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WORKING MEMORY STUDIES  
USING  
FUNCTIONAL MAGNETIC RESONANCE IMAGING

DOCTORAL DISSERTATION

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Olomouc 2014

**Declaration:**

I hereby declare that I have elaborated this thesis by myself, under the supervision of prof. MUDr. Ing. Petr Hlušík, Ph.D., using sources listed in the bibliography.

Olomouc, April 15, 2014

Zbyněk Tüdös

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## List of relevant abbreviations

ACC	Anterior Cingulate Cortex
BA	Brodmann Area
BOLD	Blood Oxygenation Level Dependent
DMN	Default Mode Network
EPI	Echo Planar Imaging
FEF	Frontal Eye Field
FOV	Field of View
fMRI	functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
GLM	General Linear Model
HRF	Hemodynamic Response Function
IFG	Inferior Frontal Gyrus
IFJ	Inferior Frontal Junction
IPS	Intra-parietal Sulcus
LOC	Lateral Occipital Complex
LO1, LO2	dorsal and ventral part of Lateral Occipital Complex
MFG	Medial Frontal Gyrus
MNI	Montreal Neurology Institute
MRI	Magnetic Resonance Imaging
SPM	Statistical Parametric Map
TE	Excitation Time
TR	Time to Repeat
PASAT	Paced Auditory Serial-Addition Task
PET	Positron Emission Tomography
PVSAT	Paced Visual Serial-Addition Task
ROI	Region of Interest
SMA	Supplementary Motor Area
V1, V2	Visual area 1, 2

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# 1. Introduction

Cognitive processes are the research focus of psychologists, neuroscientists and neurologists, both under normal circumstances in healthy people and also in the populations of patients suffering from neurological, psychiatric or other kind of disorders that may lead to brain malfunction and cognitive deficits. Memory and its associated processes belong to most studied field of higher brain functions. This broad research spans the whole range from the theoretical and philosophical level, behavioral experiments, throughout animal models in monkeys, electrophysiological studies, to functional brain imaging. Historically, the first imaging studies in the field of memory functions were performed with positron emission tomography (PET) in the early 90's. Since the powerful magnetic resonance imaging (MRI) scanners have become available, extensive number of papers have appeared to study the cerebral localization of memory functions using functional magnetic resonance imaging (fMRI). The spectrum of available research techniques includes also magnetoencephalography (MEG) and single-photon emission computed tomography (SPECT).

The main focus of this work is to investigate the neurobiology of working memory using imaging techniques, namely functional magnetic resonance imaging.

## 1. 1. Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is an advanced imaging technique used for functional imaging of the brain and its domain is mapping brain response to external or internal stimuli. The technique has been developing for more than two decades and contributed significantly to research mainly in the field of cognitive neuroscience and neurophysiology. Functional MRI allows only indirect detection of neuronal activity by measurements of local changes in blood oxygenation and perfusion of the cerebral cortex. In comparison with other methods of functional brain mapping, functional MRI has relatively high spatial resolution (typical of order of millimeters, even though sub-millimeter resolution is possible), on the other hand, the temporal resolution is lower in comparison with electrophysiological methods (electroencephalography and magnetoencephalography). Functional MRI finds utilization mainly in neuroscience research, whereas routine use in clinical practice (neurology, neurosurgery, psychiatry) is still limited.

## 1. 1. 1. The physical principle of fMRI

An important feature of the brain tissue physiology is the tight coupling between neuronal activity and regional blood flow (Roy and Sherrington, 1890). Increased activity of neurons (mainly synaptic activity) leads to higher energy demand. Cellular energy is obtained in the brain almost exclusively from glucose via oxidative phosphorylation, during which the consumption of oxygen rises as well (Hoge et al., 1999; Raichle, 1998). Increased neuronal activity is followed, first, by increased regional oxygen extraction, then, after a time delay (2-3 seconds), the increased oxygen supply increases the perfusion of the region (Fox and Raichle, 1986; Gjedde, 2001). The main carrier of oxygen in blood is hemoglobin. The ratio between oxygenated (oxyhemoglobin) and deoxygenated (deoxyhemoglobin) form of hemoglobin naturally fluctuates according to changes of blood oxygen level. Unlike oxyhemoglobin, deoxyhemoglobin is paramagnetic and this property makes it a natural MRI contrast agent (Pauling and Coryell, 1936; Pauling, 1977). In regions with paramagnetic materials (e.g., deoxyhemoglobin) located within the strong external magnetic field, the local magnetic field becomes slightly stronger than in the surrounding area. This phenomenon leads to the formation of microscopic gradients in the magnetic field and thereby increasing the inhomogeneity, which results in shortening of  $T_2^*$  relaxation time.  $T_2^*$  relaxation is the transverse relaxation time ( $T_2$ ) additionally taking into account the local inhomogeneity of the magnetic field by measuring free induction decay. Total amount of deoxyhemoglobin in the tissue thus has a direct influence on the appropriate  $T_2^*$  value. This dependence is called blood oxygenation level dependent (BOLD) effect and is the basis for the most common functional MRI acquisition (Kwong et al., 1992; Ogawa et al., 1992, 1990). Time course of measured MRI signal changes in a region of neuronal activity is called hemodynamic response or hemodynamic response function. It is traditionally divided into five phases (Hoge and Pike, 2001) (Figure 1):

- 1) initial decrease in BOLD signal** (or the initial dip) results from increased consumption of oxygen due to neuronal activity, while increased inflow of oxygenated blood to the area due to neurovascular coupling has not occurred yet. The initial drop is closely related to neuronal activity and is considerably less prone to be disturbed by signal from nearby draining veins than subsequent BOLD signal increase. Unfortunately, 1.5T MRI scanner is not sensitive enough to commonly detect this very discrete change in the MRI signal (approx. 0.5%).
- 2) BOLD signal increase** (2-5 %) due to large supply of oxygenated blood (blood flow

increases about 50-70 %), that clearly exceeds the real demand for oxygen (an increase of about 5-20 %) (Fox and Raichle, 1986). This phase of hemodynamic response function is used for fMRI measurements. The maximum signal variation is achieved about 6-9 seconds after the start of a stimulus.

**3) phase of plateau,**

during which signal intensity remains more or less unchanged, occurs after the overshoot peak.

**4) decrease in BOLD**

**signal** starts after stimulus and synaptic activity have ceased, regional perfusion decreases.

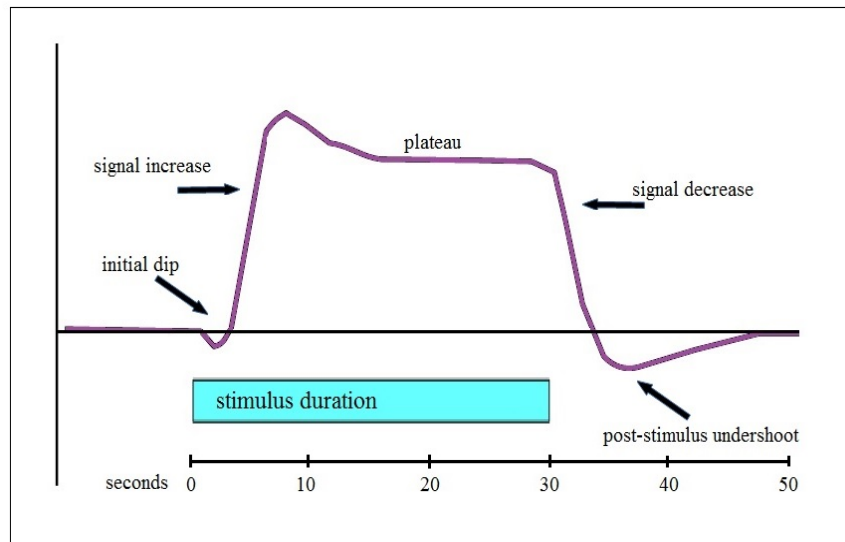


Figure 1) Hemodynamic Response Function

**5) post-stimulus**

**undershoot,** during which BOLD response drops to negative values, the exact cause of this phenomenon is not fully clear, but it is probably the persisting increased oxygen extraction and increased blood volume in the area in where blood flow returns to normal.

Complete return of the signal to the initial base value occurs after about 20 seconds since the end of stimulus.

Hemodynamic response appears after even a very short stimulus, lasting only tens or hundreds of milliseconds. Its amplitude is appropriately smaller with shorter stimulus, but its basic proportions in time are almost unchanged.

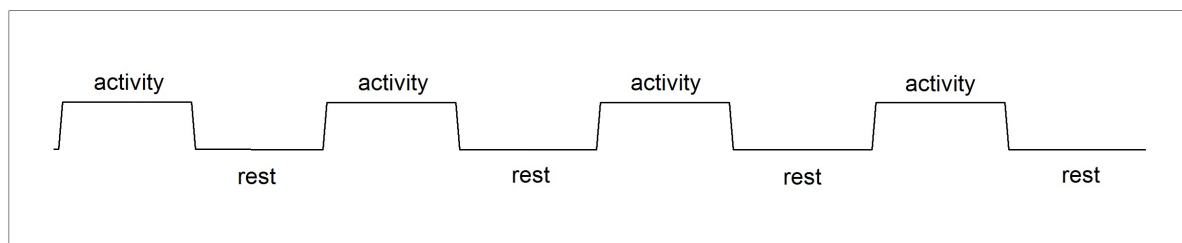
**1. 1. 2. Methodology of fMRI experiment**

A functional imaging study consists of several steps, each requiring a sound theoretical knowledge. When designing and applying a new experimental protocol, multidisciplinary collaboration is necessary (preferably including an experimental psychologist, an engineer, a neurophysiologist or neurologist, radiologist, statistician or physicist). Crucial disadvantage of fMRI is a very small change in signal intensity associated with hemodynamic response, as



already mentioned, signal change is about 1-5 % at 1.5 Tesla). In addition, there are no standardized normative baseline values of cerebral BOLD signal, since there are great inter-subject and inter-regional differences. To overcome this issue, one needs to compare images acquired during the active condition and during the reference control (or rest) condition. To distinguish experiment-dependent changes from noise, we need quite many images to compare, at least several tens or hundreds to reach necessary statistical robustness (sensitivity). So the whole brain volume (e.g. 30 slices) needs to be acquired many times repeatedly during the active task (e.g., limb movement, speech or a memory task) and at rest (or during performing a control tasks) and obtained data must be subsequently statistically evaluated. Each examination is characterized by a particular temporal arrangement, which we call design of experiment. There are two basic types of designs: block design and event-related design (Chlebus et al., 2005).

**Block design** is easier to arrange and more convenient for the subsequent statistical processing. This design alternates periods of stimulation (or activation) with periods of rest (or control condition) (Figure 2). Longer periods of stimulation receive a higher level of BOLD signal compared to the response to a single stimulus. However, block design does not



*Figure 2) Block design (regular alternation of active and rest periods)*

allow detecting the shape of the hemodynamic response or distinguishing separate parts of cognitive processes. Furthermore, this type of design can not be used in the investigation of cognitive tasks based on a spontaneous performance of a specific activity. Block design is successfully used for motor tasks (e.g. finger tapping), language (e.g. verbal fluency task, reading or listening), some memory tasks, etc.

**Event-related design** is the design for the detection of hemodynamic response to single event (or specific sequence of events) (Blamire et al., 1992; Buckner et al., 1996).

The event (or stimulus) is very short compared to acquisition time of one whole brain volume, which is usually 2-4 seconds). The period between two events is usually several acquisition times, allowing detailed observation of BOLD signal over time (Figure 3). A disadvantage of the design is very long experiment with large amount of redundant scan data requiring

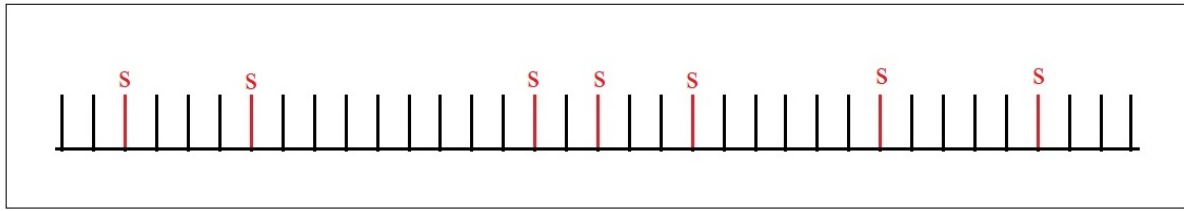


Figure 3) Event related design (task-relevant target stimuli are highlighted by S)

complicated and time-consuming postprocessing. Event-related design is suitable for studying processes that require irregular or random pattern of stimulation, such as some attention tasks (e.g., the odd-ball task, Stroop task), it allows separating desired cognitive process out of a complex performance (e.g. only decision-making) or analyzing activation pattern only in wrong answers. Event-related design results in somewhat smaller sensitivity compared to block design.

Mixed event-related and block designs were also introduced to the practice (Donaldson, 2004).

### 1. 1. 3. Data acquisition

The acquisition of functional images is also very sensitive to movement artifacts (including minimal movement of the head when swallowing or blinking) so the head must be fixed properly. Functional MRI is an examination, which requires high degree of patient cooperation. Proper execution of the task is absolutely crucial.

Examination usually starts with conventional axial T<sub>1</sub>-weighted images, which provide an anatomical underlay to display the resulting activation maps. Common practice is also acquisition of a high-resolution 3-dimensional scan (magnetization-prepared rapid acquisition gradient echo, MPRAGE) for precise anatomical reference. The fluid attenuated inversion recovery (FLAIR) images to screen for suspected or unsuspected brain lesions can be also obtained. It is also advisable to obtain a field map in order to deal with image artifacts related to magnetic field inhomogeneity (Jezzard and Balaban, 1995).

Echo planar imaging (EPI) sequence has become the standard tool for BOLD data acquisition – it is rapid and sensitive to magnetic field inhomogeneities, thus allowing T<sub>2</sub>\* weighting (Schmitt et al., 1998; Stehling et al., 1991). The sequence is unique for its ability to sample an entire two dimensional *k*-space matrix following a single radiofrequency excitation pulse, which enables a scanner to obtain entire brain volume in several seconds (Jezzard and Clare,

2001). Recommended parameters for gradient-echo EPI at 1.5T are the following: the echo time (TE) around 40 ms, the image matrix size 64×64, the field of view (FOV) 240 mm, the slice thickness is 4-5 mm, TR 2000-3000 ms. For block design, significant signal changes can be observed within an activation cycle lasting 30 s. Continuous BOLD acquisitions (time series, runs) are typically on the order of 5–8 minutes in duration. The number of functional runs is generally determined by how long the subject can be comfortably kept in the scanner.

Typically, researchers have about an hour of useful fMRI scanning time per subject, so they fill this hour as well as they can (Bandettini, 2007).

The acquired data is finally transferred from MRI workstation to a powerful computer for preprocessing and statistical analysis.

### **1. 1. 4. Preprocessing of data**

Preprocessing of functional images means software mathematical and statistical optimization of the measured data in multiple steps for further analysis (Chlebus et al., 2005; Smith, 2001).

***Motion correction*** is one of the most important operations with functional images. Even minor movements of the head in order of mm can lead to artifacts in fMRI results. In principle, the first volume of brain images serve as a reference and for every following volume, motion correction software tool attempts to find the best overlap with reference images by simulating movement in different directions (Brammer, 2001).

