Research Report

Age effects on load-dependent brain activations in working memory for novel material

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ABSTRACT

Three competing models of cognitive aging (neural compensation, capacity limitations, neural inefficiency) were examined in relation to working memory for novel non-verbal material. To accomplish this goal young (*n*=25) and old (*n*=25) participants performed a delayed item recognition (DIR) task while being scanned with bold fMRI. The stimuli in the DIR task consisted of computer-generated closed-curve shapes with each shape presented only once in the testing conditions of each participant. This ensured that both the novelty and appearance of the shapes maximized visual demands and limited the extent of phonologic processing. Behaviorally, as expected, the old participants were slower and less accurate compared to the young participants. Spatial patterns of brain activation that corresponded to load-dependent (stimulus set size ranged from 1 to 3) fMRI signal during the three phases of the DIR task (memory set presentation, retention delay, probe presentation) were evaluated in both age groups. Support for neural compensation and capacity limitation was evident in retention delay and the probe phase, respectively. Data were inconsistent with the neural inefficiency model. The process specific support for the theories we examined is consistent with a large corpus of research showing that the substrates underlying the encoding, retention and probe phases are different. That is, cognitive aging theories can be specific to the neural networks/regions underlying the different phases of working memory. Delineating how these theories work in concert can increase knowledge of age-related effects on working memory.

1. Introduction

Working memory refers to the retention and manipulation of information, typically in a time scale of seconds. There is almost a universal consensus that working memory is critical for a range of cognitive abilities including planning (Prabhakaran et al., 2000) reasoning (De Neys and Verschueren, 2006) language comprehension (Baddeley, 1992) general fluid intelligence (Engle et al., 1999a) and problem solving skills (Thevenot and Oakhill, 2006). Traditionally, working memory

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has been divided into verbal and visual buffers subordinate to a central executive system (Baddeley, 1986, 1992) but more recently (Baddeley and Logie, 1999) the visual buffer has been further divided into two components subserving object and spatiotemporal information (see Postle, 2006 for a recent overview concerning previous and current approaches to the study of working memory).

Working memory shows a downward trajectory across the adult lifespan in non-demented individuals (Park et al., 2002) with deficits often observed in paradigms that manipulate memory load (Anders et al., 1972; De Beni and Palladino, 2004; Eriksen et al., 1973; Orsini et al., 1987) and demands on the attention and executive systems (Holtzer et al., 2004, 2005). The latter findings are consistent with the premise that working memory depends on attention resources (Kane et al., 2001; Engle et al., 1999b) that decline with age (Craik and Byrd, 1982). Several studies showed that the negative effect of old age is more pronounced in non-verbal compared to verbal working memory tasks (Jenkins et al., 2000; Myerson et al., 1999). Such findings are consistent with the notion that certain aspects of language and semantic knowledge remain relatively constant across the adult life span (Stine-Morrow et al., 2006). However, evidence for comparable decline in verbal and non-verbal working memory also exists (Park et al., 2002; Salthouse and Babcock, 1991; Salthouse, 1994). The degree to which older adults are familiar with the items to be studied may also mediate the effect of aging on working memory. For instance, previous research found that recollection and familiarity have separate influences on memory performance (Anderson and Craik, 2006; Hay and Jacoby, 1996; Hay and Jacoby, 1999; Jacoby, 1991). Whereas familiarity relies upon automatic activation, recollection is a more effortful process of retrieval that involves executive control and tracking of contextual information (Mulligan and Hirshman, 1997; Steffens et al., 2000). Old age has negative effect on recollection but not on familiarity (Hay and Jacoby, 1999) in effortful and effortless learning paradigms (Anderson and Craik, 2006). In the context of imaging studies examining the effect of aging on working memory it is reasonable to hypothesize that the functional brain circuitry that underlies age-related deficits will vary depending on whether the stimuli used are novel or well-rehearsed and familiar.

