maximum is typically found in young persons. For P3b the central (Cz) amplitude is stable across the age range, resulting in a trend for Fz amplitude to become higher than Cz in the oldest group. This is consistent with the tendency for older persons to develop a frontal focus observed by Friedman et al. [6].

Previous studies (i.e., [6, 16]) have raised doubts if P3a and P3b show a differential relationship to aging. The factor analysis of the present data indicate that this is the case both for the latency and amplitude variables, where separate factors derived from both P3a and P3b show significant relationships.

Cognitive studies of aging have concluded that reduced speed of processing may be a common denominator of age effects. The ERP results indicate that the physiological changes underlying the attention related aspects of this reduction may be complex and involve both increased processing time (indexed by increase in ERP latencies) and reduction in available attentional resources (indexed by reduced ERP amplitudes). Neuroimaging studies of aging [2] have indicated that compensatory changes in distribution of cerebral activation may take place in cognitively demanding tasks during aging. The present results are consistent with the view that some compensatory increase in frontal activation takes place in a high functioning older group performing an attention demanding task.

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VI.

Effect of Gender on Brain Activity and Cognition

P3a and P3b from Visual Stimuli: Gender Effects and Normative Variability

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Abstract

Gender differences and normative variability were assessed in 120 young adults (60F, 60M) using a visual three-stimulus event-related brain potential (ERP) oddball paradigm (standard, target, distracter) in which subjects responded to an infrequent target. P3a components were obtained from the infrequently presented non-target distracter stimulus (a large blue square). P3b components were obtained from the target stimulus, which was a blue circle that differed slightly in diameter from the standard stimulus blue circle. Amplitude measures from the midline electrode sites demonstrated generally normal distributions, with P3a maximal at Cz and P3b maximal at Pz; latency measures increased for both potentials from frontal to parietal recording sites. P3a and P3b potentials from male subjects were typically smaller and earlier than those from female subjects. The findings suggest that P3a and P3b amplitude and latency from a three-stimulus distracter paradigm can be different between genders and are normally distributed.

P3a and P3b

The P300 event-related brain potential (ERP) component is often obtained using the “oddball” paradigm, wherein two stimuli are presented in a random order with one occurring more frequently than the other. The subject is required to discriminate the infrequent target stimulus from the frequent standard stimulus by responding to the target. The three-stimulus paradigm is a modification of the oddball task in which infrequent non-target or "distracter" stimuli are inserted into the sequence of target and standard stimuli. When perceptually "novel" (e.g., dog barks, colour forms, etc.) non-targets occur in a series of more "typical" (e.g., tones, letters of the alphabet, etc.) stimuli, a P300 component that is large over the frontal or central scalp areas is elicited. Recent analyses have confirmed that this potential, sometimes called the "P3a", is the same as the "novelty" P300 [26, 27]. As the novelty P300 exhibits a frontal/central scalp distribution, relatively short peak latency, and habituates rapidly, it has been interpreted as reflecting frontal lobe function and can be elicited in different populations and modalities [e.g., 3, 11, 29].

Stimulus context

Katayama and Polich [9] examined how stimulus context affects P300 scalp distribution by assessing discrimination task difficulty in a three-stimulus paradigm. The perceptual distinctiveness (and therefore discrimination difficulty) between the target and standard stimuli was manipulated in an auditory task using typical tone stimuli. For the conditions in which the target/standard discrimination was easy and the distracter highly discrepant, P300 amplitude for both target and distracter stimuli was largest over the parietal locations. However, for the conditions in which the target/standard discrimination was difficult and the distracter highly discrepant, P300 amplitude for the distracter was largest and its latency shortest over the central/parietal locations relative to target component measures. The results were replicated with visual stimuli, and the typical distracter stimuli elicited a P300 with a central/parietal maximum when the discrimination task was difficult [2].

These results suggest that typical stimuli can produce P3a and P3b components when the target/standard perceptual discrimination is difficult. Indeed, a direct comparison of visual novel and typical distracter stimuli across easy and difficult target/standard discrimination tasks produced a central/parietal maximum for the distracter (P3a) and a parietal maximum for the target (P3b) stimuli [3, 20]. This outcome implies that the P3a is generated when the attentional focus required for the primary discrimination task is interrupted by a distracting stimulus even if it is not novel. Hence, the relative perceptual distinctiveness among stimuli determines P300 amplitude topography for distracter and target stimuli, because these different components are generated by distinct neural structures [10, 12]. Magnetic resonance imaging (MRI) of grey matter volumes and fMRI data have demonstrated that P300 amplitudes from distracter stimuli are associated with frontal lobe area size and activation patterns, whereas P300 amplitudes from target stimuli are correlated with parietal area size [6, 16]. Additional ERP and neuroimaging findings also implicate frontal/central activity for the detection of rare and alerting stimuli, although the relationships among various negative and positive-going waveforms are debated [4, 15].

