Modelling neural correlates of working memory: A coordinate-based meta-analysis

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ABSTRACT

Working memory subsumes the capability to memorize, retrieve and utilize information for a limited period of time which is essential to many human behaviours. Moreover, impairments of working memory functions may be found in nearly all neurological and psychiatric diseases.

To examine what brain regions are commonly and differently active during various working memory tasks, we performed a coordinate-based meta-analysis over 189 fMRI experiments on healthy subjects. The main effect yielded a widespread bilateral fronto-parietal network. Further meta-analyses revealed that several regions were sensitive to specific task components, e.g. Broca's region was selectively active during verbal tasks or ventral and dorsal premotor cortex were preferentially involved in memory for object identity and location, respectively. Moreover, the lateral prefrontal cortex showed a division in a rostral and a caudal part based on differential involvement in task set and load effects. Nevertheless, a consistent but more restricted "core" network emerged from conjunctions across analyses of specific task designs and contrasts.

This "core" network appears to comprise the quintessence of regions, which are necessary during working memory tasks. It may be argued that the core regions form a distributed executive network with potentially generalized functions for focussing on competing representations in the brain.

The present study demonstrates that meta-analyses are a powerful tool to integrate the data of functional imaging studies on a (broader) psychological construct, probing the consistency across various paradigms as well as the differential effects of different experimental implementations.

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Introduction

Most psychological and neurobiological models on the organization of human memory share the long-held dichotomy between short-term (STM) and long-term memory (LTM) (Atkinson and Shiffrin, 1968; Brown, 1958; Hebb, 1949; Peterson and Petersen, 1959). STM serves storing a limited but immediately accessible amount of information for a shorter time (Brown, 1958; Peterson and Petersen, 1959), whereas LTM may permanently store vast amounts of information, which, however, require specific recall processes to be accessed. It has been assumed that this distinction reflects differences in the way storage is implemented neuronally. LTM seems to be largely implemented by structural features, e.g., long-term potentiation of synaptic efficacy (Laroche, 1994), structural changes of synaptic boutons, and even the growth of new connections between neurons (Bailey, 1999; Barkai, 2005; Ramirez-Amaya et al., 2001). In contrast, STM seems to be more

dependent on functional electro-chemical phenomena, i.e., activation states (Frost et al., 1988; Schiffmann, 1989). It should be noted though, that at the ultra-structural level this distinction appears to become blurred as even temporarily circulating information may lead to short-term ultra-structural adaptation (Doubell and Stewart, 1993). Importantly, both systems (STM and LTM) interact with each other, as STM may be considered the (potential) input into LTM while in turn information from LTM may be retrieved into STM (Atkinson and Shiffrin, 1968).

In this context, it has to be mentioned that, particularly over the last years, the terms "STM" and "working memory (WM)" have been used virtually indistinguishably. This stems in part from the apparent lack of an unequivocally accepted distinction between both concepts (Cowan, 2008). It has been proposed that STM should refer to the pure storage of information, while WM includes (the possibility of) content manipulation and transfer between inputs (e.g., visual or tactile sensory information) and outputs (e.g., manual actions or speech) (Engle et al., 1999). We consider this tentative distinction as a gradual difference in the degree of manipulation (i.e. the number of different cognitive operations on the stored information) required by the different tasks that tap mnemonic functions across a shorter period of time.

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In this paper, therefore, the apparently broader term working memory (WM) will be used throughout.

The organization of human WM has long been the topic of psychological models (Atkinson and Shiffrin, 1968; Hebb, 1949), with maybe the most influential having been proposed by Baddeley and Hitch (1974). These authors hypothesized the existence of a central executive controlling the priority of incoming information and their dissemination to two subsystems: the phonological loop, responsible for storing verbal material, and the visuospatial sketchpad, responsible for integrating visual input, spatial information (e.g., locations) and object properties (i.e. colour and size) (Baddeley, 2003). Later the concept of an "episodic buffer" was added, forming a limited-capacity system for the ultrashort-term, intermediate storage of incoming sensory information (Baddeley, 2000, 2003). While other models have expanded and modified this view, several key features have remained influential to the present date (Brown et al., 1996b; Snowling et al., 1991). In particular, the distinction between spatial and verbal components with specific buffer capacities and the idea of an amodal central executive (Stuss and Knight, 2002) remains dominant. The central executive is not only considered to control the flow of information to the specific subsystems, but is also thought to play a pivotal role in integrating stored material and executive functions needed for comparison, manipulation or, more generally, the further use of the stored material.

One of the motivations underlying the long-standing efforts to understand the organization of the human WM system is the fact that WM impairments have been described in a large variety of neurological and psychiatric diseases. These deficits often have a considerable impact on the quality of life and the socio-economic status of patients. For example, virtually all forms of dementia show WM deficits (Huntley and Howard, 2010; Iachini et al., 2009; Maestu et al., 2011) as do patients with movement disorders like Parkinson's (Beato et al., 2008; Gilbert et al., 2005; Possin et al., 2008) and Huntington's disease (Huber and Paulson, 1987; Lemiere et al., 2004). Interestingly, some WM deficits may be irreversible, (e.g., as part of the debilitating negative symptoms seen in patients with chronic schizophrenia) (Berberian et al., 2009; Driesen et al., 2008; Fuller et al., 2009; Horan et al., 2008; Yi et al., 2009), whereas others are only evident in the acute phase of a disease (e.g. in depression; cf. (Christopher and MacDonald, 2005; Rose and Ebmeier, 2006). Understanding the neural organization of human WM is therefore not only important from a psychological perspective but may also help to unravel the differential pathophysiology of its various impairments.

To date there have been numerous functional neuroimaging studies addressing neural activation patterns associated with WM functions. In spite of this large body of literature, however, there is little agreement on various issues pertaining to the organization of human WM. These include:

- Are effects related to WM task performance per se and effects of increasing WM load represented in the same areas?
- How do representations of verbal and non-verbal material differ from each other, i.e., which brain regions may implement phonological and visuospatial buffers?
- Do different to-be-retained object features (e.g., location vs. identify) or task demands entail differential brain responses?
- Which regions are consistently involved in WM independently of experimental peculiarities?

One of the main reasons for this discrepancy between the large amount of available data and the relatively little knowledge gained from it may be the heterogeneity of tasks used in WM experiments. In particular, over the years, researchers have employed multiple paradigms, of which four have been used most widely: the n-back task, the Sternberg task as well as delayed matching to sample (DMTS) and delayed simple matching tasks (comparison 12). N-back tasks include a consecutive presentation of stimuli, each requiring a decision whether the current one is the same as the previous (1-back) or the second to last (2-back). While in Sternberg tasks a set of stimuli is presented followed by a single probe stimulus requiring the decision whether the probe was part of the set, in DMTS tasks a single stimulus is presented first and has to be recognized afterwards among a set of multiple stimuli. Finally, delayed simple matching tasks entail the presentation of a single stimulus that has to be compared to a second, subsequently presented one. That is, there are already at least four major experimental approaches to examine the neural correlates of WM. This diversity was further enhanced by less common paradigms as well as the fact that researchers employed a large variety of stimuli (e.g. verbal material, natural objects or abstract symbols) and various additional experimental manipulations (such as varying load, retention interval or distraction). Further considering that the results of functional imaging studies strongly depend on the chosen contrast, given the relative nature of neuroimaging signals, it may not surprise that results are diverse and consensus is sparse.

From this short overview, it may not surprise, that there is a very large but also extremely heterogeneous and at times inconsistent body of work related to the neural correlates of working memory. In the present study, we now sought to integrate the current literature on the neural correlates of human WM as identified by functional neuroimaging using quantitative coordinate-based meta-analysis over almost 200 individual experiments. Such synthesis of the available neuroimaging data should help to reach a consensus among the extensive literature and to trace back inconsistencies to variations in the experimental approaches. Using this approach towards an unbiased summary of the literature, we thus strive to identify consistent findings, answer the main questions outlined earlier and provide an overview on the neural organization of human WM.

Material and methods

Criteria selection of data used for meta-analysis

Neuroimaging experiments using functional magnetic resonance imaging (fMRI) included in this meta-analysis were obtained from the BrainMap database (www.brainmap.org; (Fox and Lancaster, 2002; Laird et al., 2005) and a PubMed literature search (www.pubmed.org, search-strings: "fMRI," ["working memory" OR "short term memory"], "healthy subjects"). Further studies were identified by review articles and reference tracing of retrieved studies. Only studies that reported results of whole-brain group analyses as coordinates in a standard reference space (Talairach/Tournoux or MNI) were included, while single-subject reports and results of region of interest analyses were excluded. Likewise, experiments investigating between- or within-group effects pertaining to disease, handedness, gender or pharmacological manipulation were excluded.

Finally, positron emission tomography (PET) experiments were likewise excluded due to potential systematic differences between fMRI and PET with respect to resolution, statistical power, spatial normalisation or sample size. Based on these criteria, 113 papers were identified as eligible for inclusion into the meta-analysis. Together, these studies comprised data from 1653 subjects and reported 2662 activation foci observed in 189 experiments (Table 1, cf. Supp. Table1). Differences in coordinate spaces (MNI vs. Talairach space) between experiments were accounted for by transforming coordinates reported in Talairach space into MNI coordinates using a linear transformation (Lancaster et al., 2007).

The reported tasks were largely subsumed into the four main categories noted in the Introduction: (i) n-back; (ii) Sternberg; (iii) DMTS and (iv) delayed simple matching. In addition, several studies used other, less common tasks. In each category, tasks could differ from each other by the nature of the stimuli (e.g., letters, numbers, words, abstract shapes, figurative pictures) or the stimulus feature remembered (e.g., location or identity). Finally, we drew a distinction between contrasts aiming at "task" and "load" effects,

Table 1
Overview of all studies included in this coordinate based meta-analysis of working memory.