Age-related pathological changes in brain structures are ubiquitous (Kemper, 1994; Raz, 2000). Hence, examining from a theory-based perspective whether functional brain circuitry is age variant or age invariant vis-à-vis working memory performance is of interest, especially in light of the existing neuropathology in the aging brain. Two models do not predict qualitative changes in patterns of brain activation with aging. A limited capacity hypothesis predicts that young and old individuals recruit the same brain networks/regions in response to a cognitive challenge but that the elders will show reduced levels of brain activation in those regions. Indeed, reductions in brain activity in aging have been found across cortical regions (Cabeza et al., 2004; Grady et al., 1995; Madden et al., 1996; Reuter-Lorenz et al., 2000); and some age-related reductions in activations were associated with poorer cognitive performance (Jonides et al., 2000; Rypma and D'Esposito, 2000). In contrast, increased activation of networks that is correlated with poorer or equivalent cognitive perfor-

mance has been considered an indication of age-related neural inefficiency (Rypma et al., 2002; Zarahn et al., 2007).

Alternatively, there are models that do predict qualitative changes in patterns of brain activation with aging compensatory models posit that re-organization of brain circuits in old individuals involving recruitment of new networks and/or underutilization of brain regions activated in young individuals can compensate for the neuropathological consequences of aging (Cabeza, 2002; Cabeza et al., 2002; Grady and Craik, 2000; Stern et al., 2000). As evident from a recent review of imaging studies examining age-related changes in brain activations in working memory, much of this research is focused on the prefrontal cortex (Rajah and D'Esposito, 2005). In that context, the hemispheric asymmetry reduction in old adults (HAROLD) model, an example of a compensatory reallocation model predicting increased bilateral activation in the prefrontal cortex in old compared to young individuals, has stimulated a great deal of research and has garnered empirical support as well (Cabeza et al., 2000; Cabeza, 2001, 2002). Inherent in compensatory reallocation model(s) is the premise that among older adults those who express a brain activation pattern that is age specific to higher degree perform better on cognitive tasks compared to those who express the same pattern to a lesser degree. However, as pointed by Rajah and D'Esposito, (2005) the HAROLD model does not address whether these laterality effects are specific to the prefrontal cortex or are common other brain regions; and nor does it specify the mechanisms underlying neural age-related reductions in lateralized activity.

A less stringent view of compensation would consider a brain pattern compensatory when it is uniquely expressed by an impaired group (such as in aging) but not by an unimpaired group. This approach, which we have termed neural compensation (Stern et al., 2005; Stern, 2006) does not require a direct correlation between expression of a unique age-related brain activation pattern and performance. Rather it acknowledges the possibility that a network recruited in old but not younger individuals may be required simply to support performance in the face of age-related neural changes. Further, it is important to emphasize that neural compensation does not restrict the study of age-related differences in brain activation and compensation of working memory (and of other cognitive functions) to the prefrontal cortex. Often studies have found that concomitant with decreased age-related brain activation in some areas were increased activations in other areas (Cabeza et al., 2004; Milham et al., 2002). This scenario is inconsistent with a simple limited capacity theory or with a simple compensatory reallocation model. However, it is consistent with neural compensation in that a second brain activation pattern that is observed in old but not young individuals may serve to support a first pattern that is common in both age groups. The dedifferentiation hypothesis provides an alternative account of this differential recruitment of brain networks between young and old individuals (Baltes and Lindenberger, 1997; Li and Lindenberger, 1999). In dedifferentiation changes are assumed to be secondary to the deleterious effect of aging on the brain and are not conceptualized as necessarily beneficial to cognitive function. Dedifferentiation implies a breakdown in the optimal state of neurologic organization, or decreased functional integration

between brain regions (Logan et al., 2002). As such, dedifferentiation is not much different than non-selective over-activation: it is a reduced ability to achieve task-relevant focal activation and to suppress task-irrelevant areas (Cabeza, 2002; Esposito et al., 1999; Lahvis et al., 1995).