***Slice-timing correction*** is applied to overcome the fact that scanning one volume of brain images takes 2-3 second, whereas theoretically all images (slices) in the volume should be acquired at the same time. Linear interpolation can be used to correct the timing differences.

***Spatial smoothing*** means filtering out of high spatial frequencies in order to suppress the noise in the data. As already mentioned, the signal to noise ratio might be an issue and there are techniques to increase the ratio. The spatial filtering is most often performed by a Gaussian filter defined by the spatial frequency threshold or parameter full width at half maximum (FWHM).

***Intensity normalization*** suppresses differences in global BOLD intensity (i.e., image brightness), that can randomly fluctuate between images and thus create artificial changes in signal time-series for individual voxels. It is therefore necessary to pre-set the global image signal (i.e. image brightness) to uniform level. In technique of grand-mean intensity normalization, the average intensity is calculated for entire experiment and intensity of all

scans is then set to this mean value.

***Spatial normalization*** is an operation that transforms acquired real brain images into a standard stereotactic space, e.g. Talairach space (Talairach and Tournoux, 1988) or Montreal Neurological Institute (MNI) system (Evans et al., 1993). The process of transformation includes translations (shifts) and rotations similar to movement correction, but additionally scaling (zoom in/out) and a skew or nonlinear distortion of the images can be applied for best fit of the real brain to standard template. The resulting data can be compared between different people and anatomical structures and voxels can be addressed by the standardized coordinate system. This step is necessary, when group analysis is to follow (Jenkinson, 2001).

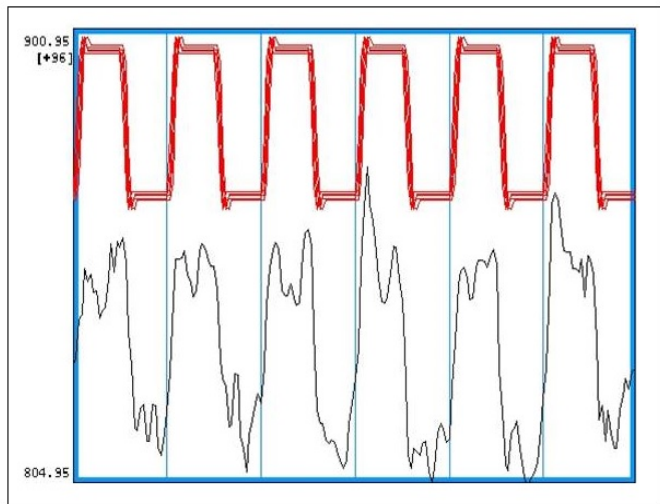
***Temporal filtering*** deals with noise and undesired signal variations, that can be either low-frequency, e.g. those resulting from breathing and heart, or high-frequency noise.

***Co-registration*** of the functional and structural images is important for the evaluation of activation maps and presentation of results.

## **1. 1. 5. Statistical analysis**

Most of methods for detecting the activation is based on univariate statistics. Most commonly used approach is the voxel-by-voxel analysis when the time series data are evaluated separately for each voxel (Friston et al., 1995; Worsley and Friston, 1995). The simplest way possible (and also the most susceptible to various artifacts) is comparison of the average voxel-wise value of the signal obtained during the activation and the average value of the signal obtained during the rest (simple subtraction). Slightly better results can be obtained with Student's t-test, since the difference of average values is "weighted" by the standard deviation, thus variability of data is accounted for in order to avoid false positive results. Even better are methods that assume a particular shape of the measured signal, such as modeling of the expected hemodynamic response. Correlation and regression analysis can be used to compare the acquired time-series and hemodynamic response function. Regression analysis has become a flexible tool to explain the variability of the data using regressors (modeled waveforms) and to test their significance. Other statistical techniques can also be used, e.g., analysis of variance. An approach that partly generalizes the above-mentioned techniques is so called general linear model (GLM) (Figure 4). In case we can not predict data variability (e.g., normal distribution of signal intensity in space or time, etc.) necessary for reliability of parametric statistical methods, non-parametric statistical methods are suggested.

The result of voxel-by-voxel analysis approach is obtained in the format of statistical parametric map (SPM), (non-parametric with non-parametric statistics). The resulting single-subject statistical map contains in each point a statistics parameter value according to the selected distribution, e.g., a t-value of the Student distribution. However, such a map is not very suitable for further visual review and evaluation, therefore a thresholding is usually performed, which means that statistical value for each point is compared with a given threshold



*Figure 4) General Linear Model  
Top: Ideal signal waveform  
Bottom: Real signal time-course in single selected voxel*

value and considered significant or not. Resulting thresholded statistical map is considered the final map of detected activation (displayed as colored clusters) and is subsequently used to evaluate the outcome of the experiment.

Such single-subject map is appropriate for evaluation of individual patients or subjects, such as pre-operative mapping before brain surgery. Other uses require evaluating a sample from the target population, whether the goal is neuroscience research on particular brain functions and processes, or assessing whether a specific experimental paradigm will be suitable for studying a defined population, e.g., neurological patients with focal or diffuse brain damage (stroke, multiple sclerosis, neurodegenerative dementias).

After each individual study has been spatially normalized to common anatomical space (see “Spatial Normalization”, above), a higher-level statistical analysis is set up (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008), e.g., to generate a group mean statistical map, representing the average brain activation across the studied group.

## **1. 1. 6. Interpretation of results**

The final result of the fMRI examination is an activation or functional map, which displays a set of voxels that reached given threshold of statistical significance. The activation map is overlaid onto anatomical images to help locating and then interpreting the results of fMRI.

When evaluating the results of fMRI, we must be aware of a wide range of artifacts that arise

primarily during the data acquisition (susceptibility artifacts, motion artifacts, false positive signal from the draining veins etc.), but also during the postprocessing. FMRI results should therefore be interpreted with caution and with sound knowledge of all stages of the examination and computational analysis.

## **1. 2. Working memory**

### **1. 2. 1. History of working memory model**

The effort to approach and define memory had already engaged ancient Romans and Greeks, who were already aware that memory is not a simple straightforward mental process of preserving memories and they usually distinguished “natural memory” and “artificial memory”, the former type was considered to describe information obtained “naturally” during the lifetime, while the latter meant information obtained by active memorizing. The artificial memory was then considered one of the five classical canons of rhetoric (West, 2006).

Later in the history, the phenomenon of memory was addressed by many thinkers, especially philosophers, for instance Plato, Aristotle, Cicero, Thomas Aquinas, Descartes, Immanuel Kant, and many others.

In modern history, the breakthrough work of the German philosopher and psychologist Hermann Ebbinghaus appeared in the late 19<sup>th</sup> century (Ebbinghaus, 1885). His work included results of an empirical study, that he performed on himself over several years and tested options and patterns of learning and forgetting. During memorizing and subsequent forgetting of many sets of nonsense syllables Ebbinghaus discovered, recorded and interpreted the phenomena that eventually became known as the learning curve and the forgetting curve, although he did not use these terms himself. Another key observation reported by Ebbinghaus was the ability to temporarily keep in memory a set of nonsense syllables: “the series is caught on the wing as it were, often to the learner's surprise; but the series cannot long be retained” (Ebbinghaus, 1885, chapter III, section 14), which actually described the principal of verbal working memory. Also worth mentioning was the observation that, on average, he was able to keep in the memory a set of seven syllables after the first reading (cf Miller, 1956). Although the methodology of the work raised some criticism, such as the study was performed on one person who was also the researcher at the same time, the publication represented a breakthrough in the investigation of memory that shifted from philosophical and theoretical essays to experimental research. As an interesting historical note, Ebbinghaus arranged his paper to sections Introduction, Methodology, Results and Discussion. This systematic and comprehensive style of publication impressed his contemporaries and gradually became worldwide standard in the scientific community.

Another psychologist, who published an influential paper on memory in the late 19<sup>th</sup> cent. was William James, who devoted a chapter to the memory in his book Principles of

Psychology (James, 1890), that distinguished the primary and secondary memory. According to James, primary memory is directly dependent on sensory input and effective vigilance and can be seen as the equivalent of contemporary concept of short-term memory. His definition of secondary memory more or less corresponds to contemporary definition of long-term memory: "Memory proper, or secondary memory as it might be styled, is the knowledge of a former state of mind after it has already once dropped from consciousness; or rather it is the knowledge of an event, or fact, of which meantime we have not been thinking, with the additional consciousness that we have thought or experienced it before." (James, 1890, p. 648). Although James proposed this division of memory, the principle of distinct memory stores was not generally accepted at the end of the 19<sup>th</sup> century and first half of 20<sup>th</sup> century. In more recent history, Atkinson and Shiffrin (1968) introduced a new general model, which elicited great feedback, debate and controversy. The model divided process of memory retention into three types: a sensory memory, a short-term memory and long-term memory (Figure 5), their function is according to Atkinson and Shiffrin as follows:

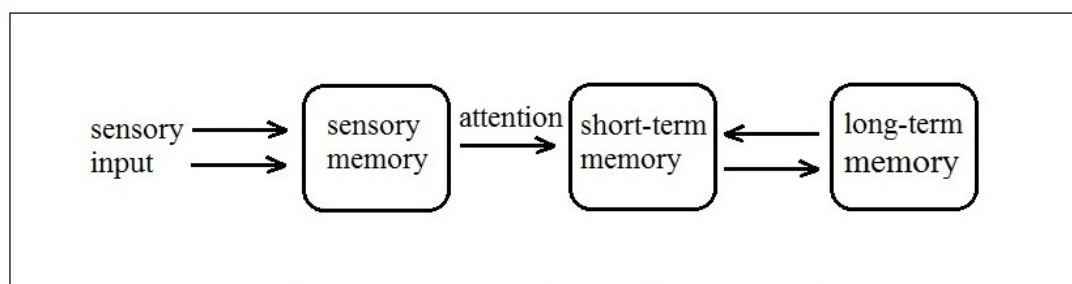


Figure 5)  
Multi-store model of memory, according to Atkinson and Shiffrin (1968)

**Sensory memory**, labeled by authors as buffer or register, is able to keep sensory information in a matter of seconds; according to sensory modality, the respective terms “iconic memory” for visual sensory memory and “echoic memory” for auditory sensory memory are sometimes used. Analogue registers theoretically exist also for other senses, but are experimentally difficult to approach and therefore understudied and poorly understood. The crucial process that enables transfer of information from sensory systems to short-term memory is (focused) attention, serving as a selective filter.

**Short-term memory** receives cues from sensory and can retain them for up to 20 seconds, this time can be significantly prolonged by the process of active repeating. Information is retained in short-term memory as long as it is actively attended to. The capacity of short-term memory is usually derived from Miller's magic number  $7 \pm 2$ , i.e., 5 - 9 items or chunks (Miller, 1956).



Transfer from short-term to long-term memory may be automatic or purposefully achieved by repeating as already described by Ebbinghaus (Ebbinghaus, 1885).

Unlike short-term memory, *long-term memory* has theoretically an unlimited capacity and the information can be kept for the rest of life. Reciprocal transfer from the long-term store to the short-term store is mostly under the control of the subject; such transfer occurs, for example, in problem solving, hypothesis testing, and “thinking” in general.

The described model elicited a great response, but also criticism. One of the contradictory points was the inclusion of sensory perception as a separate storage system. Furthermore, some cast doubt upon rehearsal being the most important step in the process of transfer of verbal material into long-term memory and suggested meaning or emotional tone to be more important for long-term store retain (Baddeley, 2010). Vague definition and insufficient elaboration of both long-term and short-term store concept was also pointed out. Another weakness appeared to be a linear character of the information flow, according to the scheme on Figure 5, the disturbance in short-term store would completely prevent transfer to long-term learning, whereas long-term store failure would cause serious malfunction of short term memory. Published case reports, however, challenge this opinion, therefore the linear relationship between the two types of memory seems improbable (Shallice and Warrington, 1977).

Comments to Atkinson model came also from Baddeley and Hitch, who extended the concept of short-term store into the concept of the so-called working memory (Baddeley and Hitch, 1974). The term working memory was coined by Miller et al. (1960) and in their context, working memory is a mental process that maintains information necessary for the completion of the task (they use the term "Plan"), allows the progress of the “Plan”, division of the “Plan” to subsequent steps where possible and necessary and switching between multiple “Plans”. Baddeley and Hitch adopted the term “working memory” to distinguish it from Atkinson's short-term memory. They decided to abandon the unitary short-term memory model and proposed a three-component model assuming existence of an attentional control system, the central executive, aided by two short-term storage systems, one for visual material, the visuo-spatial

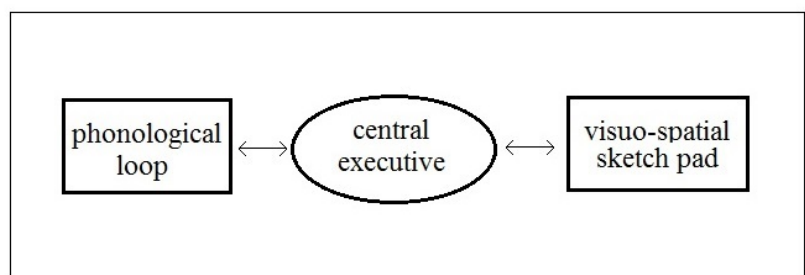


Figure 6)  
Original working memory model, Baddeley and Hitch (1974)

sketchpad, and one for verbal-acoustic material, the phonological loop (Baddeley, 1996; Baddeley and Hitch, 1974) (Figure 6).

In their concept, the ability to temporary maintain information was supplemented by ability to manipulate information and make decisions. To account for a broad range of empirical data that could not be explained using the original tripartite model, the fourth part, the episodic buffer, was later postulated by Baddeley (2001). The model has become the embodiment of the most influential and broadly accepted theory of working and short-term memory; a recent form of the model is fully described in next section.

### 1. 2. 2. The contemporary working memory model

The model of working memory proposed by Baddeley and Hitch has been developed since its publication until now. This section summarizes the contemporary version of the model, that is adopted from Alan Baddeley's latest review articles (Baddeley, 2010; Repovš and Baddeley, 2006).

As mentioned above, working memory consists of phonological loop, visuospatial sketchpad, central executive and episodic buffer (Figure 7).