Paper	Subjects	Contrast	Task	Modality	Stimuli Type	Operation	Phase
Allen et al. 2006	10	Task > control	n-back	Visual	Letter	Identity verification	
Altamura et al. 2007	18	Task > control	Sternberg	Visual	Letter	Identity verification	
Altamura et al. 2007	18	Activation modulated by load	Sternberg	Visual	Letter	Identity verification	
Audoin et al. 2005	18	Task > control	Calculation	Auditory	Numbers	Manipulation	
Axmacher et al. 2007	23	Task > baseline	Sternberg	Visual	Faces	Identity verification	Encoding
Axmacher et al. 2007	23	Task > baseline	Sternberg	Visual	Faces	Identity verification	Maintenance
Axmacher et al. 2007	23	Activation modulated by load	Sternberg	Visual	Faces	Identity verification	Encoding
Axmacher et al. 2007	23	Activation modulated by load	Sternberg	Visual	Faces	Identity verification	Maintenance
Axmacher et al. 2009	30	Difficult > easy	Sternberg	Visual	Figures	Identity verification	
Bedwell et al. 2005	14	Task > control	Sternberg	Visual	Letter	Identity verification	Encoding
Bedwell et al. 2005	14	Task > control	Sternberg	Visual	Letter	Identity verification	Maintenance
Bedwell et al. 2005	14	Task > control	Sternberg	Visual	Letter	Identity verification	Recall
Benevanti et al. 2007	12	Task > baseline	n-back	Visual	Shapes	Identity verification	
Binder et al. 2006	12	Task > control	n-back	Visual	Letter	Identity verification	
Binder et al. 2006	12	Task > control	n-back	Visual	Shapes	Identity verification	
Bunge et al. 2001	16	Difficult > easy	Sternberg	Visual	Letter	Identity verification	
Cader et al. 2006	16	Task > control	n-back	Visual	Letter	Identity verification	
Cader et al. 2006	16	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Cairo et al. 2004	18	Task > baseline	Sternberg	Visual	Letter	Identity verification	Encoding
Cairo et al. 2004	18	Activation modulated by load	Sternberg	Visual	Letter	Identity verification	Encoding
Cairo et al. 2004	18	Activation modulated by load	Sternberg	Visual	Letter	Identity verification	Maintenance
Cairo et al. 2004	18	Task > baseline	Sternberg	Visual	Letter	Identity verification	Recall
Cairo et al. 2004	18	Activation modulated by load	Sternberg	Visual	Letter	Identity verification	Recall
Caldwell et al. 2005	10	Task > control	Sternberg	Visual	Letter	Identity verification	
Callicott et al. 1999	9	Activation modulated by load	n-back	Visual	Numbers	Identity verification	
Camchong et al. 2006	14	Task > baseline	Reproduction by saccade	Visual	Shapes	Location verification	Recall
Caseras et al. 2006	12	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Cerasa et al. 2008	30	Task > control	n-back	Visual	Shapes	Identity verification	
Choo et al. 2005	12	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Christodouolou et al. 2001	7	Task > control	Calculation	Auditory	Numbers	Manipulation	
Ciesielski et al. 2006	10	Task > control	n-back	Visual	Figures	Identity verification	
Cohen et al. 1997	10	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Cross et al. 2007	27	Task > baseline	Manual reproduction	Visual	Numbers		Maintenance
Cross et al. 2007	27	Task > baseline	Manual reproduction	Visual	Numbers		Recall
Deckersbach et al. 2008	17	Task > baseline	n-back	Visual	Letter	Identity verification	
Desmond et al. 2003	13	Difficult > easy	Sternberg	Visual	Letter	Identity verification	
Doehnel et al. 2008	16	Task > baseline	n-back	Visual	Figures	Identity verification	
Drapier et al. 2008	20	Task > control	n-back	Visual	Letter	Identity verification	
Druzgal et al. 2001	9	Activation modulated by load	n-back	Visual	Faces	Identity verification	
Elliott et al. 1999	10	Task > control	DMTS	Visual	Shapes	Identity verification	
Elzinga et al. 2007	14	Task > control	n-back	Visual	Letter	Identity verification	
Engstrom et al. 2009	12	Activation modulated by load	Sternberg	Visual	Words	Identity verification	
Forn et al. 2006	10	Task > control	Calculation	Auditory	Numbers	Manipulation	
Forn et al. 2007	10	Task > control	n-back	Auditory	Letter	Identity verification	
Frangou et al. 2008	7	Task > control	n-back	Visual	Letter	Identity verification	
Frangou et al. 2008	7	activation modulated by load	n-back	Visual	Letter	Identity verification	
Garavan et al. 2000	12	Task > control	Sternberg	Visual	Shapes	Location verification	
Garavan et al. 2000 (2)	11	Task > baseline	Calculation	Visual	Shapes	Manipulation	
Garraux et al. 2005	15	Task > baseline	Manual reproduction	Visual	Letter	Order verification	Recall
Goldstein et al. 2005	7 (2 different)	Task > control	n-back	Auditory	Letter	Manipulation	
Grosbras et al. 2001	10	Task > baseline	Reproduction by saccade	Visual	Shapes	Location verification	Recall
Gruber et al. 2010	18	Task > control	Sternberg	Visual	Letter	Identity verification	Maintenance
Harvey et al. 2005	10	Task > control	n-back	Visual	Letter	Identity verification	
Honey et al. 2000	20	Task > control	n-back	Visual	Letter	Identity verification	
Honey et al. 2003	27	Task > control	n-back	Visual	Letter	Identity verification	
Johnson et al. 2006	18	Activation modulated by load	Sternberg	Visual	Letter	Identity verification	Encoding
Johnson et al. 2006	18	Activation modulated by load	Sternberg	Visual	Letter	Identity verification	Recall
Johnson et al. 2006	18	Difficult > easy	Sternberg	Visual	Letter	Identity verification	Encoding
Johnson et al. 2006	18	Difficult > easy	Sternberg	Visual	Letter	Identity verification	Recall
Kaas et al. 2007	7	Task > baseline	Manual reproduction	Tactile			Encoding
Kaas et al. 2007	7	Task > baseline	Manual reproduction	Tactile			Recall
Kim et al. 2006	12	Task > baseline	n-back	Visual	Letter	Identity verification	
Koelsch et al. 2009	12	Task > control (2-different)	Comparison12	Auditory	Tones	Identity verification	
Koppelstaetter et al. 2008	15	Task > control	n-back	Visual	Letter	Identity verification	
Koshino et al. 2008	11	Task > baseline	n-back	Visual	Faces	Identity verification	
Kumari et al. 2003	11	task > baseline	n-back	Visual	Numbers	Identity/location verification	
Kumari et al. 2006	13	task > control	n-back (2-different)	Visual	Shapes	Identity verification	
Kumari et al. 2006	13	task > baseline	n-back	Visual	Shapes	Identity verification	
Lagopoulos et al. 2007	10	task > baseline	Sternberg	Visual	Words	Identity verification	Encoding
Lagopoulos et al. 2007	10	task > baseline	Sternberg	Visual	Words	Identity verification	Maintenance
Lagopoulos et al. 2007	10	task > baseline		visual	words	identity verification	recall
Landau et al. 2004	10	task > baseline	Sternberg	Visual	Faces	Identity verification	Encoding
Landau et al. 2004	10	task > baseline	Sternberg	Visual	Faces	Identity verification	Recall
Landau et al. 2009	23	activation modulated by load	Sternberg	Visual	Letter	Identity verification	Encoding
Landau et al. 2009	23	activation modulated by load	Sternberg	Visual	Letter	Identity verification	Maintenance

Table 1 (*continued*)

Paper	Subjects	Contrast	Task	Modality	Stimuli Type	Operation	Phase
Lim et al. 2008	12	task > baseline	n-back	Visual	Letter	Identity verification	
Linden et al., 2003	12	task > baseline	Sternberg	Visual	Shapes	Identity verification	Encoding
Linden et al., 2003	12	Task > baseline	Sternberg	Visual	Shapes	Identity verification	Maintenance
LoPresti et al. 2008	19	Task > control	Comparison12	Visual	Faces	Identity verification	Maintenance
Loughead et al. 2009	33	Activation modulated by load	n-back	Visual	Shapes	Identity verification	
Luck et al. 2009	17	Task > baseline	Sternberg	Visual	Letter	Location/identity verification	Encoding
Luck et al. 2009	17	Task > baseline	Sternberg	Visual	Letter	Location/identity verification	Maintenance
Luck et al. 2009	17	Task > baseline	Sternberg	Visual	Letter	Location/identity verification	Recall
Mainero et al. 2004	22	Task > baseline	Calculation	Auditory	Numbers	Manipulation	
Manoach et al. 2000	9	Task > control	Sternberg	Visual	Numbers	Identity verification	
Manoach et al. 2003	12	Task > baseline	Sternberg	Visual	Numbers	Identity verification	Encoding
Manoach et al. 2003	12	Task > baseline	Sternberg	Visual	Numbers	Identity verification	Recall
Marquand et al. 2008	20	Task > control	n-back	Visual	Letter	Identity verification	
Maruishi et al. 2007	12	Task > control	Calculation	Visual	Numbers	Manipulation	
Marvel et al. 2010	16	Difficult > easy	Sternberg	Visual	Letter	Manipulation	Encoding
Marvel et al. 2010	16	Difficult > easy	Sternberg	Visual	Letter	Manipulation	Maintenance
Marvel et al. 2010	16	Difficult > easy	Sternberg	Visual	Letter	Manipulation	Recall
Matsuo et al. 2007	15	Task > control	n-back	Visual	Numbers	Location verification	
Mayer et al. 2007	18	Difficult > easy	Sternberg	Visual	Shapes	Identity verification	Encoding
McAllister et al. 1999	11	Task > control	n-back (2-different)	Auditory	Letter	Identity verification	
McAllister et al. 1999	11	Difficult > easy	n-back	Auditory	Letter	Identity verification	
McGeown et al. 2008	9	Task > control	n-back	Visual	Words	Identity verification	
McNab et al. 2008	11	Task > control	Sternberg	Visual	Letter	Identity/order verification	
McNab et al. 2008	11	Task > control	Sternberg	Visual	Shapes	Identity/order verification	
Meisenzahl et al. 2006	12	Task > baseline	n-back (2-different)	Visual	Letter	Identity verification	
Monks et al. 2004	12	Task > control	n-back	Visual	Letter	Identity verification	
Monks et al. 2004	12	Activation modulated by load	Sternberg	Visual	Numbers	Identity verification	
Mu et al. 2005	10	Task > control	Sternberg	Visual	Letter	Identity verification	
Nebel et al. 2005	19	Task > baseline	n-back	Visual	Letter/ shapes	Identity verification	
Nebel et al. 2005	17	Task > baseline	n-back	Visual	Letter/ shapes	Identity verification	
Nyberg et al. 2009	33	Activation modulated by load	n-back	Visual	Numbers	Identity verification	
Oh et al. 2009	12	Task > baseline	Sternberg	Visual	Shapes	Identity verification	Encoding
Oh et al. 2009	12	Task > baseline	Sternberg	Visual	Shapes	Identity verification	Maintenance
Otsuka et al. 2006	10	Task > control	Sternberg	Visual	Words	Identity verification	Encoding
Otsuka et al. 2006	10	Task > control	Sternberg	Visual	Words	Identity verification	recall
Öztekin et al. 2009	15	Task > baseline	Sternberg	Visual	Letter		
Pessoa et al. 2002	9	Task > control	Comparison12	Visual	Shapes	Identity verification	
Picchioni et al. 2007	14	Task > baseline	DMTS	Visual	Figures	Matching	Recall
Piekema et al. 2010	19	Task > baseline	Sternberg	Visual	Figures	Identity verification	Maintenance
Pochon et al. 2001	8	Task > control	Comparison12	Visual	Shapes	Location verification	Maintenance
Pochon et al. 2001	8	Task > control	Manual reproduction	Visual	Shapes	Order verification	Maintenance
Postle et al. 2007	12	Task > baseline	Comparison12	Visual	Shapes	Location verification	Maintenance
Postle et al. 2007	12	Task > baseline	Comparison12	Visual	Shapes	Identity verification	Maintenance
Qin et al. 2009	27	Task > control	n-back	Visual	Letter	Identity verification	
Quintana et al. 2003	8	Task > baseline	DMTS	Visual	Shapes	Identity verification	
Quintana et al. 2003	8	Task > baseline	DMTS	Visual	Faces	Identity verification	
Ragland et al. 2002	11	Task > control (2-different)	n-back	Visual	Letter	Identity verification	
Ragland et al. 2002	11	Difficult > easy (2-different)	n-back	Visual	Shapes	Identity verification	
Ragland et al. 2004	15	Task > baseline	Modulated Sternberg	Visual	Words	Identity verification	Encoding
Ragland et al. 2004	15	Task > baseline	Modulated Sternberg	Visual	Words	Identity verification	Recall
Rama et al. 2001	8	Task > control	n-back (2-different)	Auditory	Words	Identity verification	
Relander et al. 2009	10	Task > control	Comparison12	Auditory	Voices	Identity verification	Encoding
Relander et al. 2009	10	Task > control	Comparison12	Auditory	Words	Identity verification	Encoding
Relander et al. 2009	10	Task > control	Comparison12	Auditory	Voices	Identity verification	Maintenance
Relander et al. 2009	10	Task > control	Comparison12	Auditory	Words	Identity verification	Maintenance
Relander et al. 2009	10	Task > control	Comparison12	Auditory	Voices	Identity verification	Recall
Relander et al. 2009	10	Task > control	Comparison12	Auditory	Words	Identity verification	Recall
Remy et al. 2005	11	Task > control	Comparison12	Visual	Words	Identity verification	Encoding
Remy et al. 2005	11	Task > control	Comparison12	Visual	Words	Identity verification	Recall
Reynolds et al. 2009	18	Activation modulated by load	n-back	Visual	Words	Identity verification	
Ricciardi et al. 2006	6	Task > baseline	n-back	Tactile	Shapes	Identity verification	
Ricciardi et al. 2006	6	Task > baseline	n-back	Visual	Shapes	Identity verification	
Sanchez-Carrion et al. 2008	14	Task > control	n-back (2-different)	Visual	Numbers	Identity verification	
Scheuerecker et al., 2008	23	Task > control	n-back (2-different)	Visual	Letter	Identity verification	
Schloesser et al. 2008	41	Difficult > easy	Reordering	Visual	Letter		Maintenance
Schmidt et al. 2009	25	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Schmidt et al. 2009	21	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Schulze et al. 2009	10	Task > control	Comparison12	Auditory	Tones	Identity verification	
Shen et al. 1999	9	Task > baseline	n-back	Visual	Shapes	Identity verification	
Simons et al. 2006	16	Task > control	DMTS	Visual	Words		Recall
Simons et al. 2006	16	Task > control	DMTS	Visual	Words	Location verification	Recall