Present study

A major advantage of obtaining the P3a using typical (rather than novel) stimuli is that variability from stimulus factors can be experimentally well controlled. Pilot studies have found that robust visual stimulus P3a components can be obtained using difficult-to-discriminate standard and target circles that are similar in size with a relatively large blue square as the distracter stimulus. Subjects are instructed to respond only to the target, which produces a P3b. The present study was conducted to characterize the possible gender differences and normal variation for P3a and P3b by assessing a large sample of young adults as has been reported for P300 (P3b) from auditory stimuli [8, 18].

Methods

Subjects: A total of 120 young adult (60M, 60F) university students served as subjects (M = 19.2, SD = 1.0 yrs) and received course credit or pecuniary remuneration for their participation. All subjects reported being free of neurological and psychiatric disorders and provided written, informed consent.

Recording conditions: Electroencephalographic (EEG) activity was recorded from 15 electrodes that included Fz, Cz, Pz, F3/4, F7/8, C3/4, T7/8, P3/4, P7/8, referred to linked earlobes, with a forehead ground and impedances at 10 KΩ or less. Additional electrodes were placed at the outer left canthus and below the left eye to measure EOG activity with a bipolar recording. The bandpass was 0.01 to 30 Hz (6 dB octave/slope), and the EEG was digitised at 4.0 ms per point for 1024 ms, with a 100 ms pre-stimulus baseline. Waveforms were averaged off-line, such that trials on which the EEG or EOG exceeded ±100 μV were rejected; single-trial data were also subjected to an EOG correction procedure to remove any remaining artifact.

Stimuli and procedure: Visual stimulus categories were defined as the standard (circle, 4.5 cm diameter), target (circle, 5.0 cm in diameter), and distracter (square, 18.4 cm on a side), presented in a random series with probabilities of 0.76, 0.12, and 0.12, respectively. All stimuli were filled blue shapes presented on a light grey background from a computer monitor 1.5 m in front of the subject at a medium intensity level once every 2 s, with a duration of 75 ms. Response time and error rate were recorded. Prior to the paradigm presentation, a practice block consisting of 15 stimulus trials was presented to familiarize the subjects with the discrimination task.

Data analyses: The P300 component was defined as the largest positive-going peak occurring within 300 to 800 ms at each electrode. Peak amplitude was measured relative to the pre-stimulus baseline, and peak latency was measured from the time of stimulus onset. Only the P3a and P3b data from the midline electrodes were statistically analysed to facilitate evaluation of the anterior-to-parietal scalp topography among conditions, and other ERPs were not assessed.

Results

Task performance: A one-way analysis of variance (two genders) was performed on the percent error and response time from the target stimuli. No difference in error rate for each gender (F = 12.7 %, M = 10.8 %) was obtained ($P > 0.20$). Response time was longer for female compared to male (F = 610 ms, M = 577 ms) subjects, $F(1,118) = 4.9$, $P < .03$.

ERP analysis: Figure 1 presents the grand average ERPs from the midline electrodes for the target and nontarget stimuli for each gender. A two-factor (2 gender x 3 electrode) analysis of variance was applied to the amplitude and latency data for the P3a and P3b, with Geisser-Greenhouse corrections to the df employed. The results of these analyses are summarized in *Table 1*. Newman-Keuls post-hoc tests were also computed to assess specific mean comparisons.

Table 1: Summary of F-ratios and probability from 2 gender x 3 midline electrode ANOVAs performed on P3a and P3b amplitude and latency data.

	P3a				P3b			
	Amplitude		Latency		Amplitude		Latency	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Gender (1, 118)	16.54	0.001	8.09	0.005	1.79	---	9.42	0.003
Electrode (2, 236)	68.75	0.001	43.11	0.001	239.16	0.001	13.73	0.001
G x E (2, 236)	1.54	---	<1	---	7.06	0.001	<1	---