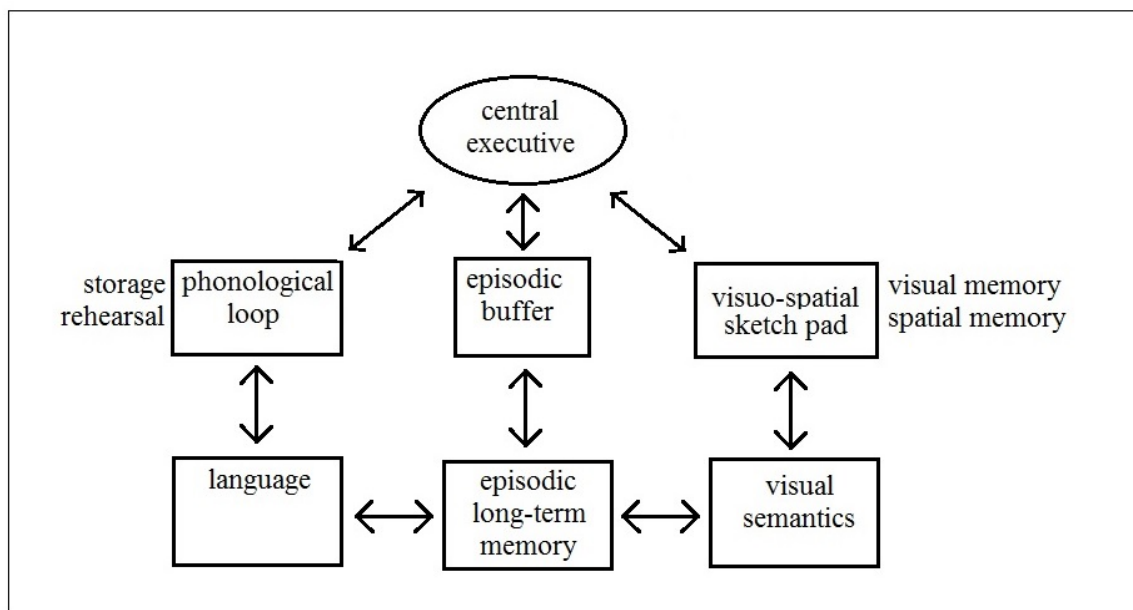


Figure 7) Contemporary model of working memory, according to Baddeley (2010)

## **Phonological loop**

Phonological loop works with phonological and auditory material. It is responsible for storing auditory and verbal information in working memory and rehearsal of such information to keep it available for mental processes until it ceases to be necessary or is replaced by new information. It manifests as an inner voice that sounds in one's head during covert reading, counting or repeating a phone number, etc. There are several phenomena that influence functioning of phonological loop:

### *Limited span*

Alan Baddeley correlated Miller's rule of short-term memory capacity  $7 \pm 2$  items with the speed of repetition of words in the phonological loop: 5 - 9 units represent number of items that subject is able to rehearse in two seconds. However, number of items held in memory depends on their characteristics.

### *The phonological similarity effect*

Similar sounding verbal items (e.g. letters V, B, G, T, P and C) and are harder to remember than that dissimilar sounding items (e.g. letters W, X, K, R, Y and Q). The semantic similarity, on the other hand, has almost no effect.

### *The word length effect*

A string of longer words are harder to remember than a string of short words. Study in which bilingualists who could approximately equally well speak English and Welsh revealed that memorizing a series of English numerals was more successful than memorizing the series of Welsh numerals because English numerals are shorter than Welsh (Ellis and Hennelly, 1980).

### *The effect of articulatory suppression*

Articulatory repeating of an irrelevant syllable or word prevents a subject performing verbal memory test from using subvocal rehearsal of target items and thus fewer items are remembered. Articulatory suppression also disturbs transcoding of visual stimuli to the phonological store.

### *The irrelevant sound effect*

Exposure to irrelevant speech either concurrent or subsequent to presentation of list items

significantly reduces serial recall of verbal material.

### **The visuospatial sketchpad**

The visuospatial sketchpad is assumed to be capable of maintaining and manipulating visual and spatial information, a process that is crucial for performing a range of cognitive tasks. Visuospatial working memory can be further divided into visual and spatial subcomponents, each with separate and independent passive storage, representations, mechanisms of maintenance, and manipulation. Both subcomponents have been shown to be closely related to forms of visual attention.

### **The episodic buffer**

The episodic buffer, the third slave system, was designed by Baddeley in 2001. It is therefore much less explored than other parts of the model and some books do not mention it. It is episodic in that it is capable of holding multidimensional episodes or chunks, which may combine visual and auditory information possibly also with smell and taste. It is a buffer in that it provides a temporary store in which the various components of working memory, each based on a different coding system, can interact through participation in a multidimensional code, and can interface with information from perception and long-term memory. The episodic buffer is assumed to have a limited capacity of about four chunks or episodes, and to be accessible through conscious awareness. In its initial form, the buffer was assumed to play an active and attentionally-demanding role in binding together information from different sources, but further investigation suggests that it serves as a passive store rather than an active processor.

### **The central executive**

The central executive has been the most important but least understood and least empirically studied component. Its role is to control, coordinate and process the information from slave subsystems and focus attention. It does not have any storage capacity, but it seems to be involved whenever information within the stores needs to be manipulated. Four basic capacities were postulated and explored: the ability to focus, to divide and to switch attention, and the ability to relate the content of working memory to long-term memory.

## 1. 2. 3. Common working memory tasks

### 1. 2. 3. 1. Item recognition task

Item recognition task was developed from Saul Sternberg's paradigm published in the 1960's. During the experiment, a small group of items called the *positive set* is sequentially presented to subject to memorize. Subject is then shown a single *test item* that may, or may not, have been shown before. Subject have to respond 'yes' or 'no' accordingly. This procedure is repeated over several trials in which the number of items in the positive set is varied (Sternberg, 1966). The main purpose of the paradigm was to study memory scanning and to measure reaction times under the different mental load.

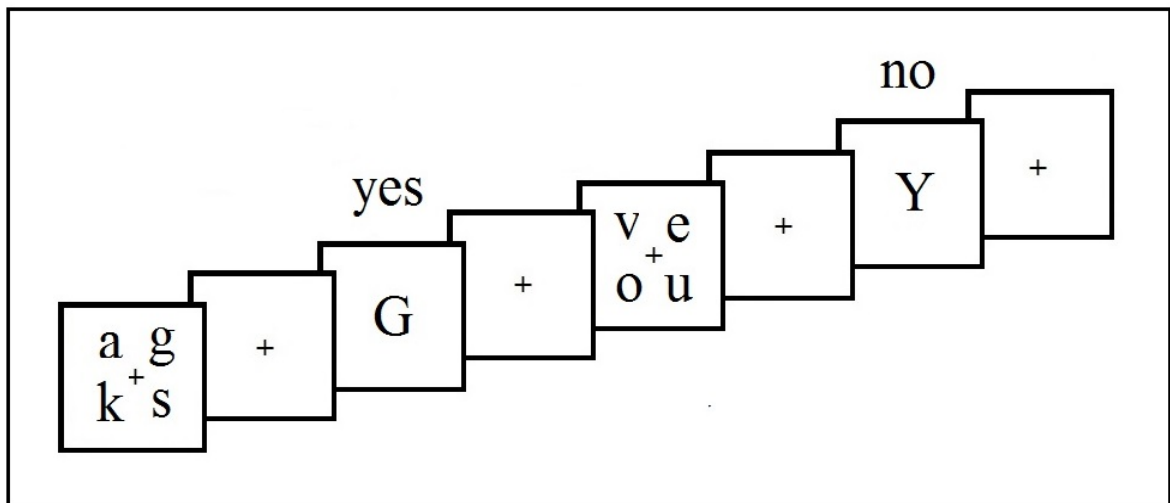


Figure 8) Item Recognition Task

This task was later adopted for neuroimaging studies in its visual version, when usually four target items are presented simultaneously on the screen, followed by a several-seconds blank delay period (during which subjects have to remember the items), followed by a probe item, to which subjects responded “yes” or “no” (by pressing one of two buttons) indicating whether the probe was identical to one of the four target items (Figure 8). This task necessitates working memory storage and rehearsal, but it includes other processes as well, e.g., perception of the stimuli and execution of a response (Smith and Jonides, 1998). Items to be memorized could be verbal, visual or spatial.

### 1. 2. 3. 2. N-back task

The n-back task was introduced by Wayne Kirchner (1958). Letter “n” in the name of the task stands for the number of item needed to be kept in the working memory at the time, e.g. 2-back task requires two subsequent items. During the 2-back task, that is the most common, subjects view (or hear) a continuous stream of items (each presented usually for 500 ms) with an interval between successive items (usually 2500 ms). For each item, subjects have to decide whether it is identical to the item two back in the sequence (Smith and Jonides, 1998) (Figure 9). In a PET study using letters, subjects reported a specific strategy, when they tried to repeat the letters to themselves, adding the new letter and deleting the old one (Schumacher et al., 1996).

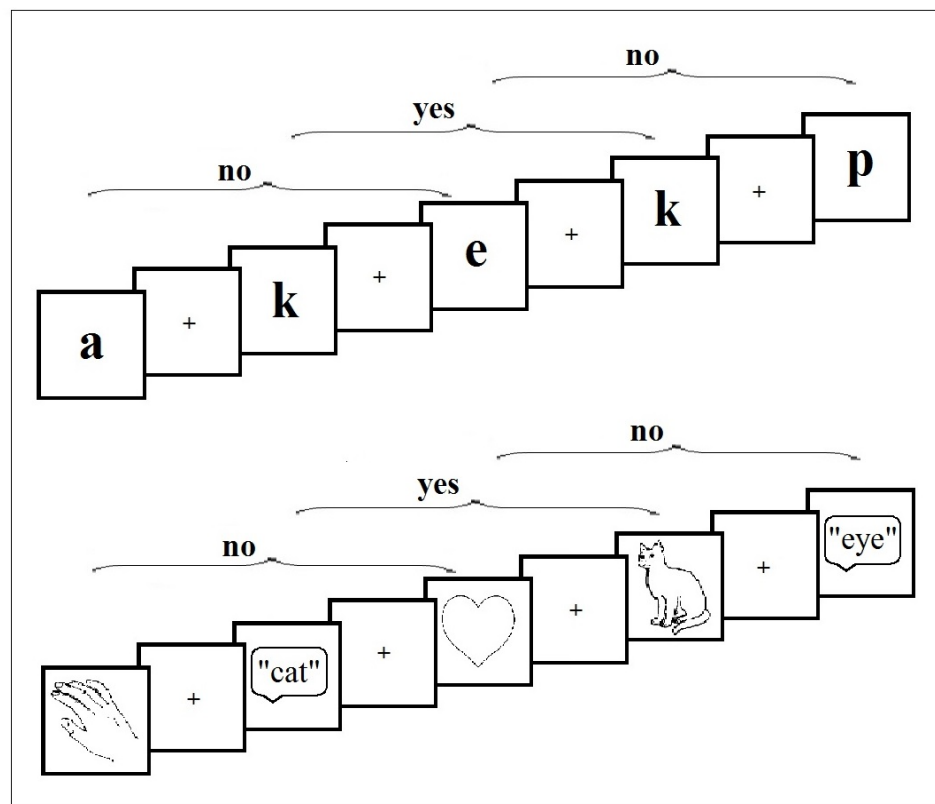


Figure 9)

Top: Common version of verbal 2-back task

Bottom: Cross-modal version of 2-back task, according to Suchan et al. (2006)

Working memory load could be modulated by selecting different “n”, speed of mental processing could be modified by the length of inter-stimulus interval. As already mentioned, the gold standard in neuroimaging is 2-back task, since remembering only one previous item it too easy and storing 3 subsequent item is very demanding even for young healthy volunteers. Both visual and auditory presentation is possible, items to be memorized could be verbal, visual or spatial.

### 1. 2. 3. 3. PASAT

Paced Auditory Serial-Addition Task (PASAT) was introduced in the late 1970's and has been often used to neuropsychologically examine patients with diffuse brain damage, e.g., patients after traumatic brain injury or suffering from multiple sclerosis. In the original format, the PASAT test consisted of 60 random digits which were sequentially presented by investigator or from a tape. The subject was instructed to add the last digit to the preceding one, for every number supplied. The resulting sum had to be vocalized before the next digit was presented. Different presentation rates have been used (typically 2 or 3 s/digit) (Gronwall, 1977). The test was later included in standard cognitive testing of multiple sclerosis patients, e.g., the brief repeatable battery of neuropsychological tests in multiple sclerosis (BRBMS) (Cutter et al., 1999) or Multiple-Sclerosis Functional Composite (MSFC) score (Fischer et al., 1999). PASAT became popular in diseases with underlying diffuse brain pathologies for its complex recruitment of cognitive processes, since PASAT imposes high demands on the subject's sustained attention, verbal working memory capacity, requiring controlled information

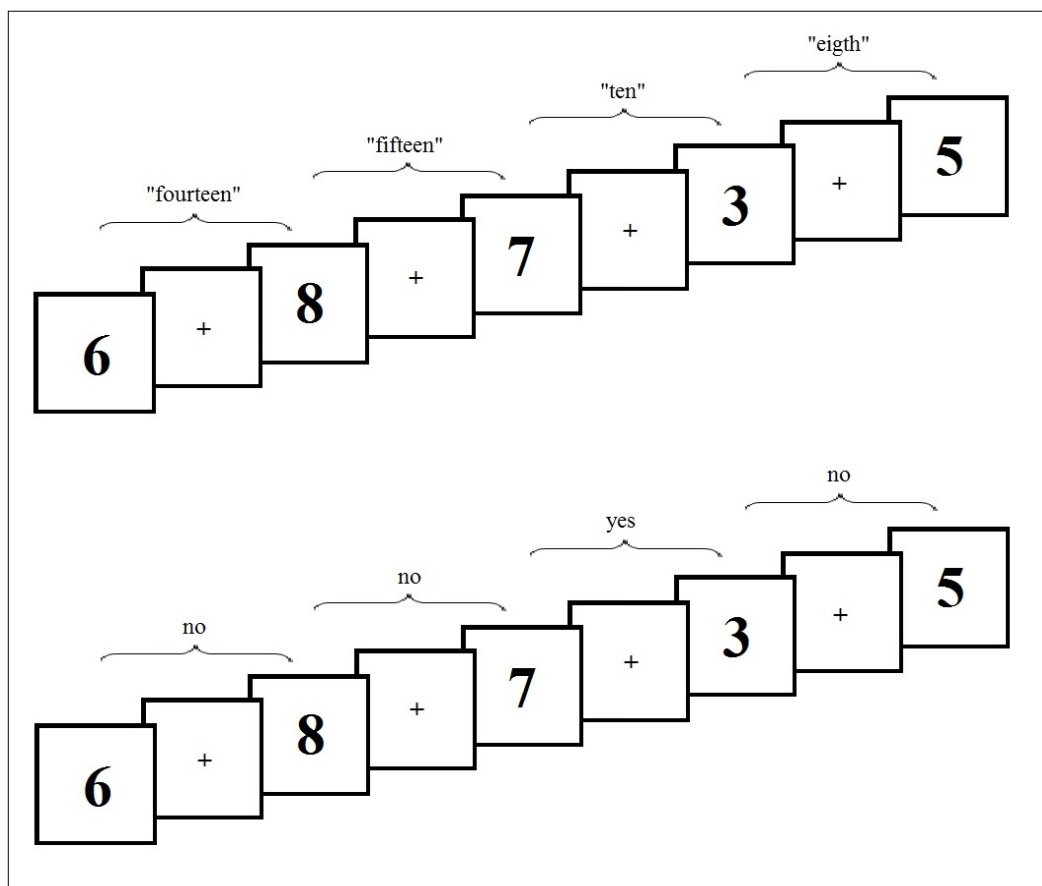


Figure 10)

Top: Original version of PASAT (every sum is overtly pronounced)

Bottom: Modified version of PASAT (positive response if sum = 10)

processing, good auditory functioning and calculating abilities (Sherman et al., 1997). Visual version of the task (Paced Visual Serial-Addition Task, PVSAT), in which digits are displayed on a screen, was also described (Diamond et al., 1997). Two possible approaches appeared among researchers trying to adapt the task for neuroimaging. Some used the a standard PASAT paradigm, which requires a verbal response to each sum of two previously presented numbers (e.g. Audoin et al., 2005; Forn et al., 2006). Another approach is sometimes called modified PASAT, in which the participants are required to respond with a button press when the serially present numbers summed to 10 (e.g. Chiaravalloti et al., 2005; Mainero et al., 2004).