These aforementioned models of cognitive aging were previously tested in the context of working memory for letters (Zarahn et al., 2007). In that study working memory was operationalized using a delayed item recognition (DIR) task, which affords examination of brain activity during set presentation, retention delay and probe presentation. Stimuli were letters of the alphabet that varied in set size. Findings were consistent with neural inefficiency for load dependent processing during set presentation and load independent processing during retention delay. That is, young and old subjects expressed the identical brain pattern, but the older subjects expressed it to a greater degree while performing more poorly. Two patterns of brain activation corresponded to load dependent processing during the retention delay component of the DIR task, one that was identical in the young and old subjects, and a second that was unique to the old subjects. Older subjects who expressed this second pattern to a greater degree performed more poorly than their peers who expressed it to a lesser degree. Therefore this pattern would not fit the model of compensatory reallocation that requires better performance to accompany unique patterns of brain activity in older adults. This scenario would be consistent with the idea of neural compensation, in that this additional pattern might represent a brain network that is needed by some of the older subjects to maintain performance. Alternatively, this second pattern might be consistent with the dedifferentiation hypothesis. The findings did not support the limited capacity hypotheses of aging.

Recognition of letters of the alphabet for English speaking individuals is a well-rehearsed, familiar and automatic process that is not likely to be negatively influenced by aging (Hay and Jacoby, 1999). It is therefore of interest to examine whether and how each of these three models of cognitive aging (neural compensation, capacity limitation, neural inefficiency) might explain age-related differences in working memory using an identical experimental paradigm but novel stimuli that are not language-based. Indeed, previous research suggested that recruitment of brain regions and networks in working memory varied depending on the nature of the stimuli. For instance, the hippocampus does not appear to be engaged in working memory maintenance tasks that rely on familiar items such as letters of the alphabet (Courtney et al., 1996, 1997; Smith et al., 1996). However, when novel stimuli such as faces are introduced the hippocampus becomes engaged (Haxby et al., 1996; Ranganath, 2006; Ranganath and D'Esposito, 2001).

The current study examined whether age effects on load-dependent brain activations can be identified in working memory for novel non-verbal material in young and old individuals. Specifically, we evaluated which of the models of cognitive aging (neural compensation, capacity limitations, neural inefficiency) provided the best fit for the brain imaging and behavioral data in the context of specific phases (set presentation, retention delay, probe) of working memory. Lastly, the results were compared to previous work (Zarahn et al., 2007) to evaluate similarities and differences with respect

to the effect of aging on load-dependent brain activations during working memory for letters (familiar) and non-verbal (novel) material.

To accomplish these goals we used a DIR paradigm identical to that in our previous study but substituted the letter stimuli with novel non-verbal computer-generated closed-curve shapes (Holtzer et al., 2004). Additionally, to facilitate comparisons with our previous work we replicated the analytic approach using sequential latent root testing in the context of canonical variates analysis (CVA) for imaging data with spatially correlated errors (Worsley et al., 1997). The methodological advantages of this application of CVA, which is often referred to as Multivariate Linear Modeling (MLM) as well as the limitations that are inherent in other approaches that aim to compare brain activations between groups were previously discussed (Zarahn et al., 2007). Most importantly, this approach can directly test whether young and old subjects activate the same or different brain patterns during task performance.

2. Results

2.1. DIR: behavior analysis—reaction time (Huynh–Feldt corrected)

The DIR task (see Fig. 4 for schematic presentation and experimental procedure for details) is a nonverbal adaptation of the Sternberg task (Rypma et al., 1999; Sternberg, 1966, 1969). Each trial consists of set presentation, retention delay and probe. Stimulus set size ranged from 1 to 3 shapes and was varied pseudo-randomly across trials via a random-without-replacement scheme. The non-verbal stimuli consisted of 450 different computer-generated closed-curve shapes. There were three experimental blocks each consisting of 10 trials with 5 true positive and 5 true negative probes per set size yielding a total of 30 trials per block and 90 trials for the entire task per participant. The participants indicated whether the probe item was included in the initial set by a differential button press (left hand=no, right hand=yes). The participants were instructed to respond as quickly as possible.