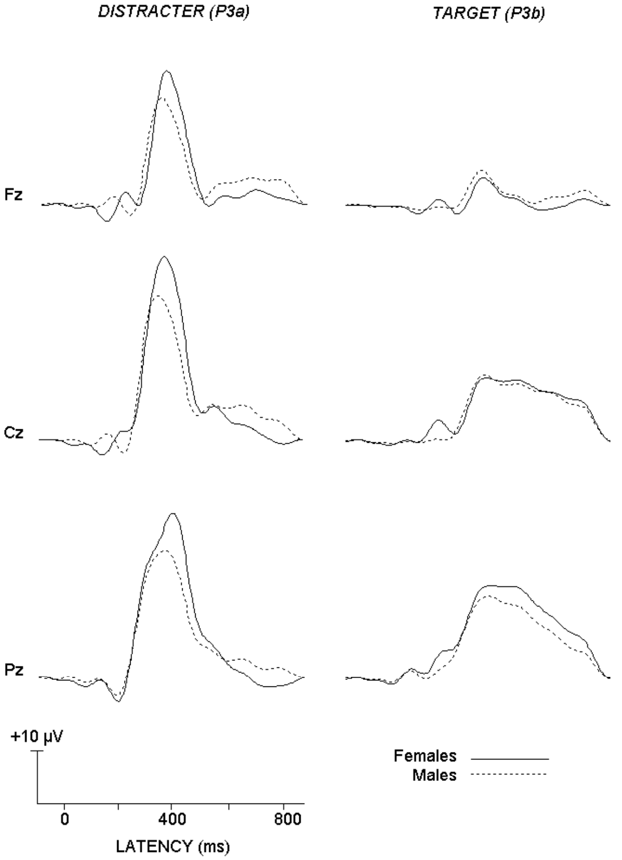

Figure 1: Grand averaged distracter (left) and target (right) ERPs from the midline electrode for female and male subjects (n = 60/gender).

Amplitude: Figure 2 (upper panel) illustrates the mean amplitude from each stimulus condition for each gender as a function of midline electrode site. For P3a from the distractor stimuli, females produced larger components than males. Amplitude was largest at the Cz electrode ($p < .0001$ for all comparisons). For the P3b from the target stimuli, no overall gender effect was found. Component amplitude increased from the frontal to parietal recording sites. Females produced marginally larger amplitudes than males over the parietal recording site, which yielded a significant gender x electrode interaction. The amplitude difference between the genders at Pz was marginally significant ($p < 0.10$).

Latency: Figure 2 (lower panel) illustrates the mean latency from each stimulus condition for each gender as a function of midline electrode site. For P3a from the distractor stimuli, females produced longer peak latencies than males. Latency increased from the frontal to parietal recording sites. For the P3b from the target stimuli, females produced longer peak latencies than males. Latency increased from the frontal to parietal recording sites.

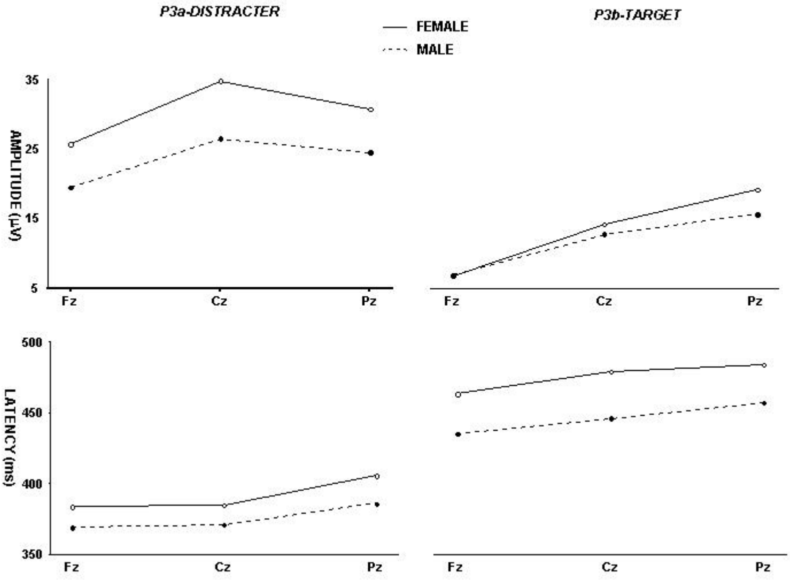

Figure 2: Mean P3a amplitude and latency (left panels) and P3b amplitude and latency (right panels) as a function of midline electrode location for female and male subjects.