Table 1 (continued)

Paper	Subjects	Contrast	Task	Modality	Stimuli Type	Operation	Phase
Stern et al. 2000	5	Task > control	Sternberg	Visual	Shapes	Identity verification	
Stern et al. 2000	5	Task > control	Sternberg	Visual	Shapes	Order verification	Recall
Stoeckel et al. 2003	7	Task > baseline	Comparison12	Tactile	Shapes	Identity verification	Encoding
Stoeckel et al. 2003	7	Task > baseline	Comparison12	Tactile	Shapes	Identity verification	Maintenance
Thomas et al. 2005	16	Task > control	n-back	Visual	Letter	Identity verification	
Thomason et al. 2009	16	Activation modulated by load	Sternberg	Visual	Letter	Location verification	
Thomason et al. 2009	14	Activation modulated by load	Sternberg	Visual	Letter	Location verification	
Tregallas et al. 2006	20	Task > control	Comparison12	Auditory	Sounds	Identity verification	
van den Heuvel et al. 2005	22	Task > baseline	Tower of London	Visual	Shapes	Manipulation	Recall
van den Heuvel et al. 2005	22	Activation modulated by load	Tower of London	Visual	Shapes	Manipulation	Recall
Veltman et al. 2003	22	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Veltman et al. 2003	22	Activation modulated by load	Sternberg	Visual	Letter	identity verification	
Veltman et al. 2003	22	Task > baseline	Sternberg	Visual	Letter	Identity verification	Encoding
Veltman et al. 2003	22	Task > baseline	Sternberg	Visual	Letter	Identity verification	Recall
Veltman et al. 2005	11	Activation modulated by load	n-back	Visual	Letter	Identity verification	
Volle et al. 2005	11	Task > control	Manual reproduction	Visual	Figures	Order verification	Maintenance
Volle et al. 2005	11	Difficult > easy	Manual reproduction	Visual	Figures	Order verification	Maintenance
Walter et al. 2007	17	Difficult > easy	Sternberg	Visual	Letter	Identity verification	
Wildgruber et al. 1999	18	Task > control	Reverse recitation		Words	Manipulation	Recall
Wishart et al. 2006	22	Task > control	n-back	Auditory	Letter	Identity verification	
Yi et al., 2009	18	Task > control	Sternberg	Visual	Numbers	Identity verification	
Yoo et al. 2004	14	Task > baseline	n-back	Auditory	Letter	Identity verification	
Yoo et al. 2004	14	Task > baseline	n-back	Visual	Letter	Identity verification	
Yoo et al. 2005	10	Task > control	n-back	Visual	Faces	Identity verification	
Ziemus et al. 2007	9	Task > control	n-back	Visual	Letter	Identity verification	

Comparison 12 = delayed simple matching tasks.

respectively. The former category contained experiments that contrasted a WM task with a resting baseline or a sensory-motor control condition that did not include a working memory component (2-back vs. 0-back [the latter being a simple-reaction task]). Load effects, in contrast, contained experiments contrasting a high-load (more difficult) WM condition against a low-load (less difficult) WM condition (e.g., 3-back vs. 2-back tasks) as well as experiments testing for a parametric modulation of brain activity with increasing WM load (e.g., activity increases depending on the number of memorized items in a Sternberg task). That is, whereas task effects should reflect activity related to the performance of working memory paradigms per se, load effects should reflect neural substrates of increasing memory demands.

Convergence of activation coordinates reported in the literature was analysed for the main effect of all WM-related activity as well as for the different categories outlined earlier. In these analyses, we particularly focussed on the differences and commonalities between activations associated with the various aspects and forms of WM paradigms.

It may be possible, that data from the same subjects obtained in the same imaging session may enter multiple publications. This would be the case in reanalysis under a different question, focus or analysis strategy. Importantly it is virtually impossible to identify such cases in particular if not all of the subjects have entered each analysis and hence sample sizes differ between publications or if the order of the authors change (a previous co-author may now become the primary author). Secondly, if one study reported more than one experiment, the different experiments were included in this meta-analysis. As discussed in detail in Turkeltaub et al., 2011 there is an albeit moderate possibility that this may bias findings of convergence across experiments. It must be appreciated though that the average number of experiments per paper is ~1.65 (189 contrasts from 113 papers) and multiple papers contributed more than one contrast, making domination by a single population very unlikely. Moreover due to the nature of contrasts assessed in working memory experiments the different contrasts entered from a single paper usually represented task vs. load effects, differences between stimulus material or tasks. It follows that different experiments from the same paper entered our analysis in different subgroups in virtually all cases. The only exception to this is the analysis of all working memory experiments (Fig. 1). Here multiple experiments per paper were included. But, in particular this analysis however should be quite robust

against a potential bias given the very high number of included experiments. This was confirmed by the virtually identical results of a supplementary analysis in which the modifications to the ALE algorithm for analysis across papers rather than contrasts (Turkeltaub et al., 2011) was implemented.

Activation likelihood estimation algorithm

All meta-analyses were performed using the revised activation likelihood estimation (ALE) algorithm for coordinate-based meta-analysis of neuroimaging results (Eickhoff et al., 2009 2011; Laird et al., 2009a, 2009b; Turkeltaub et al., 2002) implemented as in-house MATLAB tools. This algorithm aims to identify areas showing a convergence of reported coordinates across experiments, which is higher than expected under a random spatial association. The key idea behind ALE is to treat the reported foci not as single points, but rather as centres for 3D Gaussian probability distributions capturing the spatial uncertainty associated with each focus. The width of these uncertainty functions was determined based on empirical data on the between-subject and between-template variance, which represent the main components of this uncertainty. Importantly, the applied algorithm weights the between-subject variance by the number of examined subjects per study, accommodating the notion that larger sample sizes should provide more reliable approximations of the 'true' activation effect and should therefore be modelled by 'smaller' Gaussian distributions (Eickhoff et al., 2009).

The probabilities of all foci reported in a given experiment were then combined for each voxel, resulting in a modelled activation (MA) map (Turkeltaub et al., 2011). Taking the union across these MA maps yielded voxel-wise ALE scores describing the convergence of results at each particular location of the brain. To distinguish 'true' convergence between studies from random convergence (i.e., noise), ALE scores were compared to an empirical null-distribution reflecting a random spatial association between experiments. Hereby, a random-effects inference is invoked, focussing on inference on the above-chance convergence between studies, not clustering of foci within a particular study. Computationally, deriving this null-hypothesis involved sampling a voxel at random from each of the MA maps and taking the union of these values in the same manner as done for the (spatially contingent) voxels in the true analysis. The p-value of a "true" ALE was then given by the proportion of equal or higher values obtained under the null-
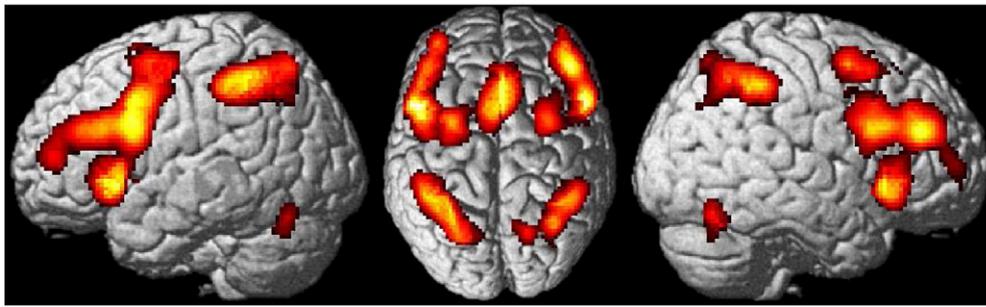
Fig. 1. *Main effect* across all 189 working memory experiments revealing consistent bilateral activation of a fronto-parietal network.

distribution. The resulting non-parametric p-values for each meta-analysis were then thresholded at a cluster-level corrected threshold of p<0.05 (cluster-forming threshold at voxel-level p<0.001) and transformed into Z-scores for display. The extent-threshold necessary to control the cluster-level family-wise error (FWE) rate was derived from a Monte-Carlo simulation of the excursion-set above cluster-forming threshold based on the analysis of randomly distributed foci under otherwise identical settings. Simulating 10,000 of such random analyses allowed deriving a null-distribution of the above-threshold cluster sizes (more precisely, the maximum size of any cluster in the excursion set within each iteration). This distribution was then used to identify the cluster-size, which was only exceeded in 5% of all random realizations, as the critical threshold for cluster-level FWE correction. Importantly, this critical size threshold is strongly dependent on the number of experiments in the particular meta-analysis (as well as their foci characteristics). It therefore was calculated specifically for each of the presented meta-analyses.