Repeated measures ANOVA examined the effect of group (between subject factor) and set size (3-level within subjects
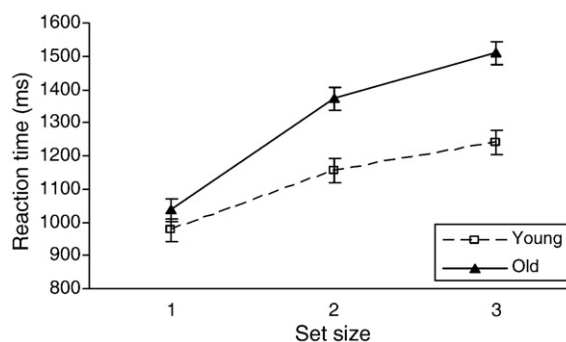

Fig. 1 – The relationship of reaction time (ms) to shapes set size plotted separately for young (n=25) and old (n=25) subjects. The lines are least-squares fits. Error bars are estimated standard errors, and so reflect sample sizes as well as standard deviations.

Fig. 2 – The relationship of *dl* to shapes set size plotted separately for young (*n*=25) and old (*n*=25) subjects. The lines are least-squares fits. Error bars are estimated standard errors, and so reflect sample sizes as well as standard deviations.
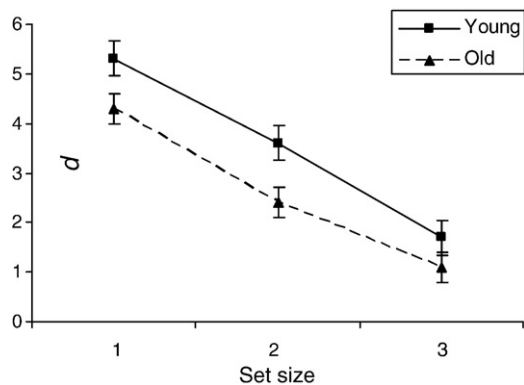
variable) on median reaction time. Main effects were significant for age $F(1, 48)=14.56$, $p<.001$ and set size $F(2, 96)=138.27$, $p<.001$. The two-way interaction of set size and age was statistically significant $F(2, 96)=9.632$, $p<.001$. Pertinent to the MLM analyses, RT slopes were significantly larger in the old (ms/shapes M=208.78, SD=95) compared to the young participants (ms/shapes M=129, SD=67), $t(48)=-3.43$, $p=.001$ (two-tailed, see Fig. 1).

2.2.　DIR: behavioral analysis—discriminability (dL)

Repeated measures ANOVA examined the effect of group (between subject factor) and set size (3-level within subjects variable) on discriminability. Main effects were significant for age $F(1, 48)=7.647$, $p<.005$ and set size $F(2, 96)=136.56$, $p<.001$. The two-way interaction of size and age was not statistically significant $F(2, 96)=1.272$, $p=.265$. dL slopes were not significantly different between the old (M=−1.6, SD=.60) and young participants (M=−1.8, SD=.87), $t(48)=-1.15$, $p=.254$ (two-tailed, see Fig. 2).

2.3.　DIR task brain activity in young and old participants

MLM analyses revealed that at least one latent spatial pattern (possible outcomes were 0, 1, or 2 patterns) was detected in the set presentation, retention delay and probe phases of the DIR task (see Table 1).

　　Two latent spatial patterns were detected in load dependent processing during retention delay. The presence of the

second latent pattern potentially indicates non-identical brain activation patterns in young and old individuals. Analyses in the set presentation and probe phases identified only one pattern, indicating that age-specific brain activation patterns were not present in these phases of the DIR task. The first and second latent activation patterns and the corresponding predicted and observed expressions for all three effects of interest are shown in Fig. 3(a–d).