### **1. 2. 4. Neuroimaging and neural correlates of working memory**

Experimental human studies searching for the neural correlate of working memory processes have been published since the beginning of the 1990's, due to the availability of noninvasive functional brain imaging using PET and fMRI. It is generally assumed that there are three functional components of working memory, whose existence can be observed by neuroimaging methods (Smith and Jonides, 1998):

- 1) pure storage component, in which content quickly decays;
- 2) rehearsal component that actively restores the content;
- 3) executive component regulating processes of working memory

There is good agreement across the results of imaging studies that the left inferior frontal gyrus (also known as Broca's area) and other speech areas are involved in the process of rehearsal, whereas storage process are located to posterior parietal cortex. Petrides et al (1993) in a PET study used a memory task in which subjects sequentially repeated sequence of numbers from 1 to 10 in order. The authors then subtracted the resulting brain activation from activations obtained in similar tasks in which subjects randomly pronounced numerals from 1 to 10 without repetition. The resulting significant areas of activation were located to bilateral mid-dorsolateral frontal, premotor, and posterior parietal cortices. The task with random numbers required remembering digits already used and those left to be pronounced. The task with digits in order imposed no demand on working memory, and thus active areas resulting from subtraction of the two tasks are therefore presumably involved in the storage and



maintenance of verbal material.

In another PET study Paulesu et al. (1993) provided evidence that the frontal areas were involved in rehearsal of the verbal material, whereas the parietal regions mediate the storage of such material. In their experiment, the subjects had to memorize a series of English letters (memory task) or to make rhyming judgments about English letters (rhyming task). The control task consisted of a nonverbal decision task about Korean letters. When activations in the memory task were subtracted from activations in the control task, the resulting differences were located to the supplementary motor area, Broca's area and the left posterior parietal cortex. Activation in the posterior parietal cortex was associated with the memory task, but not with the rhyming task, suggesting that the working memory storage is processed there. On the other hand, Broca's area was activated by both memory task and rhyming task, which led Paules et al. to a suggestion that verbal rehearsal takes place in left inferior frontal gyrus.

Awh et al. (1996) provided direct evidence that Broca's area is the part of the circuit for phonological rehearsal and posterior parietal areas are used for storage of working memory. The PET experiment included one experimental and two control tasks. The 2-back task using letters served as the experimental task. As the first control condition served a one-letter search task, during which subjects were watching series of subsequent letters similar to n-back task and gave a positive signal when predefined letter was presented. In the second control condition, subjects were covertly reading presented letters. Subtraction of one-letter search task from 2-back task revealed activation in Broca's area and left posterior parietal cortex, as well as in bilateral activation in premotor cortex, supplementary motor area, the superior parietal lobule, and cerebellum. While it is necessary to involve both rehearsal and storage during 2-back task, passive waiting for predefined during one-letter search task requires neither of the two processes.

Subtracting covert reading tasks from 2-back revealed only activation in the supplementary motor area and parietal areas. This suggests that Broca's area, premotor cortex, and the cerebellum are largely involved during rehearsal, but not during storage. A similar pattern of activation in frontal regions was described during 2-back by Cohen et al. (1994) in an fMRI experiment. Smith et al. (1996) used the 3-back task during the PET experiment and confirmed the involvement of Broca's area and left posterior parietal, left dorsolateral frontal, and bilateral superior parietal cortices.

The above listed studies provide strong support for the existence of fronto-parietal verbal working memory circuit, which was further confirmed by a meta-analysis including 60 PET

and fMRI studies of working memory tasks published between 1993 and July 2002 (Wager and Smith, 2003). The results of the meta-analysis showed consistent left-lateralized activations in Brodmann areas BA 44, 45, 46, 47, 22, 40/7 and bilateral symmetrical activations in BA 32, 24 and 6 without further differentiation of storage, rehearsal and executive components.

Working memory processes in the brain were also studied within the context of more complex PASAT and PVSAT. Both auditory (Au Duong et al., 2005; Audoin et al., 2003; Forn et al., 2006; Mainero et al., 2004) and visual (Bonzano et al., 2009; Lazeron et al., 2003; Rachbauer et al., 2006; Staffen et al., 2002) versions of PASAT or modified PASAT were subsequently adapted for functional MRI examination. The results show good agreement on the expected distributed brain networks related to the engaged processes, namely fronto-parietal working memory and attention networks.

### 1. 2. 5. Effects of sensory modality on verbal working memory

The importance of sensory perception is emphasized in all influential theoretical concepts of memory (Atkinson and Shiffrin, 1968; Baddeley, 2010; Baddeley and Hitch, 1974). In the broadly preferred Baddeley's concept, the verbal component of working memory is maintained by a rehearsal process in the

phonological loop. Auditory perception should therefore naturally flow into verbal memory, whereas visual stimuli need to be transcoded to their phonological form.

Neurophysiological processes necessary for both types of sensory input before the information may enter verbal working memory are graphically summarized in

Figure 11. Storage and rehearsal of information in verbal working

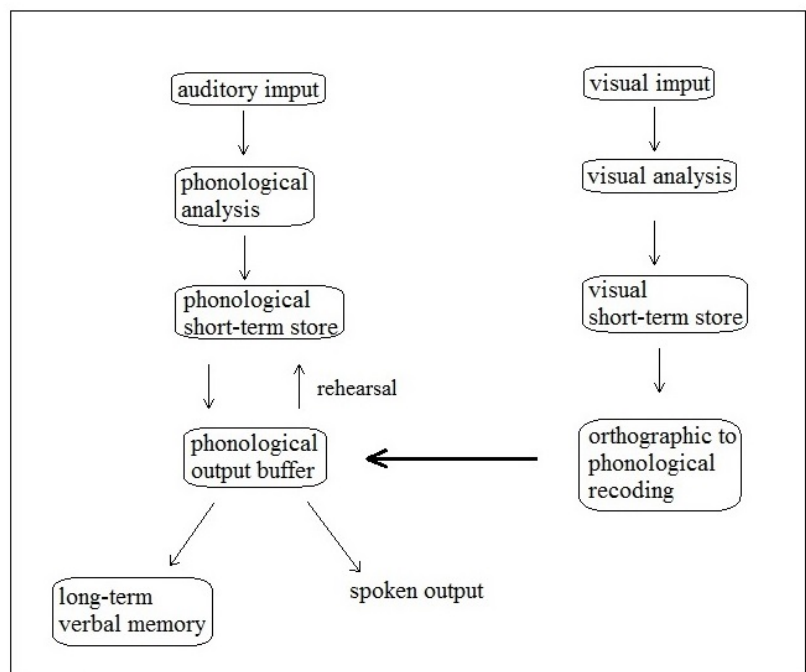


Figure 11) Sensory modality differences in verbal working memory, Baddeley (2010)

memory and possible manipulation are no longer dependent of the sensory modality according to Baddeley (2010).

However, this theory of amodal neural network involved in working memory processes was not fully in line with experimental and clinical findings. Behavioral research has pointed to differences in auditory and visual short-term memory processing leading to the suggestion that short-term memory processing in the two modalities is mediated by separate streams that have different properties and capabilities (Allport et al., 1972; Kroll et al., 1970; Penney, 1989). Also clinical lesion studies have provided some evidence for modality-specific deficits (Basso et al., 1982; Crottaz-Herbette et al., 2004; Shallice and Warrington, 1977; Warrington and Shallice, 1972, 1969). Furthermore, non-human primate research brought evidence that primate memory is arranged according to modality, e.g., superior temporal cortex specifically retains auditory information during delayed matching-to-sample task (Colombo et al., 1990). During a similar task, neuronal activity was observed in the anterior-ventral temporal cortex while maintaining visual information (Miyashita and Chang, 1988). However, since genuine verbal processes can not be tested in primates, such results are not directly applicable for the human brain function. Verbal memory study using evoked potentials in humans performed by Ruchkin et al. (1997) confirmed that the phonological loop was activated in both modalities, but auditory stimuli triggered earlier left frontal negative waves indexing retention and rehearsal operations that were more long lasting. On the other hand, posterior regions showed larger evoked potentials for visual stimuli.

The first study using neuroimaging methods to address sensory differences in verbal working memory was performed by Schumacher et al (Schumacher et al., 1996), who acquired PET images of subjects performing a visual or auditory version of the 3-back task. Direct comparison of the two activation tasks revealed an almost complete overlap between the active memory areas regardless of input modality. These areas included dorsolateral frontal, Broca's area, SMA, and premotor cortex in the left hemisphere; bilateral superior and posterior parietal cortices and anterior cingulate; and right cerebellum. The only statistically significant difference was a small area of higher activation in the left Broca's area (Brodmann area 45). Schumacher et al. pronounced this quantitative difference to be negligible and concluded that verbal working memory is modality independent.

Crottaz-Herbette et al. (2004) replicated Schumacher's study design using 2-back task and functional MRI. They reported higher activation in the posterior parietal cortex (BA 40/7)

during visual working memory in contrast to higher activation in the left dorsolateral prefrontal cortex (BA 9 and 44/45) during working memory with auditory stimuli. An almost identical study was repeated by Rodriguez-Jimenez et al. (2009), as a result they observed predominantly left-sided significant differences in the frontal areas and superior temporal gyrus during the auditory task and bilateral occipitotemporal areas during the visual task. Another fMRI experiment used cross-modal version of the 2-back task (see bottom of Figure 9) with event-related design in an attempt to clarify the process of transcoding of visual stimulus into phonological form. The shift from the visual to the auditory modality revealed activation in the left primary auditory cortex (superior temporal gyrus, BA 41/22). No significant clusters were found during the change from the auditory to the visual modality (Suchan et al., 2006).

Similar patterns of modality-dependent activations were confirmed in the Sternberg task by Kirschen et al. (2010), who in direct comparison observed prominent activations in right superior cerebellum, bilateral occipital (BA 17/18/19) and parietal (BA 7/40) cortex evoked by visual presentations while auditory presentation showed robust activations predominantly in bilateral temporal regions (BA 41/21/22) and less pronounced bilateral activations in inferior frontal gyrus (BA 46) and anterior cingulum (BA 32).

So far, no study directly confirmed whether or not the differences similar to those seen in n-back and Sternberg task do exist between auditory and visual version of the Paced Serial Addition Task.

To summarize this section, we can see converging evidence that auditory verbal working memory tasks tend to significantly more activate bilateral or left-lateralized regions of prefrontal cortex, mainly in BA 9, 47 or 45, and bilateral or left-lateralized temporal regions, namely BA 41/21/22. On the other hand, visual verbal working memory tasks tend to activate bilateral occipital regions (BA 17/18/19) and bilateral or left-lateralized parietal regions (BA 7/40).

Interpretations of these differences remain largely unresolved. According to Crottaz-Herbette et al., activation of the left intraparietal sulcus during visual 2-back task is possibly the result of additional processing involving access to parietal storage mechanisms. Alternatively, it is also possible that these differences may arise from fundamental differences in the neural representations of auditory and visual stimuli in phonological storage; however, fMRI has poor spatial and temporal resolution to resolve this issue (Crottaz-Herbette et al., 2004). As for the lateral prefrontal cortex, differences seem to be primarily quantitative. These

regions, namely the dorsolateral prefrontal cortex, were demonstrated to play role in maintenance of information, but also control and monitoring processes during working memory tasks. As suggested by Crottaz-Herbette et al., modality differences observed in the dorsolateral prefrontal cortex reflect a more prolonged control and monitoring processes during the auditory version of 2-back task (Crottaz-Herbette et al., 2004).

As for the temporal and occipital regions, we can assume some higher processes of sensory perception that are needed for task performance, or we can simply admit that control condition failed to subtract unspecific sensory processes. Another cause of differences are task-induced deactivations as pointed out by Crottaz-Herbette et al. (2004).

### **1. 2. 6. Default mode network**

Task-induced decreases of activation, or deactivations, may be detected in all tasks used in neuroscientific research ranging from simple sensory and motor task to complex cognitive paradigms. To interpret the deactivated regions, a theoretical concept of the default mode network (DMN) has been introduced (Raichle et al., 2001; Greicius et al., 2003) based on empirical observation of task-induced decreases of activation compared to resting state (i.e. passive visual fixation or eyes closed resting). Interestingly, activation decreases were remarkably consistent across a wide variety of task conditions (Marcus E Raichle and Snyder, 2007). There is also evidence, that the amplitude of deactivation, the number and volume of deactivated regions gradually increase with task difficulty and complexity (Daselaar et al., 2004; Prilipko et al., 2011; Singh and Fawcett, 2008; Todd et al., 2005).

For a simple task (e.g. sustained attention and visual sensory stimulation), the areas of deactivation include the medial posterior cingulate cortex (BA 23/31) and the adjacent parts of precuneus and ventromedial cortex (BA 10) (Raichle et al., 2001). When task difficulty increases, additional deactivation occurs in the angular gyri (BA 39) and medial anterior cingulate cortex (Singh and Fawcett, 2008; Krajčovičová et al., 2010). Using a visual spatial working memory task, Greicius et al. described deactivations in the already mentioned regions and additionally in bilateral areas of pre- and postcentral gyri, parahippocampal gyri and in insula (Greicius et al., 2003).

Despite the fact that individual anatomical regions comprising the DMN are rather well known, its exact role for human function remains unclear. From psychological and theoretical point of view, a resting state represents an introspectively oriented, self-referential

mode of mental activity, labeled by some as stimulus-independent thoughts, or “mind wandering”, that may serve to enable individuals to maintain an optimal level of arousal to facilitate performance on mundane tasks, or as a spontaneous mental time travel it might lend a sense of coherence to one’s past, present, and future experiences, or finally the mind may generate stimulus-independent thoughts not to attain some extrinsic goal, but simply because it evolved a general ability to divide attention and to manage concurrent mental tasks and creative problem solving (Mason et al., 2007; Mooneyham and Schooler, 2013).

At the level of neural networks, a correlate of resting state can be observed as fMRI low-frequency BOLD signal changes (0.012-0.1 Hz) in the resting brain (Fransson, 2005). The analysis of low-frequency fluctuations has demonstrated the presence of a high temporal coherence between spatially distinct, functionally-related brain regions, constituting the resting state networks of the human brain, which resemble specific neuroanatomical networks devoted to specific sensory, motor, and cognitive functions. The temporally coherent resting-state fluctuations are thought to reflect the intrinsic functional organization of the brain (Filippi et al., 2013).

Awake brain thus probably shifts between intrinsic self-referential mode and extrinsic activity requiring sustained (focused) attention to the external environment and adaption to it, such extrinsic activity then leads to decreased activity in default mode network areas (Fransson, 2005).

Although the exact role of DMN remains a matter of debate and theorizing, it is very well proven that disturbance of DMN and low-frequency fluctuations is associated with cognitive deficits. DMN dysfunction has already been demonstrated in dementia, schizophrenia, epilepsy, anxiety and depression, autism and attention deficit/hyperactivity disorder and multiple sclerosis (Broyd et al., 2009; Filippi et al., 2013).

## 2. Aims of the Dissertation

The purpose of the work was two-fold. In the first part, we repeated a previously published verbal working memory task to test MRI-compatible visual stimulation system installed in the end of year 2009. After successful replication of the experimental results, we proceeded to the second part, in which we performed direct comparison of the auditory and visual stimulation modality on verbal working memory processing during PASAT and PVSAT.