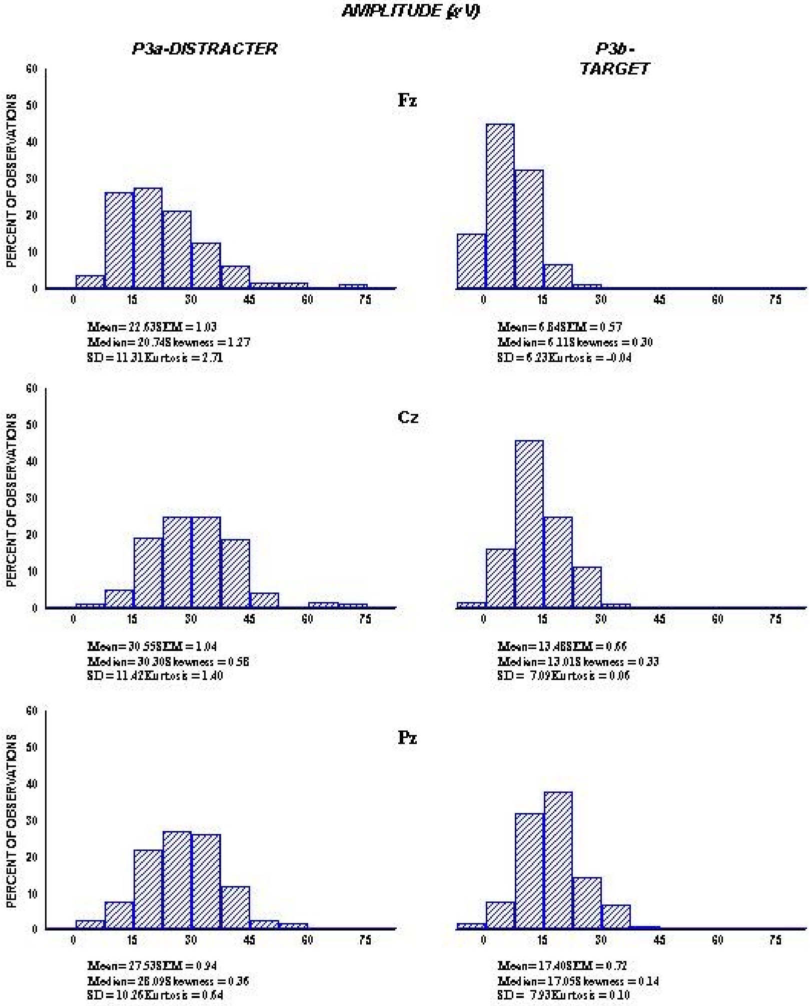

Figure 3: Histogram frequency distributions for P3a (left) and P3b (right) amplitude from each midline electrode with summary statistics.

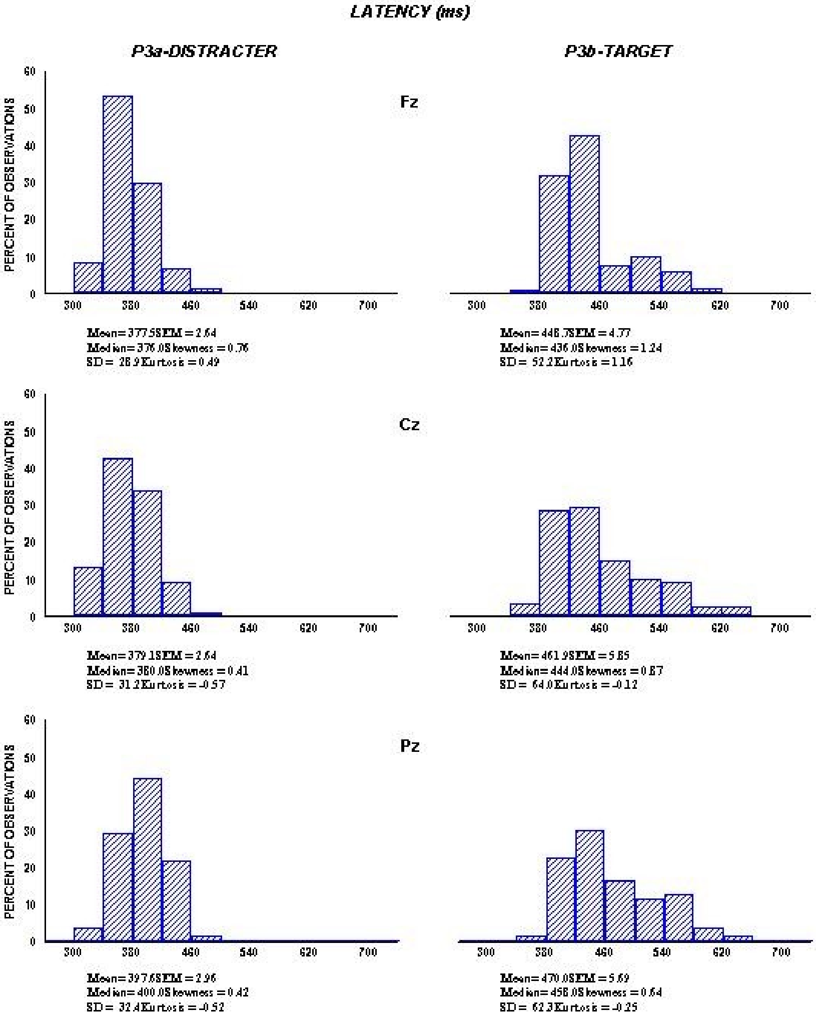

Figure 4: Histogram frequency distributions for P3a (left) and P3b (right) latency from each midline electrode with summary statistics.