　　Tabular description of the latent spatial patterns is summarized in Table 2. This information is presented for descriptive purposes.

2.4.　Capacity limitations and neural inefficiency

2.4.1.　Capacity limitations
Age-related differences in the magnitude of expressions of the first latent patterns were evaluated in the stimulus set presentation and probe phases of the DIR task. Group comparisons were not examined in retention delay due to the presence of the second latent pattern, in this phase, which was inconsistent with a capacity limitations model. The magnitude of expressions of the first latent patterns was significantly lower in the old compared to the young subjects during probe presentation $t(48)=-2.329$, $p=0.024$ (two-tailed, see Fig. 3d). It is noteworthy that the expression values are negative and the displayed areas are the negatively weighted areas of the spatial pattern. Consequently, negative expression of the negatively weighed areas yields positive activation and thus reduced activation in the old compared to the young subjects. Age-related differences in the magnitude of the expression of the latent pattern during set presentation were not significant ($p>0.05$, see Fig. 3a). Hence, these findings are consistent with the concept of capacity limitations in aging during the processing of the probe.

2.4.2.　Neural inefficiency
Neural inefficiency was computed by dividing the observed expressions of each of the first latent patterns in the stimulus set presentation and probe phases with their reciprocal performance values (i.e., RT and dL slopes). Hence, two indices of neural inefficiency were computed. Neural inefficiency was not computed for retention delay because he brain activation patterns of young and elders for this effect of interest were non-identical, and hence cannot be explained with a pure neural inefficiency model. Between group analyses (t-tests for independent samples) with age as the independent variable and the two indices of neural inefficiency as the dependent measures were not significant ($p>0.05$) suggesting that the inefficiency hypothesis was not supported in these data.