All resulting areas were anatomically labelled by reference to probabilistic cytoarchitectonic maps of the human brain using the SPM Anatomy Toolbox (Eickhoff et al., 2005, 2007). Using a Maximum Probability Map (MPM), activations were assigned to the most probable histological area at their respective locations. Details on these cytoarchitectonic regions may be found in the following publications reporting on Broca's region (Amunts et al., 1999) inferior parietal cortex (Caspers et al., 2008), premotor cortex (Geyer et al., 1996), superior parietal cortex and intraparietal sulcus (Caspers et al., 2008; Choi et al., 2006; Scheperjans et al., 2008). Regions, which are not yet cytoarchitectonically mapped based on observer-independent histological examination, were labelled macroanatomically by the probabilistic Harvard-Oxford cortical structure atlas, rather than providing tentative histological labels based on volume-approximations of the (schematic) Brodmann atlas.

Conjunctions and contrasts

Conjunction analyses aimed at identifying those voxels where a significant effect was present in two separate analyses. To compute the conjunction between two ALE analyses, we used the conservative minimum statistic (Nichols et al., 2005), which is equivalent to identifying the intersection between the two cluster-level FWE corrected results (Caspers et al., 2010). That is, only regions significant on a corrected level in both individual analyses were considered. In order to exclude smaller regions of presumably incidental overlap between the thresholded ALE maps of the individual analyses, an additional extent-threshold of 15 voxels was applied.

Differences between conditions were tested by first performing separate ALE analyses for each condition and computing the voxel-wise difference between the ensuing ALE maps (cf. Eickhoff et al., 2011b). All experiments contributing to either analysis were then pooled and randomly divided into two groups of the same size as the two original sets of experiments reflecting the contrasted ALE analyses. ALE-scores for these two randomly assembled groups were calculated and the

difference between these ALE-scores was recorded for each voxel in the brain. Repeating this process 10,000 times then yielded an expected distribution of ALE-score differences under the assumption of exchangeability. The "true" difference in ALE scores was then tested against this null-distribution yielding a posterior probability that the true difference was not due to random noise in an exchangeable set of labels, based on the proportion of lower differences in the random exchange. The resulting probability values were thresholded at P>0.95 (95% chance for true difference) and inclusively masked by the respective main effects, i.e., the significant effects of the ALE analysis for the particular condition. In addition, an extent-threshold of k>50 voxels was applied. It is further important to note, that (evidently apart from the comparison between task and load effects) all comparisons/conjunctions were only based on categorical contrasts against a non working memory control condition. This was to prevent an unequal proportion of load- vs. task-related contrasts in the two pools introducing a major confound in these analyses. The potential for such bias was confirmed by significantly different proportions of task vs. load effects in various planned sub-analyses as revealed by chi-square tests. The number of load-related contrasts for the different task subsets (e.g., experiments on verbal or non-verbal material), was however, usually too small for separate analyses. Consequently neither pooling task and load effects nor a separate analysis of differences between, e.g., verbal and non-verbal material, for task and load effects was feasible given the currently available data.

We moreover note that conjunction analyses demonstrate regions where two different effects (e.g. verbal and non-verbal) *both* show significant activation while difference analysis as outlined earlier indicate regions where one of the two compared sets of experiments showed stronger convergence. That is, contrasting verbal with non-verbal tasks reveals locations where there is a significantly stronger convergence among the former relative to the latter. This, however, does not preclude a significant convergence of the latter. That is, even in regions where there is significantly stronger convergence of activation reported in verbal tasks, the convergence among activation sites reported for non-verbal tasks may be likewise significantly higher than chance. In this case, both of the analyses to be contrasted would be individually significant. Consequently, both the contrast as well as the conjunction would be significant at the very same location. Therefore, contrast and conjunction effects are not mutually exclusive but rather may overlap if two sets of experiments (e.g., verbal- and non-verbal tasks) converge significantly but one of them even more so than the other.

Results

Main effect: working memory network

Brain regions showing consistent activation across all 189 WM experiments were observed symmetrically across both hemispheres in frontal areas BA44/45, the anterior insula, posterior superior frontal gyrus (dorsal premotor cortex — dPMC) and inferior frontal gyrus (ventral premotor cortex — vPMC; extending into area 44). Bilateral activation was moreover found in the medial (pre-) supplementary

motor area (pre-)SMA), as well as the intraparietal sulcus (IPS areas hIP1-3, but mainly hIP3), the superior parietal lobule (areas 7A, 7PC) and anterior parietal area 2. Furthermore, the lateral prefrontal cortex (LPFC) showed bilateral activation in caudal and rostral parts. Bilateral activation was additionally found in ventral visual cortex as well as in lobule VI of the cerebellum (Fig. 1). Subcortical activation was found in bilateral regions of the thalamus that connect to prefrontal and temporal cortices (Behrens et al., 2003) and mainly the left basal ganglia. Coordinates of regions with peak convergence in the main effect are listed in Table 2.

Task-set vs. load-dependent effects

Task-set effects were identified by assessing the convergence among the coordinates reported in experiments that feature a contrast between a working memory task and a non-working memory control. These contrasts could relate to the only working memory condition in the particular experiment, the simplest condition or a main-effect across different working memory loads. Load effects on the other hand reflect experiments that assessed the neural correlates of increasing working memory load or difficulty (e.g., contrasting a 3-back to a 1-back task or probing activation that increases with the number of memorized items). A conjunction between both sets should thus reflect regions consistently activated when subjects engage in working memory tasks and also consistently more active when task difficulty increases. The contrast, in turn, should identify those regions that are more consistently recruited by the commencement of a working memory task or by the increase of working memory load, respectively. That is, the contrast analysis reflects differences in the degree of consistency with which a region is activated by task- or load-related contrasts. As noted earlier, however, contrast and conjunction are not mutually exclusive.

Comparing activations reported for task-set effects (i.e. contrasts against baseline or control conditions, 145 experiments, 2069 peaks, 1956 subjects) to those reported for load effects (i.e. activity increases with higher WM demands, 44 experiments, 593 peaks, 775 subjects) revealed stronger convergence among the former in a mainly left-hemispheric network (Fig. 2A). This set-related network comprised the left rostral LPFC, SPL/IPS (Area 7PC, hIP1 and hIP3) and postcentral sulcus (Area 2) as well as the dPMC extending onto the posterior

superior frontal gyrus. Bilateral effects were observed in the anterior insula (cf. Supplementary Table S2).

In contrast, load effects were more strongly associated with a bilateral network, consisting of ventral areas 44/45 (Broca's region), the vPMC and caudal LPFC (forming "triangles" of activation sites on the inferior frontal gyri) as well as the (pre-)SMA extending into the middle cingulate cortex and the left inferior temporal occipital cortex (cf. Supplementary Table S3).

The conjunction analysis revealed a network that closely mirrored the main effect reported earlier, except for the absence of activation in rostral parts of LPFC and the thalamus (Fig. 2B, cf. Supplementary Table S4). Most regions thus show, albeit to a varying degree, an adaptive engagement capacity, as they are consistently recruited by working memory tasks in comparison to control conditions (e.g., 2-back vs. 0-back as a sensory-motor control condition) as well as consistently being reported in experiments assessing load effects (e.g., 3-back vs. 1-back).

Verbal vs. non-verbal material

One of the major dividing lines in the assessed pool of experiments is whether the subjects were required to memorize verbal (e.g. letters, words, 71 experiments, 879 peaks, 969 subjects) or non-verbal (e.g. figures, objects, shapes, 53 experiments, 807 peaks, 650 subjects) stimulus items. Contrasting verbal and non-verbal WM tasks revealed that verbal tasks were significantly more likely to recruit left Brodmann areas 44/45 (cf. Supplementary Table S5). In contrast, coordinates reported for experiments using non-verbal material showed significantly higher convergence in the left (pre-) SMA and bilateral dPMC (Fig. 3A, cf. Supplementary Table S6).

A conjunction analysis of verbal and non-verbal experiments again revealed a bilateral network similar to the main effect. Different from the latter, however, we did not find convergent activation in bilateral dPMC / superior frontal gyrus, as this region was only recruited in non-verbal tasks (Fig. 3B). Moreover, in contrast to the main effect, this conjunction analysis did not yield significant convergence in the right rostral part of the LPFC, cerebellar and subcortical regions (cf. Supplementary Table S7).

Table 2
Peaks of activation for the main effect.