### **Experiment I**

*Aim:* to perform the item-recognition task in a group of healthy volunteers, to describe the activated and deactivated brain regions and to compare our result to the previously published papers. Our own data could be utilized as normative in subsequent research on populations of patients with manifest or possible cognitive deficit.

*Hypothesis I:* the item recognition task will activate prefrontal cortex (namely Broca's area and dorsolateral prefrontal cortex) and parietal regions with left-sided dominance.

Furthermore, task will most probably activate other language-related regions, SMA, basal ganglia or the cerebellum.

*Hypothesis II:* the tasks will deactivate regions of the default mode system.

### **Experiment II**

*Aim:* to directly compare the auditory and visual versions of the paced serial addition test (PASAT/PVSAT) in a group of healthy volunteers and describe the commonalities and differences in both activated and deactivated brain regions. To our knowledge, no such direct comparison was performed and published before.

*Hypothesis I:* both tasks will share active brain networks underlying attention, working memory (see above), calculation and other central executive functions.

*Hypothesis II:* both tasks will deactivate the default mode system to high extent.

*Hypothesis III:* the differences will be probably related to higher-level sensory processing, phonological encoding of visual stimuli or differences in task performance.

## **3. Experiment I**

Data published in: Tüdös Z, Hok P, Hluštík P. Verbal working memory investigation using functional MRI [In Czech], *Ces Radiol*, 2011;65(1): 14 -18.

### **3. 1. Material and methods**

#### **3. 1. 1. Participants**

Twenty volunteers (ten women, ten men with a mean age of  $22.5 \pm 1.7$ , resp.  $24.1 \pm 2.9$  years) participated in this study. All participants were university students or recent graduates, all were right-handed according to Edinburgh inventory (Oldfield, 1971). All subject denied history of neurological, psychiatric disease or significant craniocerebral trauma. Subjects participated after providing written informed consent.

#### **3. 1. 2. fMRI tasks**

Block-design modified item-recognition task was used to engage the verbal working memory (Smith and Jonides, 1998). In our setting, we used rear projection and a mirror mounted on the top of head coil to first display a slide with four target words; participants had to remember the words and their position on the screen. The target words were displayed for 4 seconds, then there was 7-second blank delay interval followed by single probe word in one of four possible positions displayed for 3 seconds. Subject had to respond, whether probe word corresponded to one of the target word and whether it had the same position (see Figure 8).

The control task had the same timing but instead of target words we projected ordinal numbers in four positions ("first", "second", "third", "fourth"), which subjects did not have to remember and the probe word ("first" or "second") was always correct. This control condition was used to subtract visual processing and to keep subject aware.

Each single trial lasted 15 seconds. Two memory trials alternated with two control trials, thus providing 30-seconds timing of block design.

Before positioning a participants into the gantry of MRI scanner, the participants were instructed on how to perform the tasks and repeatedly asked whether the instructions were understood.

#### **3. 1. 3. Data acquisition**

MRI data were acquired on 1.5-Tesla scanner (Siemens Avanto, Erlangen, Germany) with a



standard head coil. The subject's head was immobilized with cushions to assure maximum comfort and minimize head motion. The MR imaging protocol covered the whole brain with 30 axial slices parallel to the anterior commissure - posterior commissure (AC-PC) line, 5-mm thick, including anatomical T<sub>1</sub>-weighted images to provide an immediate overlay with functional data, fluid attenuated inversion recovery (FLAIR) images to screen for unsuspected brain lesions and functional T<sub>2</sub>\*-weighted BOLD images during task performance and control state. BOLD images were acquired with gradient echo EPI (TR/TE = 2500/41 ms, flip angle 80°, FOV = 220 mm, matrix 64×64) to provide 3.4-mm × 3.4-mm × 5.0-mm resolution. In total, 144 images were acquired per each 6-minute functional run. For better anatomical reference, a high-resolution 3-dimensional scan (magnetization-prepared rapid acquisition gradient echo, MP-RAGE) was performed as well.

### **3. 1. 4. Statistical analysis**

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). The version 5.91 of FEAT was used for the original publication in 2011, version 6.00 was used to extend the results for the thesis in 2014. The following pre-statistics processing was applied; motion correction using Motion Correction FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using Brain Extraction Tool (BET) (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 8.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=30.0s). Time-series statistical analysis was carried out using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich et al., 2001). Registration to high resolution structural and/or standard space images was carried out using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Higher-level analysis was carried out using FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by  $Z > 3.8$  and a (corrected) cluster significance threshold of  $P = 0.05$  (Worsley, 2001). Z-stat images were masked with white matter and cerebrospinal fluid exclusion mask (available in built-in atlases in FSL) before thresholding.

The resulting clusters of activation were superimposed on T<sub>1</sub>-weighted MNI standard brain (Grabner et al., 2006) and their anatomical locations were derived from the Harvard-Oxford brain atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) and probabilistic cerebellar atlas (Diedrichsen et al., 2009) incorporated in FSL. The same statistics was performed to obtain significant task-induced signal decreases, i.e. deactivations.

### **3. 2. Results**

Performance of the task was good in all subjects, the error rate throughout the session was 0-2 errors per run.

The results of the group analysis revealed bilateral regions of activation in the frontal, parietal, temporal and occipital lobes, basal ganglia, the brainstem and in the cerebellum (see Figure 12 and 13). Despite rather high single-voxel statistical threshold, there was large confluent activation in frontal lobes, basal ganglia, the brainstem and cerebellum forming one large cluster of voxels involving inferior frontal lobes, middle frontal lobes, frontal eye fields, anterior cingulate cortex, the putamen and caudate. Local maxima within this extensive cluster were localized to the left BA 9 and 46, in the inferior frontal gyrus (BA 44 and 47), in the left putamen and head of caudate bilaterally. Activations were also clearly visible in the left BA 44, BA13 and BA6 (Frontal Eye Field). All of these areas were activated also in the right hemisphere, but left-sided dominance was obvious. The largest cluster further comprised bilateral symmetrical activations in the anterior cingulate cortex (BA 32) and the medial portion of the premotor area BA 6 (SMA).

Parietal regions of activation involved bilateral intraparietal sulcus and superior parietal lobule (BA 7/40) with a predominance in the left hemisphere. The temporal lobes showed apparent activity in the posterior division of superior temporal gyrus (BA 21/22) and in both hippocampi. The occipital lobes were activated within Brodmann areas 18 and 19. Areas of activation in both cerebellar hemispheres and vermis were large and symmetric. Clusters and local maxima are summarized in Table 1.

Clusters of significant deactivation during the task were found bilaterally in the temporal poles (BA 21/38), in the right inferior parietal lobule (BA 39), frontal pole (BA 10/11) and parietal operculum (BA 40/43). Clusters of deactivation were very small compared to the extensive confluent pattern of activations.

Table1

Brain location	Cluster size	Local maxima			
		Z max	x	y	z
<i>a) Task-induced activations</i>					
Left Middle Frontal Gyrus (BA 9/46 )	33822	6.86	-48	2	42
		6.74	-40	32	22
Left Putamen		6.83	-18	4	10
Left Inferior Frontal Gyrus / Insular cortex (BA 44/45/47 )		6.15	-36	28	-12
		6.15	-36	24	-10
		6.09	-40	20	14
		6.06	-28	28	-8
Left Caudate		6.08	-16	6	14
Right Caudate		6.00	12	4	16
Left Intraparietal Sulcus (BA 5/7/40)	2486	5.33	-42	-38	36
		4.99	-44	-44	48
		4.98	-26	-48	46
Right Intraparietal Sulcus (BA 5/7/40)	1374	4.88	42	-42	46
		4.73	46	-38	46
		4.73	24	-56	66
Left Superior Temporal Gyrus, Posterior division (BA 22)	737	5.01	-48	-40	10
		4.91	-54	-38	6
		4.68	-62	-22	-4
Right Frontal Eye Field (BA 6)	645	5.07	28	-2	42
		5.01	30	8	62
		4.84	28	6	58
Left Superior Temporal Gyrus, Posterior division (BA 22)	328	4.88	52	-34	2
		4.40	60	-28	0
		4.37	66	-28	-2
Right Cerebellum	193	4.47	28	-34	-44
Right Occipital Pole (BA 17/18)	100	4.27	20	-98	8
		4.17	16	-98	10
		3.94	26	-94	12
Left Cerebellum	74	4.20	-32	-62	-56
		4.18	-28	-66	-56
<i>b) Task-induced deactivations</i>					
Right Temporal Pole and Middle Temporal Gyrus (BA 21/38)	946	5.91	38	20	-46
		5.59	44	18	-36
Left Temporal Pole and Middle Temporal Gyrus (BA 21/38)	585	5.33	-38	6	-36
		4.64	-40	18	-44
Medial Prefrontal Cortex (BA 10/11)	90	4.48	14	68	28
		4.18	12	70	20
Right Inferior Parietal Lobule (BA 39)	77	5.00	52	-70	40
		4.72	50	-74	26
Right Parietal Operculum (BA 40/43)	69	5.20	70	-20	30
Significant a) activations and b) deactivations during the item-recognition task. Cluster size = number of voxels; local maximum = voxel with the peak Z-score; x, y, z = MNI coordinates of the local maximum; BA = Brodmann area					

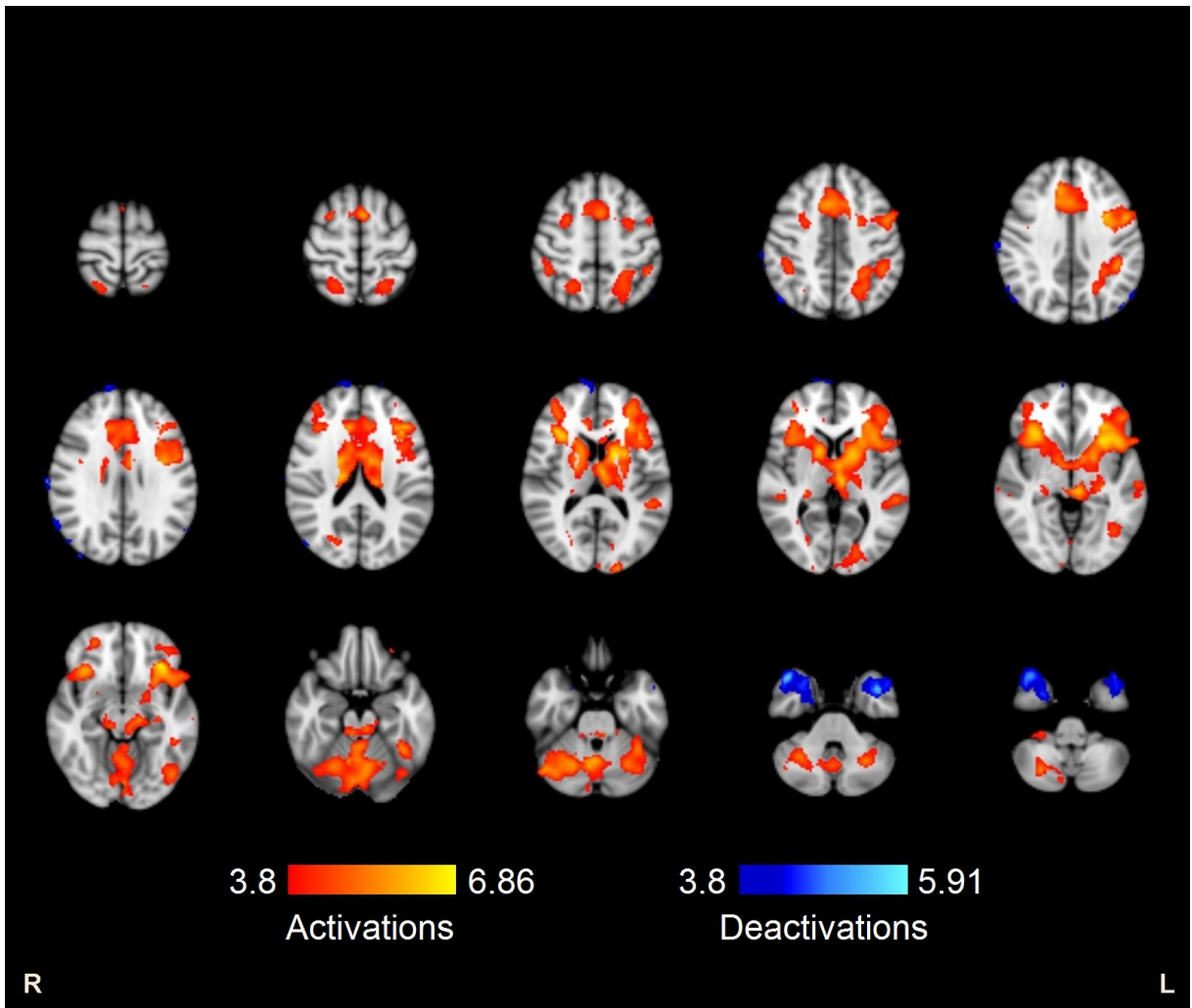


Figure 12) Statistically significant activations (red-yellow scale) and deactivations (blue scale) during item recognition task overlaid onto MNI152 T1-weighted standard brain axial slices for anatomical reference. Range of Z values is shown.

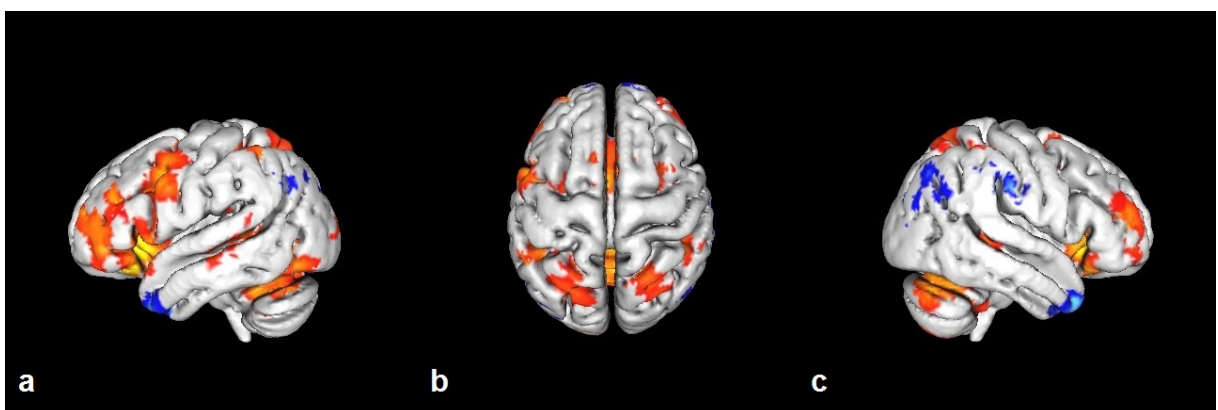


Figure 13) Areas of significant activation and deactivation during item recognition task projected onto rendered standard brain surface; a) left, b) superior, c) right view.

### 3. 3. Discussion

Generally, the results correspond to our expectations and do not contradict the common view of the neurophysiology of memory tasks.

Compared to the previous studies (Smith and Jonides, 1998; Wager and Smith, 2003), our modification emphasized the verbal component and thus strongly recruited processes responsible for phonological rehearsal (Baddeley, 2010, 1996). The circuit of the phonological loop includes primary speech areas, but also areas responsible for motor articulation and speech planning (Awh et al., 1996).

In accordance with this assumption, significant activation were found in the left Broca's area (BA 44, 45) and ventrolateral prefrontal cortex (BA 47), which is a constant finding throughout all verbal tasks; mirror activations in corresponding right-sided areas is also common (Wager and Smith, 2003).