| **Table 1 – Sequential latent root testing results for contrasts representing young and elder brain activity associated with visual WM task**					
2-dimensional effects of interest	Test for at least one component		Test for two components		Inferred number of spatial patterns at $\alpha=0.05$
	F(1089, 52448)	p	F(544, 35030)	p	
Load-dependent processing during memory set presentation	5.22	<.0001	.84	1.00	1
Load-dependent processing during retention delay	1.41	<.0001	1.18	.003	2
Load-dependent processing during probe presentation	2.76	<.0001	.95	.81	1
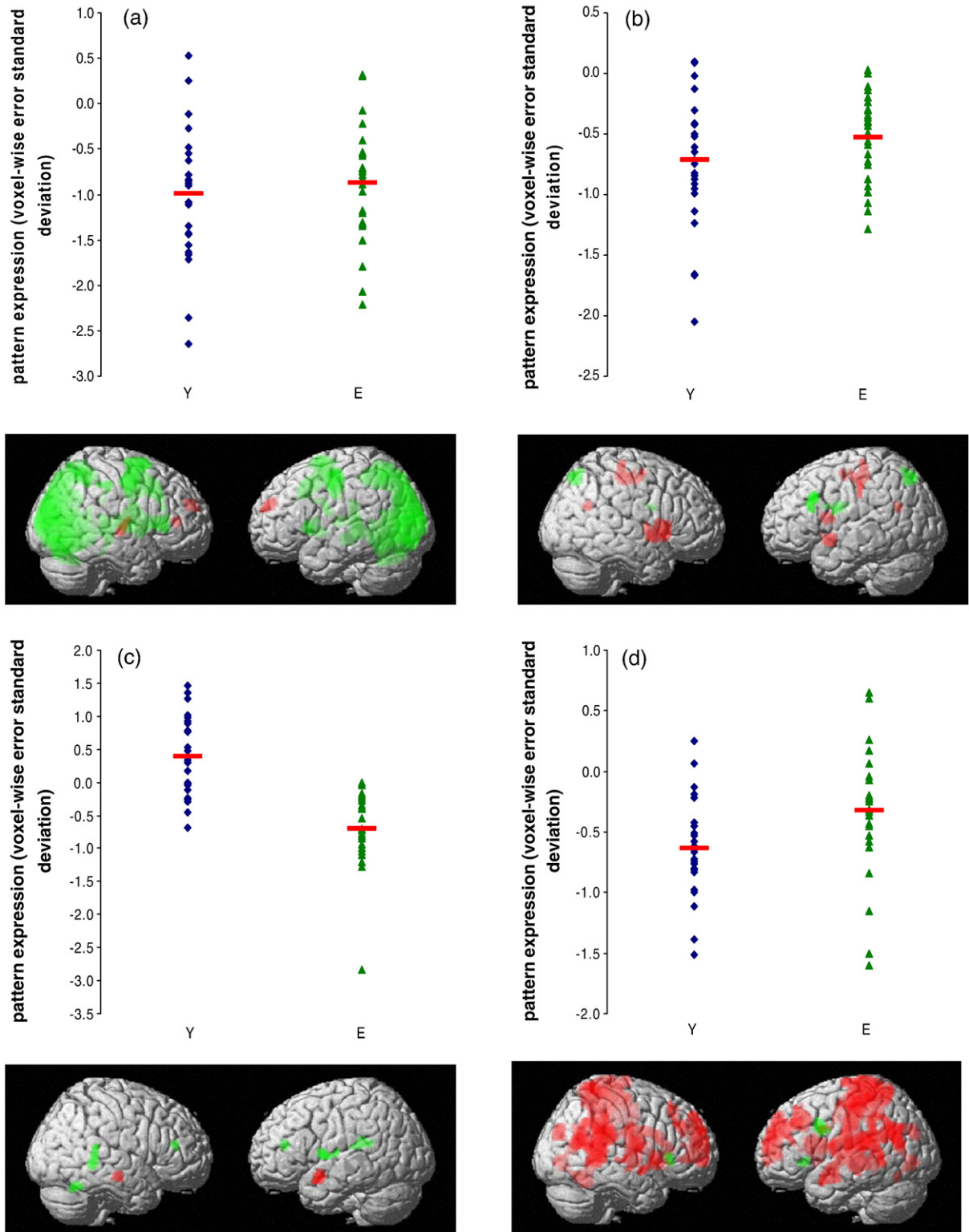
Fig. 3 – Scaled latent spatial patterns (red: positive voxel weights, green: negative voxel weights) and observed (young ♦, old ▲) and predicted (—) subject-wise expressions of the corresponding pattern. Patterns shown are the first latent spatial pattern unless indicated otherwise. (a) slope of fMRI response amplitude vs. set size associated with memory set presentation, (b) slope associated with retention delay, (c) second latent spatial pattern of slope associated with retention delay, (d) slope associated with probe presentation.

Table 2 – Brain regions associated with the first and second brain patterns during set presentation, retention delay and probe presentation of the DIR task