Component Variation: Figure 3 presents the histograms and descriptive statistics for the amplitude distributions for each midline electrode and stimulus type across subject gender. *Figure 4* presents the corresponding values for the latency results. The distributions are relatively normal, although each has a slightly positive skew.

Discussion

The error rate data indicate that the perceptual distinction between the target and standard stimuli was relatively difficult. Response times for females were longer than those from males. P3a amplitude was larger for females compared to males, whereas P3b amplitude increased for females more than males from the frontal to the parietal recording sites. P3a and P3b latency were longer for female than male subjects. P3a and P3b amplitude and latency distributions were relatively normal across the genders, with a slight positive skew observed for each variable. Taken together, these findings suggest that the present three-stimulus discrimination task can produce reliable P3a potentials from a distracter stimulus that does not change with each trial [24].

ERP gender differences: P3a amplitude was appreciably larger for female relative to male subjects, although P3b amplitude gender differences were not as strong and were related to scalp topography as has been observed previously [8, 18]. The origins of these effects are uncertain but might be related to sex-related differences in brain size, skull thickness, or other biological gender variation [17, 21]. Given the highly similar topographic amplitude and latency distributions for the P3a between the two genders, it seems likely that neural generator size effects underlie the gender-related measures. These outcomes may be specifically related to sex differences in the size of the corpus callosum, which has been found to be consistently related to P3b measures when female and male right- and left-handers are compared [22].

P3a and P3b normal variation: The relatively large sample employed facilitates a strong description of the underling distributions for P3a and P3b amplitude and latency measures. The present findings indicate the P3a and P3b differ in their inherent variability: P3a amplitude is more variable, skewed, and platykurtic (frontal and central electrodes) than P3b amplitude; P3a latency is much less variable, skewed and platykurtic (across electrodes) than P3b latency. The underlying causes of these distributional differences are unknown but may relate to the nature of the eliciting stimuli and task situation. P3a is produced by an infrequently occurring, large distracter stimulus so that its amplitude is relative large and more variable frontally and centrally – perhaps reflecting individual variation in frontal-lobe generating mechanisms. P3a peak latency is more narrowly distributed, which may reflect its utility as a sensitive measure of frontal lobe function [24]. P3b amplitude is relatively narrow in range and less variable across subjects in a fashion typical for oddball tasks [18]. P3b latency is much wider and more variable than typically found, most likely because of the level of discrimination task difficulty that can affect this measure [28]. Taken together, the results suggest that application of P3a and P3b from the three-stimulus task needs to consider the underlying normative variation as clinical and other applications of these ERPs are developed.

Implications: The exact neural loci of P3a and P3b generation are as yet unclear [7, 13, 19, 20]. However, discriminating a target from a standard stimulus should initiate frontal engagement as a consequence of attentional mechanisms engaged by task performance [14, 25], such that the neuroelectric events that underlie P3a/P3b generation appear to originate from an interaction between frontal lobe and hippocampal/temporal-parietal activity [10, 12, 24]. If so, communication between the cerebral hemispheres would occur via the corpus callosum in a manner that could affect P300 measures as has been reported [1, 22]. This hypothesis is also consistent with data on the association between P300 and grey matter volumes and functional imaging findings [6, 16]. The gender differences and normative variation obtained in the present study appear to reflect the influence of these factors.

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Sex Differences in Cognitive Functions

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Abstract

This chapter presents an overview of sex differences in cognitive functions with respect to visuospatial and verbal abilities. In addition, preliminary results from a meta-analysis on sex differences in episodic memory is presented, showing that women perform at a substantially higher level than men on verbal episodic memory and face recognition tasks, whereas there are no differences with respect to non-verbal and visuospatial episodic memory tasks. The hypothesis that steroid hormones can affect the magnitude of sex differences in cognitive functions is discussed and data from an ongoing study on hormonal status and cognitive functioning in early adolescence is presented. Preliminary results indicated that sex differences in cognitive abilities increase in size during puberty. Tentative conclusions suggest that testosterone positively influence visuospatial performance in young men, whereas estradiol has a positive impact on verbal production and verbal episodic memory performance in women.