Another crucial area recruited by working memory processes is the dorsolateral prefrontal cortex (BA 46/9), both in verbal and visual tasks, whereas visual tasks usually lead to symmetric or right-lateralized activations (Ibrahim and Tintěra, 2007; Wager and Smith, 2003) and verbal tasks activate predominantly the left hemisphere, which corresponds very well to our result.

Wernicke's speech area responsible for speech perception is traditionally located in the posterior section of superior temporal gyrus (BA 22), we found bilateral activation with left dominance.

The hippocampus is usually associated with the function of long-term memory, but verbal working memory tasks do activate this region as well, probably due to the engagement of semantic processing of information retrieved from long-term store (Bartha et al., 2003).

The cerebellum is another anatomical structure involved in the phonological loop (Awh et al., 1996; Desmond et al., 1997; Durisko and Fiez, 2010; Wager and Smith, 2003), since cerebellum is assumed to play a role in articulation and subvocal rehearsal. The articulatory component of the phonological loop further contributes to activation in the premotor cortex on the medial surface of BA6 (SMA), which is responsible for the planning of motor actions, including control of speech-related muscles. The circuit of the phonological loop also involves basal ganglia, namely putamen and the head of the caudate, which were activated bilaterally, more on the left side. This observation corresponds to literature (Wager and Smith, 2003).

Parietal activations in BA 7/40 are consistently observed during both verbal and visual memory tasks (Smith and Jonides, 1998; Wager and Smith, 2003) mainly due to short-term

storage function (Awh et al., 1996; Paulesu et al., 1993), but this area is also supposed to contribute to visuomotor coordination and partly to the executive functions.

Functional involvement of ACC (BA 32) occurs when a task requires directed attention (Paus, 2001), particularly if the processing of new information is needed. Working memory tasks commonly activate this area (Wager and Smith, 2003). ACC also contributes to central executive function, but its role in our experiment was limited.

There were minor active clusters in the secondary visual cortex of both occipital lobes (BA 18 and 19) due to visually supplied stimuli, this activity is most probably attention-related (Cate et al., 2012). Involvement of occipital visual areas in previous studies was also rather marginal (Wager and Smith, 2003), but it may also be more pronounced (Na et al., 2000).

Regions of deactivation corresponded to previously published influential papers focused on the default mode network (Greicius et al., 2003; Raichle et al., 2001), but the extent of deactivation was unexpectedly low. The explanation might be the low engagement of central executive functions during the item-recognition task, since it requires only simple maintenance of information and no manipulation. Additionally, the control task required subjects' attention, thus preventing the DNM regions from engagement typical for full resting. The disadvantage of our study is very extensive significant activation of the frontal lobes and the resulting confluence of large activated areas, which made quantification of left-right differences and calculating laterality index impossible at the group level – such an evaluation would require automatic or manual parcellation of the active regions to pre-defined regions of interest. Furthermore, it should be noted that age range of the subjects was very narrow, so the results can not be automatically applied to other age groups.

Despite these limitations, the results can be considered satisfactory and suggest that modified item-recognition tasks may be used for fMRI examinations of patients suffering from neurological and psychiatric diseases.

To conclude, using modified verbal working memory task, we examined a group of healthy volunteers and gained normative data for further use for the examination of patients, whose working memory is or might be impaired.



## **4. Experiment II**

Results included in: Tüdös Z, Hok P, Hrdina L, Hluštík P., Modality effects in paced serial addition task: differential responses to auditory and visual stimuli; manuscript revision under review in *Neuroscience* (IF 3.12).

### **4. 1. Material and methods**

#### **4. 1. 1. Participants**

Twenty volunteers (ten women, ten men), with a mean age of 23.0 (SD 2.7) years, participated in this study. All participants were university students or recent graduates, all were right-handed according to Edinburgh inventory (Oldfield, 1971). Subjects participated after providing written informed consent. Before the scan, the PASAT and PVSAT tasks were explained and practiced.

#### **4. 1. 2. fMRI tasks**

Participants completed two 6-min runs of the PASAT and two similar runs of the PVSAT modified for MRI setting as described previously (Archbold et al., 2009; Mainero et al., 2004; Staffen et al., 2002) (see bottom of Figure 10).

During six blocks of 30 s each, the subjects were required to add up the presented semi-randomized single digits (ranging from one to nine), adding each digit to the one immediately preceding it. A new stimulus was presented every 3 s. Subjects were instructed to add up the numbers silently and to raise their right thumb whenever the sum equaled 10. There were 14 or 15 such instances during each run. A single observer recorded response accuracy during image acquisition. Six PASAT/PVSAT-blocks were alternated with six control periods of 30 s each in which digits were presented in the same timing and subjects were instructed to raise their right thumb whenever the number “10” was presented (Archbold et al., 2009; Mainero et al., 2004).

In PASAT, auditory stimuli were presented through fMRI compatible headphones. The duration of auditory stimuli was 305-634 ms (mean 475 ms). Sound volume was adjusted so that each participant could hear the stimuli properly. Participant had their eyes closed during the PASAT runs.

In PVSAT, visual stimuli were presented via a rear projection screen and a mirror on top of the head coil. Single digits were located in the center of the screen (font Arial, vertical view angle 4.4°), every digit was displayed for 500 ms followed by 2500 ms of blank screen.



The order of the PASAT and the PVSAT runs was counterbalanced across the subjects.

#### **4. 1. 3. Data acquisition**

MRI data were acquired on a 1.5-Tesla scanner (Siemens Avanto, Erlangen, Germany) with a standard head coil. The subject's head was immobilized with cushions to assure maximum comfort and minimize head motion. The MR imaging protocol included functional  $T_2^*$ -weighted blood oxygen level-dependent (BOLD) images during task performance and control state. BOLD images were acquired with gradient-echo EPI (30 axial slices parallel to the AC-PC line, 5-mm thick, TR/TE = 2500/41 ms, flip angle  $80^\circ$ , FOV = 220 mm, matrix  $64 \times 64$ ) to provide  $3.4\text{-mm} \times 3.4\text{-mm} \times 5.0\text{-mm}$  resolution. In total, 144 images were acquired per each 6-minute functional run. Anatomical in-plane  $T_1$ -weighted images and a high-resolution 3-dimensional scan (magnetization-prepared rapid acquisition gradient echo, MPRAGE) were acquired to provide an immediate overlay with functional data and better anatomical reference.

In-plane fluid attenuated inversion recovery (FLAIR) images to screen for unsuspected brain lesions.

#### **4. 1. 4. Statistical analysis**

Numbers of correct responses to target sums in PASAT and PVSAT runs were compared using paired two-sample t-test.

FMRI data processing was carried out using FEAT Version 6.00, part of FSL (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). The following pre-statistics processing was applied; motion correction using MCFLIRT (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 8.0mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with  $\sigma=30.0s$ ). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Registration to high resolution structural and/or standard space images was carried out using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Higher-level analysis was carried out using FLAME stage 1 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008).  $Z$  (Gaussianised T/F) statistic images were thresholded using clusters determined by  $Z > 3.5$  and a (corrected) cluster significance threshold of  $P=0.05$  (Worsley, 2001).

Several different contrasts were employed in order to fully explore the data: group-wise mean activation and deactivation for each task (1); activation and deactivation conjunctions (2 and 3, respectively); and between-task differences (4 and 5).

The resulting clusters of activation were superimposed on T<sub>1</sub>-weighted MNI standard brain (Grabner et al., 2006) and their anatomical locations were derived from the Harvard-Oxford brain atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) and probabilistic cerebellar atlas (Diedrichsen et al., 2009) incorporated in FSL.

The conjunction maps showing activation (Contrast 2) and deactivation (Contrast 3) were obtained using binary AND operation applied to the thresholded task-specific maps from Contrasts 1. A total average (PASAT + PVSAT) Z score was displayed in the voxels of significant conjunction rather than a binary value. This allowed for detection of local maxima within the conjunctions.

The analysis of between-task differences was carried out using two-sample paired t-test, yielding two contrasts: Auditory (PASAT) > Visual (PVSAT) labeled as Contrast 4, and Auditory < Visual labeled as Contrast 5. In order to distinguish the clusters arising from BOLD signal increase (activation) in the experimental task from those resulting from BOLD signal decrease (deactivation) in the control task (and vice versa), we employed and expanded previously described methods (Crottaz-Herbette et al., 2004). First, we inspected the underlying group effects within each cluster by extracting their mean Z scores from Contrasts 1 (i.e. from the separate PASAT and PVSAT analyses). Next, we transformed the clusters into the each individual's functional space and calculated the single-subject mean Z scores, as implemented by Featquery tool in FSL. Additionally, we performed a complementary post-hoc extraction of mean Z-scores from anatomical regions of interest (ROI) in selected clusters in order to detect possible distinct effects occurring in the same cluster. This was done if at least two distinct hot-spots spanning across multiple anatomical areas were apparent within one cluster, as assessed by visual inspection. Only the ROI's passing the whole-brain cluster significance threshold of P=0.05 (see above) are reported. Each cluster and anatomical ROI was classified as arising from activation, deactivation or as a combination of both. This classification was done based on the sign of the calculated mean Z scores and the difference between the corresponding absolute values, as measured in the underlying Contrasts 1.

## 4. 2. Results

Task performance in the scanner was excellent, none of the participants encountered any difficulties while performing the PASAT or PVSAT conditions. Mean number of correct responses during two PASAT runs was 27.8 out of 29 possible (95.9 %), corresponding mean result for two PVSAT runs was 28.05 correct responses (96,7 %). The difference between the accuracy in the visual task and the auditory task was not statistically significant ( $p=0.37$ ).

### 4. 2. 1. PASAT and PVSAT activation patterns

The task-related networks engaged by PASAT and PVSAT (i.e. Contrast 1) showed similar patterns, although certain differences were apparent. Three-dimensional rendering of the two thresholded group mean statistical parametric maps is shown on Figure 14 – PASAT on the left and PVSAT on the right. Rather than describing each activation pattern in detail, we focused on subsequent analyses reflecting similarities and differences in the two activation networks, as described below.

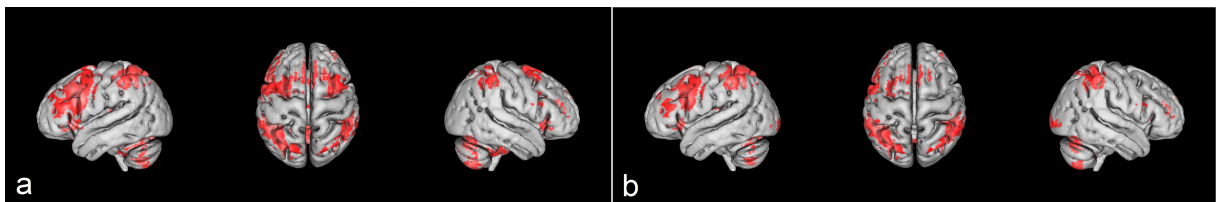


Figure 14)

*Areas of significant activation during a) PASAT and b) PVSAT compared to the control state, projected onto rendered standard brain surface.*

### 4. 2. 2. Activation conjunctions

The conjunction analysis for PASAT and PVSAT activations (Contrast 2) yielded bilateral symmetrical clusters in the supplementary motor area (SMA) (Brodmann area, BA 6), small portion of anterior cingulate cortex (ACC) (BA 24), intraparietal sulcus (IPS) (BA 5/7/40), cerebellar vermis and both cerebellar hemispheres.

Furthermore, left-lateralized bilateral activations were observed in the inferior frontal gyrus (IFG) and the ventral insula (BA 44/47), inferior frontal junction (IFJ) (BA 6/9/44), middle frontal gyrus (MFG)(BA 9/46), frontal eye field (FEF) (BA 6) and basal ganglia. See Table 2 for a list of areas jointly active for PASAT and PVSAT, including cluster sizes and MNI coordinates of their local maxima. The jointly active areas are further displayed on Figure 15 and 16 in red-yellow scale.

Table 2

Brain location	Cluster size	Local maxima			
		z max	x	y	z
<i>a) PASAT and PVSAT activation conjunctions</i>					
Supplementary Motor Area (BA 6)	4839	7.77	6	20	42
Left Inferior Frontal Gyrus / Insulate cortex (BA 44/47 )		7.56	-30	30	6
		7.28	-28	26	-2
		7.25	-52	12	30
Left Inferior Frontal Junction (BA 6/9/44)		7.25	-52	12	30
Left Inferior Parietal Sulcus (BA 5/7/40)	2968	8.09	-42	-42	44
		7.09	-28	-58	44
		6.94	-26	-66	36
Vermis	2178	7.49	8	-72	-22
Right Cerebellum		7.22	32	-68	-54
		7.2	28	-72	-58
Right Inferior Parietal Sulcus (BA 5/7/40)	1600	7.5	32	-38	30
		7.08	40	-42	40
		6.61	32	-58	44
Left Cerebellum	906	7.31	-30	-58	-38
		6.95	-34	-64	-50
Right Inferior Frontal Junction (BA 6/9/44)	380	5.99	30	4	26
		5.85	22	-2	20
Right Caudate		5.8	20	-14	22
Right Middle Frontal Gyrus (BA 9/46)	341	7.18	36	40	20
<i>b) PASAT and PVSAT deactivation conjunctions</i>					
Posterior Cingulate Cortex (BA 23/29/31)	9034	9.5	-2	-46	30
		9.4	4	-48	30
		9.38	-8	-44	34
Medial Prefrontal Cortex (BA 10/11)	8031	8.83	-8	44	-8
		8.75	0	64	2
		8.6	0	64	10
Right Middle Temporal Gyrus (BA 21/38)	7168	8.43	56	-6	-24
Right Parietal Operculum (BA 40/43)		8.07	60	-18	18
		7.97	48	12	-36
Left Middle Temporal Gyrus (BA 21/38)	5400	8.27	-56	-4	-20
		7.96	-58	2	-26
		7.85	-54	2	-22
Left Inferior Parietal Lobule (BA 39)	1761	8.39	-56	-62	30
		7.55	-50	-72	36
		7.35	-50	-64	18
Right Inferior Parietal Lobule (BA 39)	1590	7.84	52	-56	18
		7.54	46	-62	24
		6.59	46	-72	26
Right Precentral Gyrus (BA 4)	84	5.74	42	-20	60
Right Postcentral Gyrus (BA 2/3)		5.14	52	-12	52
Results of PASAT and PVSAT conjunction analysis for a) activation and b) deactivation. Cluster size = number of voxels; local maximum = voxel with the peak Z-score; x, y, z = MNI coordinates of the local maximum; BA = Brodmann area					