| Macroanatomical location	Cytoarchitectonic location	MNI coordinates			z-score
		x	y	Z	
Left anterior insula		−32	22	−2	8,30
Left inferior frontal gyrus pars opercularis	Area 44/45	−48	10	26	8,25
Left caudal lateral prefrontal cortex		−46	26	24	8,23
Left rostral lateral prefrontal cortex		−38	50	10	6,33
Right anterior insula		36	22	−6	8,26
Right inferior frontal gyrus pars triangularis	Area 44/45	50	14	24	8,22
Right caudal lateral prefrontal cortex		44	34	32	7,80
Right rostral lateral prefrontal cortex		38	54	6	4,28
Posterior medial frontal cortex		2	18	48	8,29
Left posterior superior frontal gyrus		−28	0	56	7,60
Right posterior superior frontal gyrus		30	2	56	7,06
Left intraparietal sulcus	hIP3, hIP2, hIP1	−42	−42	46	8,25
Left superior parietal lobule/intraparietal sulcus	7PC, 7A, hIP3	−34	−52	48	8,25
Left posterior superior parietal lobule	7A	−24	−66	54	6,64
Right intraparietal sulcus	hIP2/hIP3/hIP1	42	−44	44	8,22
Right intraparietal sulcus	hIP3/hIP1	32	−58	48	8,22
Right posterior superior parietal lobule	7P/7A	16	−66	56	5,17
Left thalamus (prefrontal/temporal)		−12	−12	12	5,47
Left basal ganglia (caudate)		−16	2	14	5,30
Left basal ganglia (putamen)		−18	4	6	6,33
Left basal ganglia (pallidum)		−16	0	2	5,40
Right thalamus (prefrontal/temporal)		12	−10	10	4,08
Right thalamus (prefrontal)		8	−18	4	3,64
Left cerebellum / left fusiform gyrus	Lobules VI / VIIa Crus I	−34	−66	−20	4,94
Right cerebellum / right fusiform gyrus	Lobule VI / VIIa Crus I	32	−64	−18	5,44
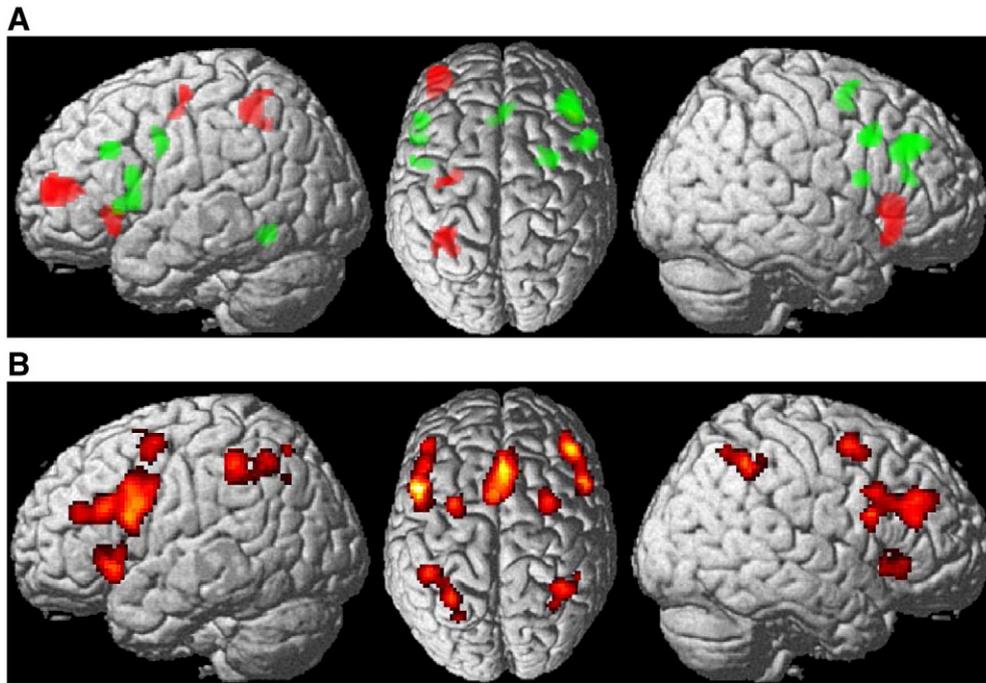
Fig. 2. A *Task set vs. load effects:* Red denotes regions, which showed higher convergence in task set effects, while regions showing stronger convergence in experiments analysing load effects are displayed in green. B A conjunction analysis of task set and load effects displayed a bilateral fronto-parietal network similar to the main effect.

Memory for object identity vs object location

The two most prevalent stimulus features to be memorized were object identity (42 experiments, 677 peaks, 575 subjects) and object location (13 experiments, 192 peaks, 200 subjects). We consequently tested for differences between experiments aiming at either feature. Verbal tasks were excluded due to potential differences in the processing of object and word identity. Moreover, including verbal material would have introduced a significant bias as only a very small number of experiments actually probed memory for the location (rather than identity) of verbal material. Memory for (non-verbal) object identity as compared to object location was significantly more likely to recruit the bilateral inferior frontal gyrus (dorsal to, but overlapping with area 44), left cerebellar lobule VI and left ventral visual cortex (Fig. 4A, cf. Supplementary Table S8). Significantly stronger convergence in tasks requiring to memorize object location as compared to identity was found bilaterally on the posterior superior frontal gyrus (dPMC), the superior parietal lobule (area 7A, extending into area 5 M on the left side) and the precuneus as well as the right inferior parietal cortex (areas PFm and PF) (cf. Supplementary Table S9).
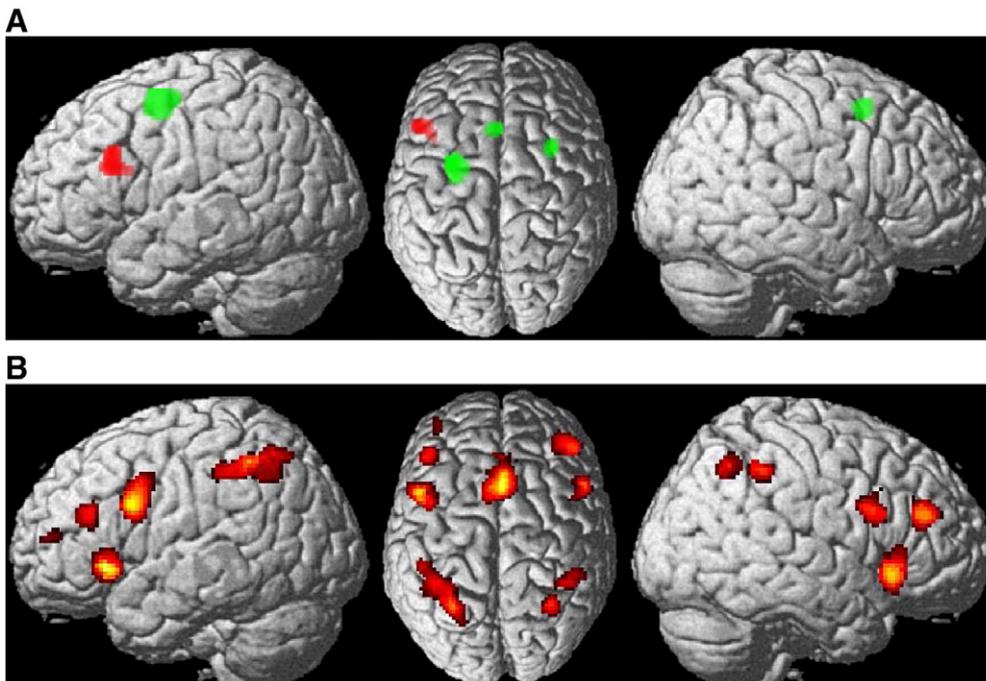
Fig. 3. A *Verbal vs. non-verbal tasks*. Significant activation for verbal tasks (red) was found in area 44/45 in the left hemisphere; regions, which showed stronger convergence for non-verbal tasks are coloured in green. B A conjunction analysis over verbal and non-verbal tasks revealed activation of a fronto-parietal network similar to the main effect.
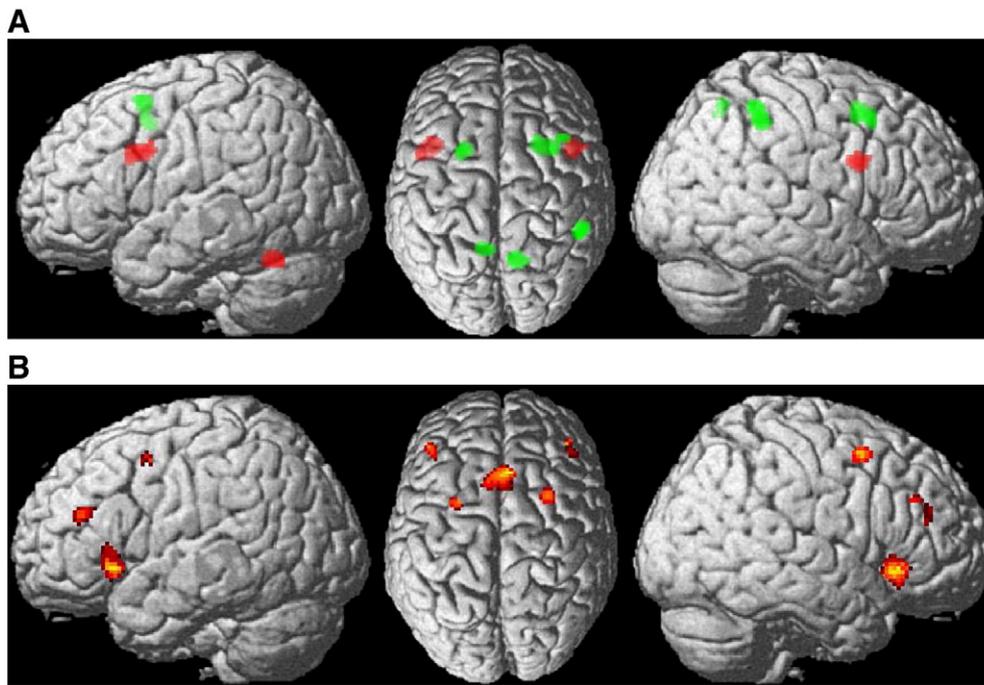
Fig. 4. A *Object identity vs. object location.* Regions where experiments on memory for object location showed a significantly higher convergence of reported activations than those probing memory for object identity are shown in green. Regions showing stronger convergence of activation in experiments on object identity are displayed in red. B Conjunction analysis of object identity and object location.

A conjunction analysis across both conditions revealed bilateral activation of the anterior insula, caudal LPFC, pre-SMA and the posterior superior frontal gyrus (dPMC). The most striking difference to the main effect was the lack of activation in the inferior frontal gyrus (areas 44/45 and vPMC), the IPS/SPL and the rostral part of bilateral LPFC (Fig. 4B, cf. Supplementary Table S10). Given the rather small number of experiments in the two compared pools, however, this divergence may also relate to the power of the performed analysis.

Differences between recall implementations and tasks

With respect to recall, we distinguished three subcategories. Simple recognition or "verification" entails indicating whether the probe was the same as a memorized item and requires the comparison of the presented probe against the item retrieved from working memory. Complex recognition or "matching" requires indicating which of multiple probe items is the same as the memorized item and hence adds processes of selection or choice to simple recognition. Finally, "reproduction" denotes the replication of a previously memorized item or sequence from memory and hence the transfer from memory into action related systems.

Verification (72 experiments, 1080 peaks, 1009 subjects), in contrast to the other two categories (matching, reproduction), was significantly stronger associated with activity in the left IPS (areas hIP1-3), SPL (7PC) and area 2 (Fig. S1A) (peak coordinate: −38/−44/54; z-score 5,65). Matching (6 experiments, 73 peaks, 62 subjects) showed significantly stronger convergence on the right inferior frontal gyrus (vPMC) (Fig. S1B) (peak coordinate: 48/4/40; z-score: 7,11) in comparison to the other variants of recall. Reproduction (11 experiments, 166 peaks, 156 subjects), finally, evoked significantly more consistent activity on the left posterior superior frontal gyrus (Fig. S1C) (peak coordinate: −28/6/48; z-score: 4,94). This supports the idea that different recall models are supported by specific brain areas.

As the majority of experiments reported either n-back (56 experiments, 847 peaks, 784 subjects) or Sternberg tasks (44 experiments, 583 peaks, 607 subjects), difference maps could only be computed reliably between these. This comparison is not only of interest as it

contrasts the consistency of regional recruitment between the two most widely used tasks and may therefore unveil potential bias by experimental design. Rather, n-back and Sternberg tasks also show fundamental differences in the necessitated mental processes. Whereas the Sternberg task consists of pure storage and retrieval, the n-back moreover has a strong manipulation, e.g., executive function component as recall, comparison and memorization of the next item take place simultaneously and targets become probes for the subsequent trial.