Introduction

Gender is one of many individual difference variables. In spite of it being perhaps the most basic one, it is often neglected in research on cognitive functions. I will first describe some basic findings on sex differences in visuospatial, verbal and episodic memory functions, by presenting results from meta-analyses and data from our own studies. In search for biological influences on cognition, steroid hormones have proven to be engaging variables, and the relationship between hormone levels and cognitive performance will be discussed.

Visuospatial ability

The most recent meta-analysis, by Voyer, Voyer and Bryden [30], concluded that the overall sex difference in visuospatial ability was *d* = -.37[1], indicating that men perform at a substantially higher level than women on most visuospatial tasks. Although men outperform women, it is clear that the size of the difference varies from being very large in mental rotations (*d* = -.56), somewhat smaller in spatial perception (*d* = -.44) and substantially smaller in spatial visualization (*d* = -.19).

These sex differences have been examined in relation to age. For example, Levine, Huttenlocher, Taylor and Langrock [20] demonstrated that boys, as young as 4 years and 6 months, showed the expected male advantage in spatial visualization and mental rotation tasks. Preliminary data from our own laboratory show, in concordance with previous studies [12, 30], that sex differences in visuospatial ability exist in puberty, as well as in adults and elderly [33]. Thus, there is ample evidence that sex differences in visuospatial ability favouring males exist throughout the lifespan.

Verbal ability

The prevailing opinion has been that women perform at a higher level than men on tasks assessing verbal ability. However, the picture is slightly more complicated, as it is clear that women outperform men mainly on tasks assessing verbal production. A meta-analysis [15] showed an overall modest advantage for women over men (*d* = .11). As in visuospatial abilities, the effect sizes vary as a function of the tasks being assessed, being fairly large in speech production tasks (*d* = .33), smaller in anagram solving (*d* = .22), nonexistent in vocabulary (*d* = .02) and favouring men in verbal analogies (*d* = -.16). Studies examining the development of sex differences in verbal abilities,

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[1] The effect size, $d = (M_{women} - M_{men})/Sd_{total}$. Here, a positive value of *d* indicates that women performed at a higher level than men, and a negative value indicated that men performed at a higher level than women.

and specifically verbal production tasks, find sex differences favouring girls as young as 5 years of age [4, 15]. The sex differences in verbal production tasks remain through middle and old age [11].

Memory

In our work on sex differences in episodic memory [9, 11, 13, 22], we have come across a number of studies showing that women perform at a higher level than men on episodic memory tasks (i.e., tasks assessing our memory for specific events). However, no meta-analysis on sex differences in episodic memory has previously been done. We searched PsychINFO and Medline with the terms SEX/GENDER DIFFERENCES and MEMORY, and found 168 publications containing relevant information. The overall analysis of the obtained 588 effect sizes showed that women, in general, perform at a higher level than men on episodic memory tasks ($d = .22$) [10].

Since we know that men perform at a higher level than women on visuospatial tasks, and that women perform at a higher level than men on verbal production tasks, we explored whether the magnitude of sex differences varied as a function of the material to be remembered. The 588 effect sizes were divided into 7 categories, based on the material to be remembered. As can be seen in *Figure 1*, such a categorization showed that women perform at a substantially higher level than men on episodic memory tasks with verbal materials ($d = .35$). Typical tasks in this category require the recall or recognition of wordlists. As also can be seen in the figure, the analyses for verbal material is based on a very large number of subjects (n = 49,473), stemming from 288 effect sizes. The same pattern is evident for recall and recognition of objects or concrete pictures, $d = .27$ and $d = .14$, respectively.

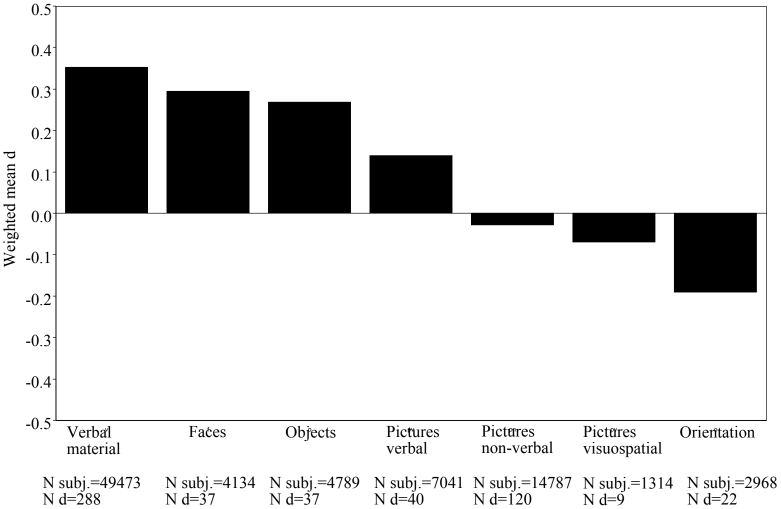

Figure 1: The magnitude of sex differences in episodic memory tasks varies as a function of the material to be remembered.