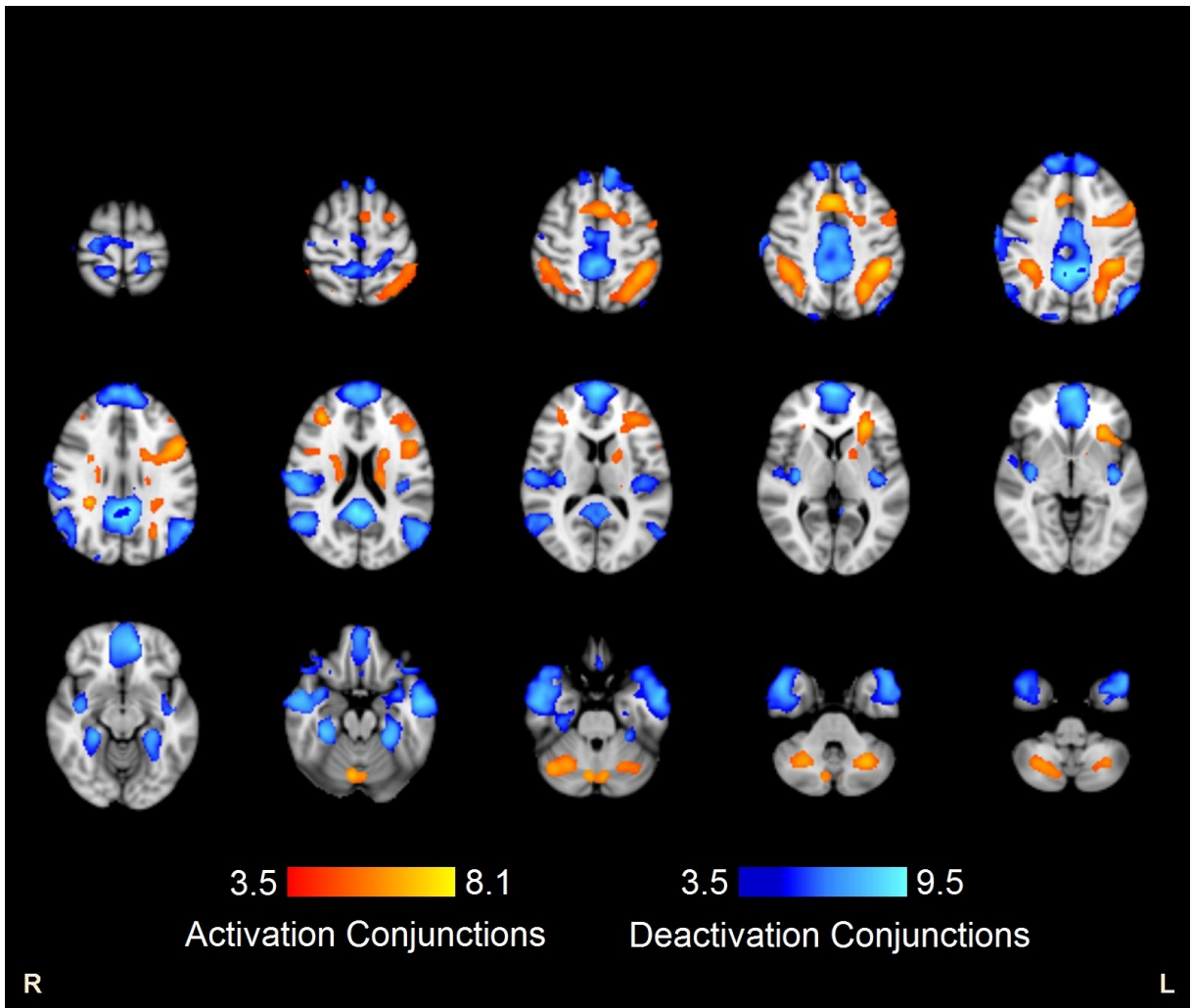


Figure 15) PASAT and PVSAT activation conjunctions (red-yellow scale) and PASAT and PVSAT deactivation conjunctions (blue scale) overlaid onto MNI152 T1-weighted standard brain axial slices for anatomical reference. Range of Z values is shown.

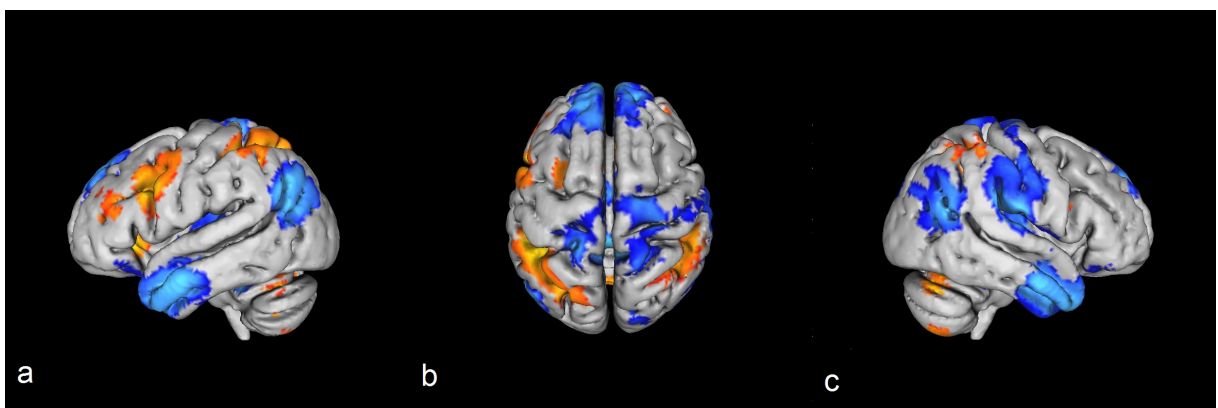


Figure 16) PASAT and PVSAT activation conjunctions (red-yellow scale) and PASAT and PVSAT deactivation conjunctions (blue scale) projected onto rendered standard brain surface; a) left, b) superior, c) right view.

### **4. 2. 3. Deactivation conjunctions**

The conjunction analysis for PASAT and PVSAT deactivations (Contrast 3) generated a bilateral and rather symmetrical pattern including posterior cingulate cortex and precuneus (BA 23/29/31), inferior parietal lobule (BA 39), precentral and postcentral gyri (BA 4, resp. BA 2/3), parahippocampal cortex (BA 35/36/37), medial temporal gyrus and temporopolar region (BA 21/38), dorsal insula, frontal pole and medial frontal regions (BA 10/11). There was bilateral but asymmetric deactivation in the parietal operculum (BA 40/43) and temporoparietal junction area, which was more extensive on the right side. See Table 2 for details and Figures 15 and 16 for display.

### **4. 2. 4. Contrast Auditory>Visual**

A direct within-subject comparison (paired t-test) of the auditory and visual tasks (Contrast 4) revealed significant differential activation in the right frontal eye field (BA 6), right lingual and fusiform gyrus (BA 18/19) and intracalcarine cortex (BA 17). In the left hemisphere, differential activations were observed in occipital pole (BA 17) and lingual gyrus (BA 17/18) (see Table 3 for details and Figures 17 and 19 for display).

Analysis of the underlying effect (see Statistical Analysis in Methods) showed that right frontal activations resulted from task-related increases during PASAT that were significantly higher than task-related increases in PVSAT. On the other hand, the difference in the right intracalcarine cortex was caused mainly by task-related decreases in PVSAT. Both task-related increases during PASAT and task-related decreases in PVSAT almost equally contributed to significant hemodynamic response differences in the right lingual and fusiform gyrus and in the left occipital pole and lingual gyrus. The observed trends seen in group cluster mean values were confirmed by comparison of regional mean Z values on single-subject level (see the top of Figure 18).

### **4. 2. 5. Contrast Visual>Auditory**

A direct comparison of the visual and auditory task (Contrast 5) revealed significant differential activation in the left temporal fusiform gyrus (BA 37) and bilateral left-lateralized activations in the lateral occipital complex (LOC) (BA 18/19) (see Table 3 and Figures 17 and 19). In subsequent analysis of the underlying effect for this contrast, the differential effects in all listed clusters resulted from almost equal task-related increases during PVSAT and task-related decreases in PASAT. The observed trends in group cluster mean values were confirmed by comparison of regional mean Z values on single-subject level (see the bottom of Fig. 18).

Table 3

Brain location	Cluster size	Local maxima				Cluster mean Z	
		z max	x	y	z	PASAT	PVSAT
<i>a) PASAT&gt;PVSAT comparison</i>							
Right Lingual and Fusiform Gyrus (BA 18/19)	442	4,92	12	-78	-6	2.10	-1.52
Right Intracalcarine Cortex (BA 17)	421	4,86	18	-90	14	1.96	-3.52
Right Eye Frontal Field (BA 6)	297	4,42	30	0	64	3.66	2.33
Left Occipital Pole (BA 17), Lingual Gyrus (BA 17/18)	239	4,64	-8	-98	-2	2.38	-2.70
<i>b) PVSAT&gt;PASAT comparison</i>							
Left Lateral Occipital Cortex, LO1 (BA 18)	672	5,36	-30	-92	-10	-2.67	1.20
Left Lateral Occipital Cortex, LO2 (BA 19), Fusiform gyrus (BA37)	778	4,69	-40	-62	-10	-1.65	1.72
Right Lateral Occipital Cortex (BA 18)	199	4,54	32	-90	4	-2.52	2.97

List of clusters revealing significant sensory modality-dependent differences.  
 Brain areas showing significantly greater BOLD response for a) PASAT compared to PVSAT (Auditory > Visual) and b) PVSAT compared to PASAT (Visual > Auditory).  
 Cluster size = number of voxels; local maximum = voxel with the peak Z-score; x, y, z = MNI coordinates of the local maximum; cluster mean Z = group-wise average Z-score of the voxels in the single task activation map calculated within the respective cluster mask

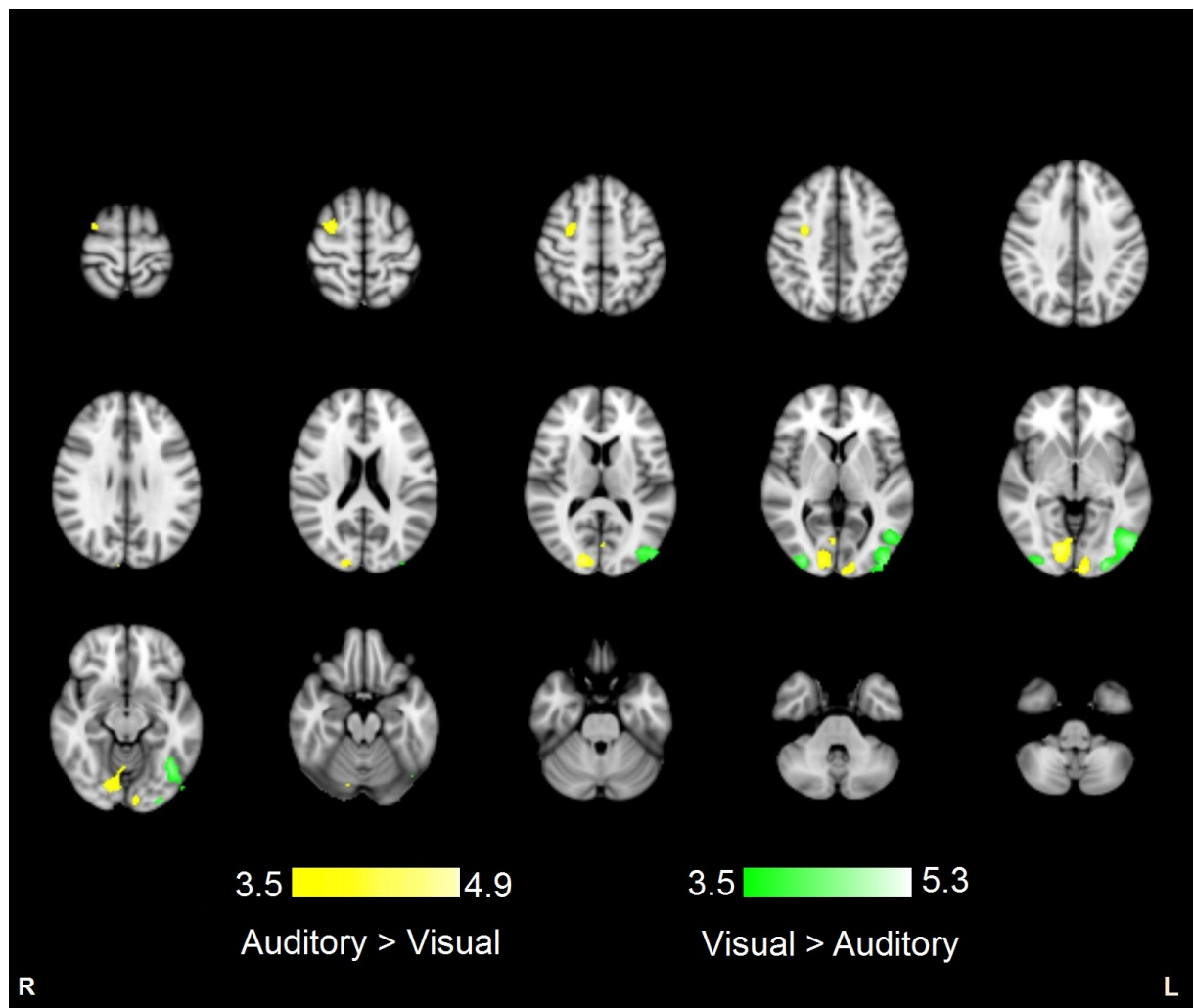


Figure 17) Statistically significant results of PASAT (Auditory) > PVSAT (Visual) comparison (yellow-white scale) and PVSAT (Visual) > PASAT (Auditory) comparison (green-white scale) overlaid onto MNI152 T1-weighted standard brain axial slices for anatomical reference. Range of Z values is shown.

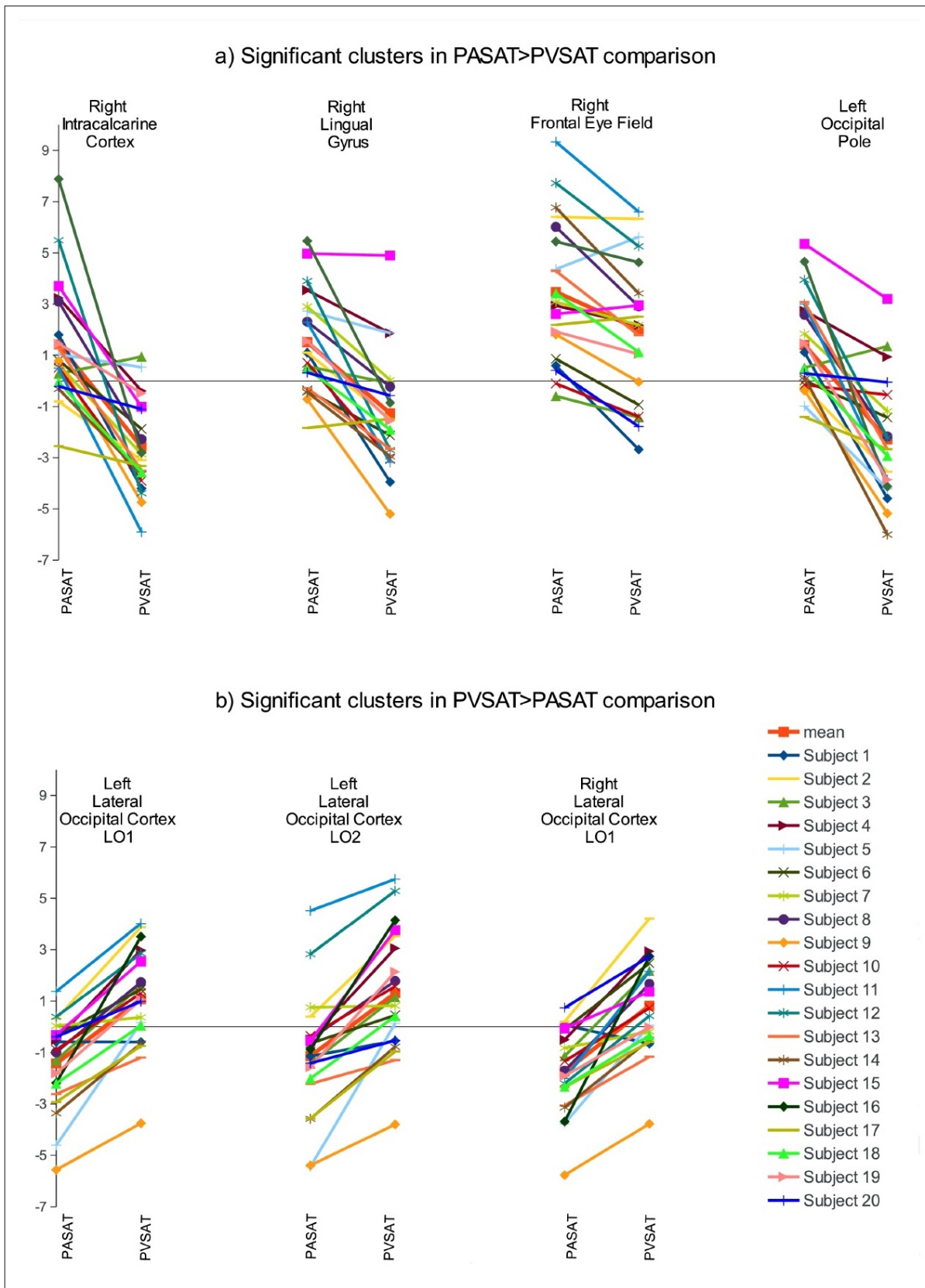


Figure 18) Within-subject analysis of regions manifesting significant differences in PASAT versus PVSAT comparison: Line graphs showing regional intra-subject comparisons of mean Z scores during PASAT versus control and PVSAT versus control for clusters listed in Table 3 and displayed in Figures 17 and 19. Note: For occipital and occipitotemporal regions, the significant difference results from a combination of activation in one task and deactivation in the other. In the right frontal eye field, both tasks result in positive BOLD response compared to the control condition but activation during PASAT is significantly stronger than during PVSAT.