N-back tasks were significantly more likely to activate the bilateral IPS (areas hIP1-3), the anterior insula, posterior superior frontal gyrus, areas 44/45 and the LPFC. Significantly stronger convergence in the (pre-) SMA as well as the inferior parietal cortex (areas PFm, PFt) was only found in the right hemisphere. In the left hemisphere, activation was found more consistently in the SPL (areas 7A, 7PC). In contrast, Sternberg tasks featured more consistent activation in the left basal ganglia and left inferior frontal gyrus (vPMC, overlapping with area 44). Convergent right-hemisphere activation was found in the posterior superior frontal gyrus (dPMC) and the IPS (area hIP3), SPL (area 7PC) and in area 2 (Fig. S2A). A conjunction analysis across n-back and Sternberg tasks revealed a network similar to the main effect but lacking activation in the rostral parts of the DLPFC, parts of the inferior frontal gyrus (dorsal to area 44, vPMC), posterior superior frontal gyrus (dPMC), cerebellum, ventral visual cortex and subcortical loci bilaterally (Fig. S2B).

The working memory "core" network

In order to identify regions consistently associated with WM processes independently of the specific aspects and task features under investigation, we performed a conjunction analysis identifying regions of significant convergence across the following analyses: task effects for n-back and Sternberg tasks, verbal and non-verbal tasks, load effects and all three task components (encoding, maintenance, recall). Given that this conjunction across 8 different analyses is intrinsically highly conservative, results were thresholded at conjunction $p < 0.05$ (corresponding to a nominal p-value of 0.05^8, i.e.,

3.9×10^{-11}). Significant convergence was observed bilaterally in dorsal area 44 (extending into the premotor cortex), anterior insula, (pre-) SMA, and IPS (areas hIP1-3). While in the left hemisphere, intraparietal activation covered areas hIP1-3 and extended into the inferior parietal cortex (area PFt), we found a clear focus on area hIP3 in the right hemisphere. Moreover, activation in the right LPFC was located anterior to area 45, whereas on the left side it slightly overlapped with this area (Fig. 5). Coordinates of regions with peak convergence in the core network are listed in Table 3.

Discussion

Summary of findings

This performed meta-analyses of neuroimaging studies on WM demonstrated consistent activation of a widespread fronto-parietal network and the existence of a "core" network emerging from a conjunction across analyses of different WM tasks, designs and contrasts. Furthermore, several noteworthy differences were observed: Whereas task-set effects were more prominent in the left hemisphere including rostral LPFC and SPL/IPS as well as the anterior insula, load effects were more consistently seen in a bilateral inferior frontal network. Verbal WM tasks showed more consistent activation in left Broca's region, whereas non-verbal tasks more consistently recruited dorsal and medial premotor areas. Memory for stimulus identity relied more on the posterior inferior frontal gyrus (vPMC), memory for location on the posterior superior frontal gyrus (dPMC). Different kinds of recall (verification, matching, reproduction) differed in their recruitment of specific parietal and frontal locations. The same was true for the difference between Sternberg and n-back tasks. In summary, we thus observed, on top of a highly consistent "core" network, several statistically significant differentiations between the neural correlates of different stimuli, tasks or contrasts.

Publication-bias and coordinate-based meta-analyses

Similar to the situation in other scientific fields, the functional neuroimaging literature is susceptible to a publication bias, which represents two main mechanisms (Dickersin et al., 1992). First, if an investigator fails to reject the null-hypothesis, these "negative" results are often deemed not important enough to attempt to be published and the data is relegated to the "file drawer" (Rosenthal, 1979). That is, findings of absent effects have a lower chance to enter the literature. Second, in particular in studies with insufficient sample sizes, results may arise by chance alone (type I error) but still get published if they exceeded the threshold for statistical significance. Publication-bias may thus lead to an overestimation of pooled effect sizes in meta-analyses (e.g., Cuijpers et al., 2010; Elvik, 2011), as smaller or absent effects do not enter meta-analysis due to a lack of publication. Evidently, publication-trends and biases in the neuroimaging literature (Jennings and van Horn, 2011; Sayo et al., 2012) may also affect ALE analysis, as the inclusion of a particular coordinate is conditioned on the fact that the original authors reported it as having a statistically significant effect size.

In this context, however, it is important to point to the conceptual differences between effect-size meta-analyses (as common, e.g., in the context of clinical trials or neuropsychological effects) and coordinate-based meta-analyses (CBMA) of neuroimaging data. Neuroimaging CBMA distinguishes itself from most other forms of meta-analyses by assessing spatial convergence between reported activation coordinates rather than quantifying the pooled effect size (which may be biased by non-published small effects and published type I errors in small samples). Consequently, the null-hypothesis to reject is not the absence of any effect but rather that spatial convergence among published coordinates is random. This substantial difference may be best illustrated by considering the effect of methods such as "trim and fill", which may account and adjust for publication bias by filling in (non-significant) studies presumed to be missing in the literature (Duval and Tweedie, 2000). These, in fact, would not affect ALE analyses as may be appreciated by two notions. First, the ALE score (union of probability values) will not change by the inclusion of experiments in which all voxels have an activation probability of zero (due to the fact of a complete null-result). Second, the null-distribution for convergence would likewise be unaffected by the inclusion of a "null-volume" as it only (randomly) changes the spatial association between experiments but otherwise uses the same computational approach, namely calculation of the union between probability values (Eickhoff et al., 2009, Eickhoff et al., 2011a). In other words, inclusion of an estimated number of unpublished results would not have any impact on the assessment of spatial convergence performed by the ALE approach.

Given these considerations, neuroimaging CBMA should be less susceptible to publication bias than effect-size meta-analyses. Nevertheless a confounding effect of publication trends may potentially still be found, if (and only if) the likelihood of a result being published is conditioned on the spatial nature of the observed activations. To illustrate this point: if the presence of activation of area X in task Y is axiomatically assumed and hence no paper without activation in area X may be published (though many studies with insufficient power as long as they report X), there would be a bias towards finding area X in a meta-analysis on task Y. In their recent analysis of publication-bias, however, Jennings and van Horn (2011) came to the conclusion: "Since these results did not differ from our overall findings, there appeared to be no systematically different bias based on functional domain. It appears that the presence of publication bias is not restricted by sub-regions of the brain or cognitive/behavioural paradigms but is likely to be broadly present across the literature." Hence, there seems to be no task- nor sub-region dependent bias in the neuroimaging literature, which ALE analyses would be highly susceptible to.

In summary, publication trends and biases as evident in the neuroimaging literature (Jennings and van Horn, 2011; Sayo et al., 2012) may confound meta-analytical approaches. In contrast to effect-size meta-analyses, however, CBMA of neuroimaging results are less
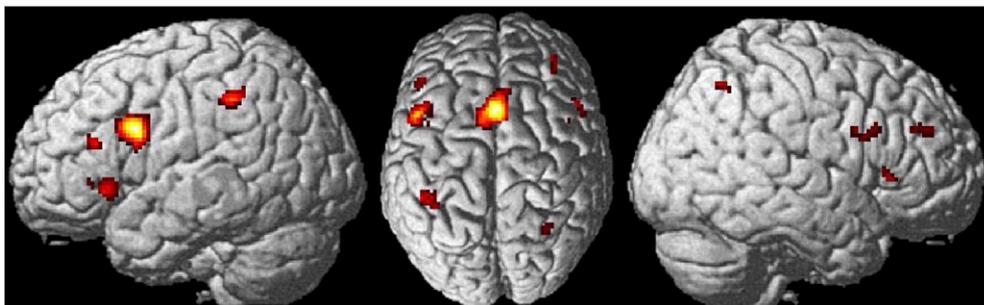

Fig. 5. *The working memory core network.* Left dominant bilateral activation of regions showing converging activations in each of the following analyses: task effects for n-back and Sternberg tasks, verbal and non-verbal tasks, load effects and all three phases (encoding, maintenance, recall).

Table 3
Peaks of activation for the core network. Abbreviations: IFG = inferior frontal gyrus.

Macroanatomical location	Cytoarchitectonic location	MNI coordinates			z-score
		x	y	Z	
Left posterior medial frontal cortex		0	14	52	4,17
Right posterior medial frontal cortex		6	24	42	2,10
Left intraparietal sulcus/intraparietal cortex	hIP1/hIP2/hIP3/PFt	−44	−40	42	2,86
Left anterior insula		−36	22	−2	2,65
Left inferior frontal gyrus pars opercularis	Area 44	−46	10	26	4,30
Left IFG/caudal lateral prefrontal gyrus	Area 45	−46	30	20	2,47
Right anterior insula		38	24	4	2,26
Right caudal lateral prefrontal cortex		34	44	26	2,07
Right inferior frontal gyrus pars opercularis	Area 44/45	50	16	26	2,15
Right intraparietal sulcus	hIP3	30	−60	50	2,26

susceptible as they do not try to establish the consistent presence of an effect but rather seek spatial inference on the convergence of reported coordinates. Nevertheless, the quantified activation likelihood and any results from an ALE study must not be considered an absolute entity. Rather, ALE scores and significances must be deemed conditional on the current literature. In other words, quantitative meta-analyses of neuroimaging data should not be considered an absolute truth but rather as a quantitative integration of the published knowledge and a statistical synopsis of the current state of the field.

Comparison to previous meta-analyses

Within a widespread fronto-parietal network observed for the WM main effect, consistent activation in conjunction analyses over stimuli, tasks, contrasts and task phases was found in a bilateral network comprising the IFG, anterior insula, IPS and (pre-) SMA. This network thus seems to reflect the "core" of WM functions engaged independently of specific requirements or peculiarities of experimental implementation. Comparing these findings to previous meta-analytic summaries of WM-related brain activity, it becomes obvious that the results are similar even though these earlier studies either focussed on one type of WM task only (Owen et al., 2005) or used a different analysis approach (Wager and Smith, 2003). Owen and colleagues performed a meta-analysis across 24 n-back studies, reporting consistent activation in bilateral IPS and inferior frontal gyrus, which is in good accordance with the core network delineated in our study. Although Owen et al. did not explicitly note convergent activity in the insula, the activation on the mid-ventrolateral frontal operculum is close to the anterior insula observed here and may largely overlap with it by judging from the figures presented in their paper. While Owen and colleagues found bilateral activation of caudal and rostral LPFC we only found the caudal part bilaterally in the core network while the bilateral rostral part was just seen in the main effect across all experiments. Their finding of consistent bilateral dPMC activation finally is again in good agreement with our main effect across all working memory studies.