Talairach coordinates				t value	Structure		BA
1st pattern: Load-dependent processing during memory set presentation							
Positive weights	−10	53	26	**4.24**	Left	Superior frontal gyrus	9
	45	−12	4	**4.19**	Right	Insula	13
	14	36	9	**3.65**	Right	Anterior cingulate	32
Negative weights	−10	−81	11	**17.51**	Left	Cuneus	17
	−10	−70	0	17.08	Left	Lingual gyrus	18
	14	−77	17	14.96	Right	Cuneus	
	−36	−9	47	**7.07**	Left	Precentral gyrus	6
	−51	−7	45	3.56	Left	Precentral gyrus	4
	−24	3	57	3.44	Left	Sub-gyral	6
	−26	14	3	**4.99**	Left	Lentiform nucleus	
	−16	8	7	4.16	Left	Lentiform nucleus	
	−40	12	3	3.68	Left	Insula	13
	−10	4	0	**4.24**	Left	Lentiform nucleus	
	40	−25	42	**4.09**	Right	Postcentral gyrus	2
	46	−33	42	3.31	Right	Inferior parietal lobule	40
	−22	−3	19	**3.64**	Left	Lentiform nucleus	
	6	−30	29	**3.61**	Right	Cingulate gyrus	23
1st pattern: Load-dependent processing during retention delay							
Positive weights	20	14	−1	**6.04**	Right	Lentiform nucleus	
	24	2	−2	5.26	Right	Lentiform nucleus	
	2	−21	49	**4.9**	Right	Medial frontal gyrus	6
	2	−22	60	3.86	Right	Medial frontal gyrus	6
	8	−3	54	3.55	Right	Medial frontal gyrus	6
	−18	8	11	**4.17**	Left	Lentiform nucleus	
	−24	6	−5	4.15	Left	Lentiform nucleus	
	−32	−21	40	3.69	Left	Postcentral gyrus	3
	8	−55	25	**3.66**	Right	Posterior cingulate	31
	−6	−57	25	3.4	Left	Posterior cingulate	31
Negative weights	0	−67	53	**4.34**	Left	Precuneus	7
	−44	23	28	**4.19**	Left	Middle frontal gyrus	9
	−28	−3	22	**4**	Left	Insula	13
	−38	1	20	3.95	Left	Insula	13
	−4	−1	24	**3.93**	Left	Cingulate gyrus	24
	−8	9	22	3.6	Left	Anterior cingulate	33
	6	3	22	3.52	Right	Cingulate gyrus	24
2nd pattern: Load-dependent processing during retention delay							
Positive weights	−20	1	−14	**4.81**	Left	Parahippocampal gyrus	34
	22	−18	−11	**4.2**	Right	Parahippocampal gyrus	35
Negative weights	24	−41	0	**4.78**	Right	Sub-gyral	
	34	−38	13	3.85	Right	Transverse temporal gyrus	41
	0	38	13	**4.41**	Left	Anterior cingulate	32
	−40	0	7	**3.88**	Left	Insula	13
	−38	−13	10	3.3	Left	Insula	13
	−24	−42	21	**3.87**	Left	Cingulate gyrus	31
	−26	−32	16	3.53	Left	Insula	13
1st pattern: Load-dependent processing during probe presentation							
Positive weights	−32	−25	45	**6.72**	Left	Postcentral gyrus	3
	−61	−28	18	6.42	Left	Postcentral gyrus	40
	−34	−34	61	6.26	Left	Postcentral gyrus	3
	−16	29	35	**6.04**	Left	Medial frontal gyrus	6
	2	53	14	**5.76**	Right	Medial frontal gyrus	10
	2	61	6	4.71	Right	Medial frontal gyrus	10
	0	−78	1	**5.8**	Left	Lingual gyrus	18
	0	−65	14	4.96	Left	Posterior cingulate	31
	−20	18	14	**5.79**	Left	Caudate	
	−24	8	12	4.87	Left	Lentiform nucleus	
	24	13	−2	**5.3**	Right	Lentiform nucleus	
	10	11	−4	3.75	Right	Caudate	
	18	21	−4	3.53	Right	Lentiform nucleus	

Table 2 *(continued)*

Talairach coordinates				t value	Structure		BA
1st pattern: Load-dependent processing during probe presentation							
Positive weights	6	−47	1	5.12	Right	Cerebellum: culmen	
	−10	−43	−8	3.3	Left	Parahippocampal gyrus	30
	8	−78	30	5.09	Right	Cuneus	19
	16	−74	26	3.89	Right	Cuneus	18
	24	54	−4	4.42	Right	Superior frontal gyrus	10
	53	12	−2	4.36	Right	Superior temporal gyrus	22
	53	0	−8	3.81	Right	Superior temporal gyrus	38
	−22	−39	2	4.14	Left	Parahippocampal gyrus	30
	−26	−43	−3	3.63	Left	Parahippocampal gyrus	19
	22	38	28	3.85	Right	Superior frontal gyrus	9
	30	33	30	3.44	Right	Superior frontal gyrus	9
	26	27	45	3.4	Right	Middle frontal gyrus	8
Negative weights	32	26	0	4.89	Right	Inferior frontal gyrus	47
	−33	24	0	4.12	Left	Inferior frontal gyrus	47
	−37	6	30	4.09	Left	Inferior frontal gyrus	9