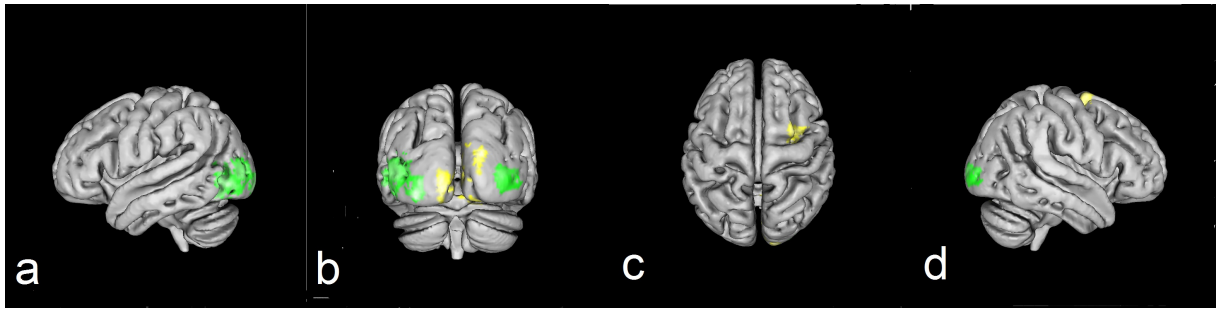


Figure 19) Statistically significant results of PASAT (Auditory) > PVSAT (Visual) comparison (yellow-white scale) and PVSAT (Visual) > PASAT (Auditory) comparison (green-white scale) projected onto rendered standard brain surface; a) right, b) posterior, c) superior, d) left view.

## 4.3 Discussion

The aim of our study was to examine the similarities and differences in brain activation during auditory and visual version of the paced serial addition test, a neuropsychological task designed to be complex and demanding in order to reveal cognitive deficit in patients with diffuse brain damage (Diamond et al., 1997; Gronwall, 1977; Sherman et al., 1997). The task engages selective attention, working memory, continual updating and arithmetic abilities. As such, the task combines features of the 1-back task and of arithmetic addition, so the following discussion includes studies using PASAT/PVSAT, the n-back task or other working memory tasks and calculation.

### 4. 3. 1. Performance

Accuracy did not differ between the visual and the auditory tasks, however, responses to target sums served mainly as an evidence that subjects performed the task according to instructions. Related studies often record and assess reaction times. As noted previously (Crottaz-Herbette et al., 2004; Schumacher et al., 1996; Suchan et al., 2006), these are shorter in the visual version of the n-back task, which is probably influenced by the need to wait till the near end of the auditory stimulus presentation before making a decision. We assume the same effect holds for PASAT/PVSAT, which limits the use of reaction times to judge task difficulty.

### 4. 3. 2. Modality-independent activation

In agreement with previously published studies using PASAT, PVSAT or the n-back task, we confirmed the existence of a modality-independent neural network including supplementary motor area, anterior cingulate cortex, lateral prefrontal cortex, parietal regions, subcortical structures and cerebellum (Smith and Jonides, 1998; Staffen et al., 2002; Audoin et al., 2003;

Lazeron et al., 2003; Crottaz-Herbette et al., 2004; Mainero et al., 2004; Au Duong et al., 2005; Forn et al., 2006; Rachbauer et al., 2006; Ibrahim and Tintěra, 2007; Bonzano et al., 2009; Rodriguez-Jimenez et al., 2009). It is common to interpret the results of working memory tasks in accordance with concept of working memory proposed by Baddeley, that divides working memory processes to central executive, visuospatial sketchpad and phonological loop (Baddeley, 1996) PASAT is assumed to put high demand on central executive control, which probably corresponds to activations in SMA, ACC and MFG bilaterally (Wager and Smith, 2003).

One of the activated areas that deserves attention lies in the transition zone between premotor and prefrontal cortex, including parts of Brodmann areas 6, 9 and 44. As reviewed by Derrfuss et al. (2005, 2004), this area, labeled inferior frontal junction, is consistently activated by a number of cognitive tasks (e.g. Stroop test, task-switching test and n-back task); the authors argue for its involvement in updating of task representations. The process of updating task representations is undoubtedly included in PASAT and according to Derrfuss et al. it also belongs to cognitive control processes. The challenge of considering IFJ involvement in cognitive tasks is its borderline localization touching upon three adjacent anatomical and functional regions (premotor, language and memory). Because of this position, task-related activation at this particular location is commonly attributed to one of the three regions and IFJ is not considered to be separate functional area (Derrfuss et al., 2005).

Neural correlates of the phonological loop are probably activations seen in the left-sided Broca's area, basal ganglia, SMA and cerebellum (Smith and Jonides, 1998)

Activations in the left IPS are often reported to be part of central executive control in verbal working memory, whereas the right IPS becomes involved in arithmetic processes (Dehaene et al., 2003; Wager and Smith, 2003; Arsalidou and Taylor, 2011). Almost symmetrical bilateral clusters in the IPS probably reflect the calculation component and the verbal nature of PASAT/PVSAT. The spatial resolution of our group data did not permit clear separation of the observed IPS activations into the known anatomically and functionally distinct subareas (Grefkes and Fink, 2005).

### **4. 3. 3. Modality-independent deactivation**

Our study revealed deactivations in areas known to belong to DMN (Greicius et al., 2003; Marcus E. Raichle and Snyder, 2007; Raichle et al., 2001) and also symmetrically in the medial temporal gyri and temporal poles. We observed deactivation in the right

temporoparietal junction in accordance with Todd et al., who used a demanding visual working memory task with concurrent verbal working memory-suppression task (Todd et al., 2005).

Compared to memory paradigms commonly used in patient populations, PASAT/PVSAT seem to be more demanding and deactivate large brain regions belonging to the DMN; a similar extent of deactivations is shown, e.g., in dual-processing tasks or the 3-back task (Todd et al., 2005; Prilipko et al., 2011).

#### **4. 3. 4. Differences between sensory modalities**

Besides the commonalities in the respective task-related networks, PASAT and PVSAT performance also resulted in significant differences. Whereas the contribution of low-level sensory and motor processing should be minimized using the respective control states, we expected some higher-level sensory areas emerging from the contrasts between the two tasks. Previous studies suggest the left IPS (Crottaz-Herbette et al., 2004) and right superior temporal gyrus (Suchan et al., 2006) as possible areas responsible for transformation of visual stimuli to phonological code as proposed by Baddeley. Neither of these areas was differentially active in our data.

In the following discussion of our results, we focus on patterns emerging from direct post-hoc linear contrasts of the two tasks (cf. Crottaz-Herbette et al., 2004), demonstrating areas of significantly stronger BOLD response in PASAT compared to PVSAT (Auditory>Visual) and vice versa (Visual>Auditory). More detailed explanation of the observed differences then resulted from within-subject analysis of the contributions of activations and deactivations to each regional effect.

##### **4. 3. 4. 1. Frontal areas**

Bilateral frontal eye fields belong to the network of frontal areas engaged in tasks involving attention and working memory (e.g., LaBar et al., 1999; Owen et al., 2005). The differential activation of the right frontal eye field (Auditory > Visual) resulted from different levels of activation (i.e., no deactivations). It is possible that the auditory task activated both FEF more symmetrically, whereas PVSAT resulted in more pronounced left > right lateralization and thus relatively weaker activation of the right-sided FEF. Similar finding was observed in PET study using 3-back task (Schumacher et al., 1996), but did not survive statistical threshold. Function of FEF is known to be modulated by attention (Mesulam, 1999), but we can also speculate, that lower activation in right FEF during PVSAT might reflect lower engagement of

neurons, since PVSAT reached insignificantly higher scores in our study and literature (Diamond et al., 1997) and thus could be assumed easier to perform.

#### **4. 3. 4. 2. Occipital areas**

Post-hoc contrast revealed significant differences in both the Auditory>Visual and Visual>Auditory comparisons in regions of striate and extrastriate cortex. Bilateral clusters located in primary visual cortex (V1 or BA 17) and the visual association cortex (V2, BA 18/19) could seem to be surprising in Auditory>Visual analysis. The BOLD response difference results from a combination of activation during the PASAT and deactivation during the PVSAT. The explanation of deactivation during the visual version could be the relatively lower demand on primary visual cortex during PVSAT (500 ms visual stimulus versus 2500 ms blank screen for each digit) and higher demand on higher visual centers (probably LOC, as discussed below) at the same time, for it is known there are feedback and inhibitory interactions between areas at different levels of visual processing (Callaway, 2004; Sillito and Jones, 2004).

Activation of areas V1 a V2 during the PASAT, which contributed to the statistical significance in Visual>Auditory contrast, may be explained by subjects' use of visual imagery to keep digits in working memory. This is in accordance with a previous PET study, that described increased activity in BA 17 during mental visual imagery compared to direct visual stimulation (Kosslyn et al., 1993). Likewise, previous papers using PASAT report activation in lingual and/or fusiform gyrus (Audoin et al., 2003, 2005; Forn et al., 2006), whereas papers using PVSAT do not list this regions as activated (Lazeron et al., 2003; Rachbauer et al., 2006; Bonzano et al., 2009).

Other significant differences in occipital regions were in Visual>Auditory contrast analysis in lateral occipital complex. This functional area is part of extrastriate visual system and was proved to play role in object recognition (Grill-Spector et al., 2001) mainly studied on recognition of everyday objects and geometrical shapes. LOC is usually is believed to be subdivided to ventrolateral and dorsomedial part (Grill-Spector et al., 2001; Larsson and Heeger, 2006; Wandell et al., 2007) labeled by Larsson and Heeger as LO1 (dorsal) and LO2 (ventral) (Larsson and Heeger, 2006). In our results, there were significant differences in in LO1 on the right and in both parts on the left, in addition left LO2 was directly connected with dorsal and medial part of left fusiform gyrus, which is very common pattern (Grill-Spector et al., 2001; Tootell et al., 2003) owing to so called fusiform face area (FFA) located in fusiform

gyrus and responsible for perception of faces, but also for perception of other objects (Kanwisher N., 2004). Difference in of LOC and FFA in Visual>Auditory contrast was caused by both activation during the PVSAT and deactivation during the PASAT. Activations during PVSAT are probably attributable to attention decrease in control state since subject were not mentally manipulating with provided digits and observed digit with less effort leading to task-induced activation. Attention-dependent activity in visual areas have already been described (Cate et al., 2012; Palomares et al., 2012).

Taken together, unlike other studies trying to find the imaging-based correlate to transformation of visual stimuli to phonological code, our results rather suggest attention fluctuations, feedback inhibitory interactions and possibly visual imagery to be the reasons of modality-dependent differences in frontal and occipital regions. Since activity in FEF and LOC are known to be attention dependent, we assume the attention modulations to be the leading effect of the differences. We can than than raise the question whether the control tasks are able to sufficiently keep the subject's attention and whether there are more suitable control conditions. There also a possibility, that subjects had to concentrate more during PASAT due to interference of auditory stimuli and scanner noise.

In conclusion, functional MR imaging during auditory and visual versions of the paced serial addition task revealed similarities in both task-positive (activation) networks, corresponding to the engaged cognitive processes and in task-negative (deactivation) networks, overlapping the default mode network. Deactivations were more pronounced than in the more popular and widespread 2-back task. Differential activation in the frontal lobe resulted from differences in the magnitude of activation, whereas occipital cortical differences could be attributed either to differences in activation or to a combined effect of task-related activation and deactivation. The observed differences arose most probably from attention fluctuations and feedback inhibitory interactions, which should be considered when preparing design and control conditions for fMRI studies.

## 5. Summary

Memory belongs to important higher-level cognitive processes, which rely on a distributed network of brain areas spanning multiple lobes in both hemispheres. It is important to localize cognitive processes that influence encoding, maintenance, manipulation and retrieval of information in the normal healthy brain, since this knowledge is necessary for describing the pathophysiology of broad spectrum of neurological, psychiatric or other kind of disorders that may lead to brain malfunction and cognitive deficits. Knowledge of normal brain memory functioning may also have impact on teaching and education approaches. Different levels of research include e.g. conceptual theories, non-human primate studies, behavioral experiments, electrophysiology and imaging. Neuroimaging studies used in the field of cognitive neuroscience rely mainly on PET and fMRI techniques. Functional MRI is safe, available and very useful imaging tool, if one keeps in mind its drawback and limitations that result from complex task performance and complicated post-processing.

In Experiment I, we succeeded in replication an item-recognition memory task on a cohort of healthy subjects and in obtaining activations in neural networks previously proven to be engaged in verbal working memory. We also obtained deactivations in regions known to belong to the default mode network. Thus we demonstrated that MRI-compatible visual stimulation system is suitable for subsequent fMRI studies using visual stimulation in working memory tasks applied to healthy volunteers or neurological or psychiatric patients.

In Experiment II, we confirmed the existence of an extensive sensory modality-independent neural system engaged in verbal working memory, attention and calculation during PASAT and PVSAT. Both tasks also jointly deactivated large areas of the default mode network. In the direct comparison between auditory and visual version of the task, we succeeded in revealing statistically significant differences in activation and deactivation, probably related to attention fluctuations and visual imagery. The issue of attention fluctuations between task and control conditions should therefore be seriously considered during verbal working memory studies planning. The differences in PASAT and PVSAT should be kept in mind when comparing the results of different published studies.

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