Wager and Smith (2003) integrated multiple WM tasks by cluster analysis over the location of reported foci rather than using an analysis of convergence as applied here. Many of the clusters reported in their study are in good convergence with the "core" network emerging from our analysis. For example, Wager and Smith also reported bilateral activation in the IPS and the inferior frontal gyrus as well as in the (pre-) SMA. In good agreement with our main effect, these authors also reported a cluster in bilateral dPMC and the LPFC. Finally, Wager and Smith also noted a high prevalence of foci on the anterior insula, which is in line with the distinctions between anterior and posterior aspects of the insular cortex (Kurth et al., 2010; Craig, 2009). However, in the clustering method applied by Wager and Smith, the anterior insula did not reveal itself as a distinct cluster of foci. Rather, it seemed that by virtue of their close spatial proximity foci located on the anterior insula and those located on the inferior frontal gyrus were merged into a single cluster.

In summary, the findings of previous meta-analyses and our presented data are in good congruence. Considering an overlap of about 1/3 between the three meta-analyses (mainly due to varying inclusion/exclusion criteria), this observation supports the robustness of brain networks involved in WM. The current analysis, however, provides more reliable estimates of convergence and considerably expands previous findings by revealing differential effects of task type, stimulus material and contrasts.

Division between rostral and caudal LPFC in working memory?

Engagement of the LPFC during WM performance is well established (Barch et al., 1997; Braver et al., 2001; Manoach et al., 1997; Owen et al., 1996a; Petrides, 1994) and previous work suggested a specialization for on-line maintenance (Curtis and D'Esposito, 2003) and memory load (Linden et al., 2003). In light of the present and previous meta-analysis results, however, it becomes evident that the term "DLPFC" may be too general to serve as a useful anatomical unit or functional concept for describing neural correlates of WM functions. In particular, it appears that this term is used to label nearly all activations anterior to the premotor cortex and Broca's region. Given this lack of anatomical or functional specificity, we here propose a distinction between rostral and caudal parts of the LPFC based on their differential associations with specific WM functions. The rostral region is located on the anterior aspect of the inferior and particularly middle frontal gyrus, the latter more caudally just anterior to BA 45. In particular the latter seems to conform to the dorsolateral PFC as described in several previous neuroimaging studies (Blumenfeld et al., 2011; Koric et al., 2011). It should be noted, however, that both loci of convergence are located superior to the classical location of the ventro-lateral PFC that is commonly located on the pars orbitalis of the inferior frontal gyrus (Inoue and Mikami, 2010; Manoach et al., 2004).

We acknowledge that this division of the (dorso-) lateral prefrontal cortex is still a highly simplified concept of prefrontal organization but neither the present data nor the previous WM meta-analyses (Owen et al., 2005; Wager and Smith, 2003), however, indicated a more fine-graded distinction. The differences between the more rostral and caudal portion of the LPFC, however, were evident from the presence of separate foci in our analysis and separate clusters in the study by Wager and Smith. Functionally, this distinction is particularly relevant for the differentiation between task-set and load-dependent effects. A similar differentiation of LPFC has also been described in individual imaging studies, i.e., within the same subjects, (Fletcher et al., 1998; Henson et al., 1999) and will be discussed in detail later (Section Task-set vs. load-dependent effects).

How does the current meta-analysis relate to previous accounts of regional distinctions within the frontal cortex in the context of working memory? Many concepts have stressed a distinction between the ventral and dorsal aspects of the human LPFC in working memory, though different hypotheses on the nature of their functional

segregation exist (Curtis and D'Esposito, 2004). One view relates this specialization to the processing of spatial and non-spatial, i.e., object related, information (Romanski, 2004, Rama, 2008). Other authors, however, have argued, that dorsal and ventral prefrontal cortices perform qualitatively different operations such as individual item processing vs. the organization of multiple pieces of information (Muller and Knight, 2006; Blumenfeld and Ranganath, 2007). Alternatively, dorsal regions have been implicated in monitoring of information and ventral regions in active judgments on these (Petrides, 2005). In our analysis, we did not find reliable evidence for a distinction between spatial and non-spatial tasks in the prefrontal cortex strictu sensu, but rather showed, that such segregation exists more posterior on the frontal lobe in the region of premotor areas. Moreover, while the present analysis is not ideally positioned to address the question of specifically supported process due to the difficulties in ascribing those to a wide range of contrasts, it is noteworthy, that we only found a single differential task-related effect in the LPFC. In particular, there was a stronger convergence for n-back tasks (which pose stronger demands on manipulation) as compared to Sternberg tasks (which reflect more passive storage-retrieval) in the dorsolateral prefrontal cortex. These results thus match the model proposed by Fletcher and Henson (2001), who attributed manipulation and monitoring to the dorsolateral portions of the LPFC. Moreover, the same authors located the selection of processes to the anterior aspects of the prefrontal cortex, which is in accordance with the present data, showing significant predilection for task-set related effects in the rostral LPFC. We would argue, that the distinction between task set in the rostral LPFC and the more posterior location of load, i.e., storage, related effects observed in our analysis also resonates well with the proposed anterior (overarching planning) to posterior (lower-level execution) axis of the prefrontal cortex in executive control (Koechlin and Summerfield, 2007, Badre, 2008).

The developing notion that the term LPFC may need further differentiation into at least two main regions becomes important when considering the attention this part of the brain has received in translational imaging research. In particular, the LPFC has been hypothesized to play an important role in the genetic vulnerability to schizophrenia (Meyer-Lindenberg et al., 2005). In particular, it has been shown that genetic variants in the activity of the Catechol-O-methyltransferase (Tan et al., 2007) and abnormal GABA-mediated neurotransmission (Hashimoto et al., 2008) are associated with dysfunctions of the LPFC. Moreover, functional changes in LPFC activity have also been reported in preclinical Huntington's disease (Wolf et al., 2007), and decreased activity in this region was found in posttraumatic stress disorder (Clark et al., 2003). Thus, this particular region seems to play a key role in many neuropsychiatric diseases and the genetically mediated vulnerability towards these. Given the current data indicating a functional distinction between at least two regions within the LPFC, it appears that pre-clinical imaging would benefit from a more precise delineation of the respective LPFC regions of interest.

Task-set vs. load-dependent effects

One of the most conspicuous distinctions between the rostral and caudal LPFC was found in the comparison between task-set and load-related effects. While the former recruited the left rostral LPFC more reliably, the latter were associated with more steady bilateral activation in the caudal aspect of the LPFC. In this context, we would like to reiterate the notion that the performed meta-analytic contrast is sensitive to regions that are more consistently recruited by the commencement of a WM task or by the increase of working memory load, respectively. That is, the contrast analysis reflects differences in the degree of consistency with which a region was reported in task- or load-related contrasts.

In this context, task set refers to the performance of a WM task (irrespective of its specific components), relative to a non-working memory control condition. On the side of the subjects, this entails engaging in the experimental setting, paying attention to the stimuli as well as memorizing and recalling them. In other words, when engaging into the task subjects know that they have to be alert for external stimuli and keep them in mind. Task set effects may therefore not only represent working memory specific processes but might also include neuronal systems responsible for arousal, attention and response selection. This may seem as a potential drawback of the set-effect contrast. On the other hand, however, it must be considered whether such processes could at all be separated from memory specific effects as they represent essential components of performing a cognitive task relative to a resting baseline or a (usually simpler and hence less demanding) sensory-motor control condition. In other words, it may be argued that, e.g., attention and response selection processes are closely intertwined with WM related processes in any of the considered experimental paradigms. The present analysis showed that these (potential conglomerate of) processes particularly involved the left rostral LPFC and the anterior insula in both hemispheres. A similar distinction has been shown before in individual WM experiments, i.e., in within-subject designs. On these grounds, it has been argued that the rostral part of the LPFC is responsible for cue specification, the caudal part for monitoring processes (Fletcher et al., 1998; Henson et al., 1999), a notion that is supported by data from motor control tasks (Buccino et al., 2004; Vogt et al., 2007). The bilateral co-activation of the anterior insula with the rostral LPFC in the general task set is moreover in good agreement with the results from a large-scale meta-analysis on insular functions (Kurth et al., 2010). In their data, the anterior insula was consistently implicated across several cognitive domains and has consequently been discussed as an important substrate of task-set maintenance, i.e., the memorization of what the task instructions were and how to comply with them (see also (Dosenbach et al., 2006, 2007; Fair et al., 2007; Kurth et al., 2010). We note that the anterior insula is found very consistently across the different meta-analyses performed here and therefore seems to participate in various task settings. This resonates well with previous findings implicating the anterior insula as part of a cognitive control network, which is related to saliency and attention (Cauda et al., 2011), may play a role in control goal directed behavior through maintenance of task sets (Dosenbach et al., 2007) and supports attentional awareness (Craig, 2009).

In turn, load effects reflect the neural activation related to the amount of information that has to be memorized, i.e., requirements on storage capacity (Cowan, 2001). Psychologically, such load effects may be heterogeneous. They could for example be interpreted as the "filling" of buffer spots by the various items to be remembered which would render them purely quantitative. On the other hand, however, there may also be qualitative differences, implicating that more extended sets of items are sustained by other mechanisms than smaller ones (as opposed to simply requiring more storage). As an example, memorization strategies could change or grouping may be introduced to deal with the increased load (Brown et al., 1996; Stuss and Knight, 2002). Given the heterogeneity of the included studies, we cannot justifiably conclude on the presence of either aspect, which moreover may not be mutually exclusive. The current meta-analysis, however, revealed that, across the various experiments, load effects are mainly associated with the bilateral inferior frontal gyrus. This activation overlaps with areas 44/45, the vPMC and caudal LPFC (Fig. 2A). The observed findings are consistent with previously reported effects of generally increased working memory load in the prefrontal cortex (Cappell et al., 2010; Gould et al., 2003; Linden et al., 2003; Wolf et al., 2010), which may interact with more specifically dedicated parietal systems depending on task requirements. Hence, we would propose that the caudal part of the LPFC seems to be an important substrate for working memory capacity that may be recruited or "orchestrated" by the more rostral one. This is in good accordance with findings of previous studies, which showed greater activation of the

caudal parts of the LPFC during active monitoring of information (D'Esposito et al., 2000; Owen et al., 1996b, 1999).

Effects of experimental implementations

The comparison of verbal with non-verbal stimuli showed that verbal stimuli evoked significantly more consistent activation in left areas 44/45, which is in line with nearly all previous studies comparing verbal and non-verbal tasks, and agrees with the speech functions ascribed to this region (Gruber and von Cramon, 2003; Smith et al., 1996; Zurowski et al., 2002). With reference to Baddeley's influential model, this location may thus be regarded as part of the phonological loop i.e., involved in verbal rehearsal (Baddeley and Hitch, 1974; (Baddeley, 1986). In analogy, could the more consistent activation of the (pre-) SMA and the posterior superior frontal gyrus (dPMC) found for non-verbal tasks correspond to the hypothesized visuospatial sketchpad? The fact that both areas are known to be involved in (spatial) motor planning indirectly supports this notion. The (pre-) SMA appears to play an important role in preparing and selecting a motor response (Petit et al., 1998), the dPMC may be particularly relevant for representing locations for target reaching (Hoshi and Tanji, 2004). Interestingly, we did not find a significant difference between verbal and non-verbal tasks in parietal areas (cf. Wager et al., 2004) but rather observed consistent activation of the IPS in the conjunction across both domains. This indicates that in spite of its role in spatial planning, this region may hold a more general function in the context of WM. Rather than contributing to the functions of a spatial sketchpad, it may thus sustain more basic storage/processing processes (similar in psychological terms to a multimodal buffer), which then interacts with different frontal sites (BA 44 or dPMC) when dealing with verbal or non-verbal material, respectively. This is in good accordance with recent findings indicating that the IPS is a multimodal or amodal region of WM capacity (Cowan et al., 2011). In other words, contrary to the common notion of primarily spatial processing in the IPS (Cieslik et al., 2010) but in line with findings of IPS engagement in verbal fluency tasks (Ischebeck et al., 2008) our data does not imply a specificity of the IPS for spatial material or tasks.