It is clear that women also perform at a higher level than men on face recognition tasks (d = .29), although we do not know whether this finding generalizes to both male and female faces. In a study specifically focusing on sex differences in face recognition [21], we hypothesized that women's superiority in face recognition was due to their higher verbal abilities, so that women were putting verbal labels on the faces at encoding (e.g., "a blond, blue-eyed man"). We manipulated the possibility to verbalize the faces by presenting either a complete face, with ears and hair, or as incomplete, egg-shaped face, without ears or hair. Our results showed that whereas there were no differences in the recognition of male faces, women recognized more female faces than men did. Verbal ability, as manipulated by type of face and rate of presentation, had no effect on the magnitude of the sex differences. Thus, the superiority that women show over men in face recognition performance may be due to women recognizing more female faces than men do, rather than to an overall recognition superiority for both male and female faces.

In addition, the preliminary results from our meta-analysis demonstrated that there were no differences between men and women on tasks using non-verbal material (*d* = -.03). In such tasks, subjects typically viewed inkblots, or other hard-to-verbalize forms, and were later asked to recognize the previously seen picture. However, when the material was visuospatial in nature, or required orientation, men performed at a higher level than women, *d* = -.07 and *d* = -.19, respectively. Pictures were considered to be visuospatial when they portrayed complex 3-dimensional geometrical forms. Material belonging to the category orientation required the subject to remember a path through a maze in real-life, or on a computer screen.

It is clear that the pattern of data seen in *Figure 1* mirrors the pattern seen in verbal production and visuospatial tasks, with two notable caveats. First, we also obtain sex differences favouring women in face recognition, a task that not readily can be classified as verbal. Second, neither do we obtain sex differences favouring women in the likewise verbal semantic memory tasks or primary memory tasks [11], nor do the sex differences in verbal episodic memory tasks diminish when we control for verbal production [9]. Thus, the female advantage in episodic memory may be somewhat more general than just being confined, or defined, by the verbal components of the tasks. Imaging studies on face perception have demonstrated that relatively focal regions within the right fusiform gyrus respond specifically to faces and not to other viewed objects [16, 27]. Similarly, different regions are activated at encoding according to the nature of the material being encoded [17], indicating that we possibly should search for several explanations regarding sex differences in episodic memory, rather than one explanation accounting for all differences.

The sex differences in verbal episodic memory appear from approximately age 5 [19] to age 80 [11]. Although few studies have assessed potential interactions between age and sex in episodic memory, the studies addressing this issue have not observed such an interaction

[2, 11, 25]. We conducted analyses of potential interactions between age and sex on the studies investigating verbal episodic memory, by dividing the large sample into five age groups (1 to 10, 11 to 20, 21 to 40, 41 to 60, 61+) [10]. Although we found that the sex difference was somewhat smaller in the 41 to 61 age group than in the other age groups, they were still of a substantial magnitude, again indicating that the sex differences in cognition appear throughout the life-span.

Explanations?

What are the explanations for the differences we observe in some cognitive functions? Well, we know that social and cultural factors can influence the magnitude of sex differences. For example, we can increase or decrease the magnitude of the difference by altering the instructions to the subjects, indeed underscoring the importance of expectations from the society [29].

Other explanations have a biological origin and much research has centred on the functional organization of cortex. Typically, it is argued that the two hemispheres are more fully differentiated or specialized in men than in women, whereas women have a more bilateral representation of function [for a review, see 18]. Evidence for such a postulate comes from studies on unilateral brain damage, and from studies on dichotic listening, and more recently from studies using imaging techniques. In the search for biological influences on cognition, steroid hormones have been proposed to have explanatory power [24].

Hormones and cognition

The term organizational effect refers to the hypothesis that hormones, early in development (prenatally), can have long-term, permanent effects on the nervous system, leading to behavioural sex differences. Evidence for such a relation comes from studies investigating girls with congenital adrenal hyperplasia (CAH), stemming from an enzyme deficiency in the cortex of the adrenal glands that causes massive overproduction of androgens. These girls have been reported to show enhanced visuospatial abilities later in life [1, 8] and to prefer masculine rather than feminine toys [26].