A second important comparison pertained to memory for object location (associated with activation in the posterior superior frontal gyrus) and identity (associated with activation of the inferior frontal gyrus). This distinction matches the difference between premotor areas F2 (dorsally) and F4 (ventrally) in non-human primates, which are implicated in reaching and grasping, respectively (Raos et al., 2003). The human homologue of F2 seems to correspond to the dPMC, whereas the homologue of F4 seems to be located in human vPMC (Rizzolatti et al., 2002). While the former is thought to be involved in inverting visuospatial object properties for motor programming in space including the representation of arbitrary stimulus response mappings and reaching (Begliomini et al., 2008; Caminiti et al., 1999; Hoshi and Tanji, 2007), the latter has been described to play a role in designing object centred motor programs including inverting visuospatial object properties for grasping and manipulation (Majdandzic et al., 2009). Moreover, this observed division seems to mirror the distinction of visual processing into a ventral and a dorsal stream. While the ventral stream is supposed to hold pathways for object vision, the dorsal is supposed to process spatial vision (Ungerleider and Haxby, 1994). Importantly, these pathways seem to extend onto different parietal systems for object related processing including precision grip on one hand and spatial coding, e.g., for reaching movements, on the other (Rizzolatti et al., 1998). Our results now indicate that in the context of working memory the premotor cortex may be similarly divided into a dorsal part active during memorizing object locations and a ventral part active when object properties have to be remembered. It may hence be speculated that memory for a particular location and reaching towards it as well as object memory and finger positioning for object manipulation may

rely on shared neural systems, respectively, supporting the hypothesized evolution of cognitive functions from action-related brain networks.

Finally, the supplementary analyses assessing potential differences in the neural correlates of working memory depending on the experimental implementation demonstrated significant effects of experimental task and contrast in many brain regions. That is, depending on the choice of the applied task (e.g., Sternberg vs. n-back) or the implementation of the response (verification vs. matching), a neuroimaging experiment on working memory function or its disturbances may be more or less likely to indicate a particular brain region. For example, whereas the Sternberg task may be regarded as a more passive storage-recall process, the n-back paradigm places higher demands on manipulation and executive functions. Likewise, simple verification tasks require less response selection related processes as those requiring the choice of a matching probe among several alternatives. While a detailed consideration of the different mental processes that may underlie these various distinctions as well as the relation of these to the associated brain regions and potential neural processes is beyond the scope of this paper, several important considerations may emerge from these observations. We feel, that our data again underlines that working memory is an overarching concept much more than a particular function with unequivocal neural underpinnings. There is no doubt that all paradigms and implementations address working memory functions and we would argue that this common denominator is represented in the core network discussed below. Yet as the current data indicates, experimental factors nevertheless entail significant variations in the likelihood of observing activation in various brain regions. It may hence be tentative to equate the neural correlates of, e.g., a particular implementation of a Sternberg task asking the subject to indicate whether a particular picture was part of the memorized set, with the neural representation of "working memory" per se. This caveat and the notion that activation probability for a given brain area may vary due to experimental implementations evidently is particularly relevant in the fields of translational and clinical research, where inferences are usually sought about dysregulation, vulnerability or aberrant functioning of particular brain areas. Given the present observation, it may be argued, that in cases where there is a particular interest in a specific structure (e.g., based on animal models, (ultra-) structural findings or receptor distribution) it may be worthwhile to optimize the selection of the experimental paradigm and its implementation towards maximising the activation likelihood of this particular region. In other words, the choice of a special task for a working memory study or the performed contrast may already introduce a potential bias towards activation in particular regions, as demonstrated by the systematic effects observed in the present study.

The working memory "core" network

One striking observation in the current meta-analysis, which is in accordance with previous work (Owen et al., 2005; Wager and Smith, 2003), is the presence of a highly stable "core" network. This bilateral network seems to be engaged by WM tasks independently of the type of stimuli, task, or contrast. It may thus form the neural core of WM processes or, in terms of psychological constructs, a central executive (Baddeley, 1986; Baddeley and Hitch, 1974). While this interpretation seems plausible due to the highly consistent engagement, it also presents a peculiar challenge to the prevalent assumption of a one-to-one mapping between psychological processes and brain regions as proposed by Posner and colleagues (Posner et al., 1988). Intriguingly, our data indicate that the function of a "central executive" may not be localized to any particular region. Rather, the central executive might consist of a set of processes – an "executive committee" (Baddeley, 1986) – implemented in a multi-node neural network. This fits with the clinical observation that WM deficits are rarely

caused by isolated brain lesions but rather seem to result mainly from diffuse pathologies involving multiple brain regions or the connectivity between them (Lee et al., 2008; Rousseaux et al., 2008; Schneider et al., 2003; Urbanski et al., 2011; Yoshida and Kuroda, 2008) such as schizophrenia (Glahn et al., 2005; Kim et al., 2010; Minzenberg et al., 2009; Nejad et al., 2011; Scheuerecker et al., 2008), hepatic encephalitis (Weissenborn et al., 2003), attention deficit hyperactivity disorder (ADHD) (Bayerl et al., 2010; Passarotti et al., 2010) or dementia (Peters et al., 2009). It may hence be speculated, that (distributed) pathology to a "central executive" core network may result in deficits overarching the domain of working memory. And indeed, several neuropsychological studies have already demonstrated that in various of the aforementioned disorders working memory deficits are closely related to an overall impairment of executive function (Behrwind et al., 2011) (Drijgers et al., 2011; Koziol and Stout, 1992).

In line with this psychopathological notion that working memory impairments are often accompanied by deficits in other higher-order cognitive functions, a network similar to our WM "core" network was also discussed as part of the selective attention system (Shulman et al., 2002, 2009). This attentional network is, however, right-dominant and additionally includes the temporo-parietal junction. Moreover, similar regions as implicated in the WM core network are also consistently recruited by motor tasks involving orientation (Marangon et al., 2011), movement integration (Wolynski et al.,2009) and planning (Bortoletto and Cunnington, 2010). Furthermore, highly congruent networks have also been described in meta-analyses of executive functions such as task switching (Wager et al., 2004) and response inhibition (Nee et al., 2007). This apparent overlap between a distributed central executive for working memory, the attention system and action control thus raises the question whether this core network may hold an even more broadly defined role in cognition and behaviour. This in turn would imply, that the computational processes implemented by this network are not specific for working memory but rather represent even more fundamental aspects of cognitive processes.

The view, that common fronto-parietal networks may underlie several cognitive domains resonates well with previous comparisons of the neural basis for different higher cognitive functions. In a summary of neuroimaging studies from their own laboratory Ikkai and Curtis (2011) found that that the same areas in the prefrontal and posterior parietal cortex show persistent activity during the maintenance of a working memory representation, spatial attention and motor intention, concluding that "activity in topographically organized maps […] could be read out to guide attention allocation, spatial memory, and motor planning". Their analysis thus supported the view proposed in Curtis and Lee (2010), that persistent activity that may be labelled as working memory is also the foundation of several other cognitive processes, including perceptual and reward-based decision making. Within such network, namely, parietal areas may primarily sustain retrospective sensory coding of space while frontal areas may be more involved in prospective (motor) coding (Curtis, 2006). In contrast to this view, which conceptualizes maintenance (and hence a form of "working memory") as the basis of other cognitive functions, LaBar et al. (1999) proposed a somewhat contrary view by suggesting that "spatial attention and working memory share common cognitive features related to the dynamic shifting of attentional resources", i.e., proposing attention as the underlying cognitive construct (cf. Marklund et al., 2007). From a different angle, Naghavi and Nyberg (2005) reasoned from a qualitative meta-analysis of neuroimaging results on the cerebral representations of attention, working memory, episodic memory retrieval and conscious awareness, that common fronto-parietal activity may reflect processes related to integration of distributed representations in the brain. This hypothesis is echoed by Wendelken et al. (2008), who conceptualized the role of fronto-parietal networks as the maintenance, organization and manipulation of structured information. Finally, the discussed, apparently widely engaged fronto-parietal network, may also represent a core

executive that mediates the control of goal-directed behaviour in general (cf. Simon et al., 2002). This view is in line with the idea of a multi-level supervisory system for coping with non-routine demands by modulation of lower-level systems that subserve routine operations (Shallice, 1994, 2004; Stuss, 2006). The observed WM "core" network is also highly congruent with a pattern found in response to increased task demands across a wide range of tasks (Duncan and Owen, 2000). As Duncan (2000) argues, this multiple-demand network may be responsible for establishing biased competition for task-relevant information throughout the brain. In particular, neurons in this "executive committee" network may be tuned to represent relevant information across a diversity of tasks, thereby producing the well-known capacity limits in attention and WM alike (Kane and Engle, 2002, 2003). Thus, the transient representations in the core network may be essential to keeping the mind focussed on the information, be it perceptual, mnemonic or motor-related, that is most relevant for achieving current goals. While we certainly cannot come to a final conclusion as to which computational process is supported by this apparent cognitive or executive core network, it should become evident, that current cognitive or neuropsychological ontologies may potentially be inadequate to characterize the underlying neuro-computational processes. We would hence conclude, that the robustly engaged fronto-parietal core network, as demonstrated here for working memory, may sustain extremely basal processes or computations that are required for virtually all cognitive functions but whose exact nature remains to be further elucidated.

Conclusions

In the present study, we used quantitative coordinate-based meta-analyses to integrate the current neuroimaging literature on human working memory as a (broader) psychological construct. This synthesis revealed i) a highly consistent core network, which, however, may not be limited to WM but span several higher cognitive functions. ii) a distinction of at least two WM-related regions within the DLPFC, with the rostral one showing a stronger predilection for task-set effects, the caudal one for load effects. iii) An apparently systematic influence of the experimental implementation on the likelihood of finding WM-related activation in several brain regions. Such biases were shown, e.g., for verbal vs. non-verbal paradigms, memory for identity vs. location or Sternberg vs. n-back tasks. The current integration of a large body of heterogeneous findings thus provided consensus evidence for a highly consistent "core" network for (at least) working memory as well as statistically significant differentiations between different stimuli, tasks or contrasts.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.11.050.

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