Studies on the relation between hormones and cognition have focused not only on the organizational role steroid hormones may play during brain development, but also on the activational role they are hypothesized to have on behaviour throughout life. Most research has focused on the activational role of estrogen (i.e., estradiol), but androgens (i.e., testosterone – T) have also attracted some interest. There are plausible biological mechanisms to support a role for estrogen and T in cognitive functions. For example, estrogen receptors are found in a variety of brain areas, such as the cerebral cortex, hypothalamus, pituitary gland and the limbic system, including the amygdala and hippocampus [3, 5] Androgen receptors are less well studied, but tend to co-localize with estrogen receptors in the rodent brain [28]. The general rationale for androgen's and estrogens' activational role on cognition is that they act by binding to their specific receptors within brain cells, thereby influencing the actions of the brain area in which the receptors are located.

When discussing hormones as a link to cognitive sex differences, periods of hormonal alterations especially should be considered. Several studies have attempted to link testosterone to visuospatial performance and estrogen to verbal ability, with varying results [for a review, see 14]. In an ongoing study on potential effects of hormones on the development of sex differences in cognitive functions, we tested 97 girls and 80 boys. The adolescents ranged in age from 12 to 14, and with respect to how far they had proceeded in their puberty development. All participants took part in cognitive testing and had their blood drawn for later hormone analysis.

The sample of adolescents showed the expected sex differences in mental rotation, verbal fluency, face recognition and verbal episodic memory. As can be seen in *Figure 2*, when the sample was divided into groups of early and late developed individuals, as measured by age adjusted hormone levels (median split for T and estradiol), we found that the magnitude of sex differences increased during puberty, indeed suggesting that sex steroids can affect the brain in the development of cognitive skills [31].

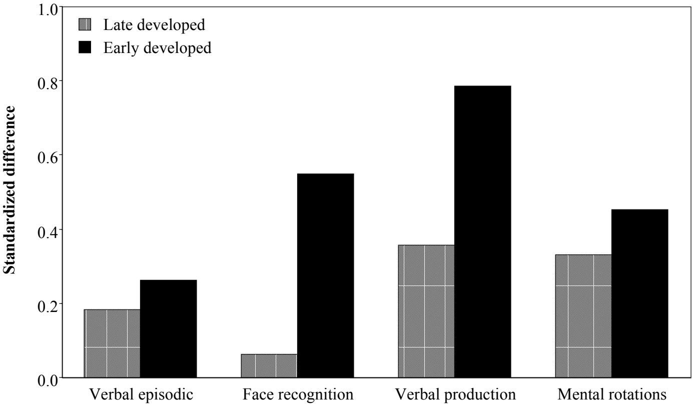

Figure 2: The magnitude of sex difference in cognitive tasks increases as a function of puberty development.

In the same sample, we also found that boys with relatively high levels of testosterone performed at a higher level than boys with relatively low levels of T, independent of age. Similarly, looking at the effect of estrogen on girls, we found that girls with relatively high levels of estradiol performed on the verbal episodic memory tasks at a higher level than girls with relatively low levels of estradiol. The same pattern of data was not present for the other cognitive tasks.

In a study on older women, we have investigated the effect of hormone replacement therapy (HRT) in menopause [32]. In this study, women receiving HRT performed at a higher level than non-users on episodic memory tasks and on a verbal production task. In addition, estradiol levels were positively correlated with episodic memory. In contrast, HRT-users and non-users performed similarly on visuospatial and semantic memory tasks, again suggesting that variations in estrogen are sufficient to exert small, yet consistently positive effect on episodic memory and verbal fluency.

These studies [12, 32] and others [e.g., 6, 7, 23] seem to indicate a positive linear relationship between testosterone and visuospatial ability in men, and a likewise positive association between estrogen and tasks assessing verbal production and verbal episodic memory in women. However, before drawing strong conclusions on the hormonal influence on cognition, it should be noted that sex differences in most cognitive abilities are present before puberty, indicating that the increasing hormone levels during puberty only have marginal effects on the magnitude of these differences. Unfortunately, findings on the relationship between hormones and cognition are often hampered by weak associations, lack of consistency and absence of replications. In addition, earlier studies investigating the effect of HRT on cognition have been contaminated by methodological inconsistencies and problems, leading to an overly optimistic view on the effects of HRT [14]. Future research should therefore expand our current knowledge by replications and by assessing the validity of results in explaining the process by which hormones and cognition are related.

Conclusions

A long history of research into the existence of sex differences in visuospatial and verbal abilities have shown that boys and men excel on most visuospatial tasks, whereas girls and women outperform males on verbal production tasks. In addition, we have reported that women perform at a higher level than men on episodic memory tasks, such as face recognition and recall and recognition of verbal materials. Although these sex differences exist before puberty, our preliminary data analyses show that they become larger in size during puberty, suggesting that sex differences in cognitive functions are weakly affected by actively circulating hormones.

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