2.5. Neural compensation

As summarized in Table 1, MLM analyses identified one latent activation patterns in two effects of interest in young and old individuals during the set presentation and probe phases of the DIR task. These findings indicate that the same spatial patterns are activated in both young and old subjects in the same direction. As shown in Fig. 3(a, b, d) these corresponding first latent patterns had the same sign of expression in both age groups. These findings indicate no qualitative age-related changes in activation in the context of set presentation and probe presentation of the DIR task. In contrast, analyses revealed second latent pattern (i.e., non-identical activations) in the load dependent processing during retention delay of the DIR task. This corresponding second latent pattern had the opposite sign of expression in the young and old subjects (see Fig. 3c). The second activation pattern during retention delay was significantly different than zero in load-dependent processing for the old (M=−.696, SD=.57), t(24)=−6.03, p<.001 (two-tailed) and young participants (M=.393, SD=.59), t(24)=3.31, p=.003 (two-tailed). As previously discussed, the presence of age-specific brain activation patterns is consistent with the neural compensation model. It is noteworthy that the second latent pattern identified during retention delay did not correlate with behavioral performance within the old sample (data not shown).

3. Discussion

The current study examined whether age-specific brain activations were associated with working memory for novel non-verbal material. The methodological approach afforded an examination of three separate phases of a working memory task–memory set presentation, retention delay, and probe presentation-that differently emphasize memory encoding, rehearsal and/or decay, and retrieval processes, respectively (Habeck et al., 2005). Within each phase, brain activation in the form of BOLD signal change was assessed in relation to memory load with the slope of the fMRI activation amplitude with respect to memory set-size. Behavioral data analysis indicated that consistent with a large corpus of research aging

had a negative effect on working memory performance. Old individuals, on average, were less accurate, slower and showed greater memory load-dependent decrements in speed of processing compared to their young counterparts. The discussion concentrates on interpreting the brain imaging results. We consider below how each of the three cognitive models of interest (capacity limitation, inefficiency, and neural compensation) fared in explaining age-related changes in spatial patterns of BOLD signal change associated with set presentation, retention delay and probe phases of working memory. We also discuss the similarities and differences in the effect of aging on working memory for non-verbal and verbal material.

3.1. Capacity limitation

Significant spatial patterns in the BOLD set size slope (load-dependent) data were identified during memory set and probe presentations. These two patterns were structured identically in young and old participants, but the extent of expression of the network differed with age only in one case. Activation in load dependent processing during the probe phase was significantly lower in the old compared to the young participants indicating a reduction in brain resources related to increased demands on memory retrieval processes, especially memory search. Of the three models of age-related functional change described previously, capacity limitation and neural inefficiency are both consistent with a single brain activation pattern shared by young and old individuals. However, only the limited capacity model is consistent with reduced brain activation and poorer performance in aging. That is, in this study in the context of the probe phase, aging seems to be associated with reduced neural capacity for memory search, especially as memory set size is increased.

It is noteworthy that, behaviorally, the reaction time slope with respect to set-size was significantly larger in the old compared to the young group. Therefore, the age-related increase in search time per memory item is consistent with the load-dependent reduction in neurophysiologic activation observed in the old participants. Examination of cortical areas that were activated during the probe presentation in the current study (see Table 2) suggests high involvement of

widespread prefrontal areas in the context of the spatial pattern shared by old and young subjects. How might reduced load-related activity in the prefrontal cortex in old individuals contribute to age-related increase in memory search time and thus slower reaction in correctly identifying novel visual material? The prefrontal cortex contributes to working memory by modulating activities in posterior areas (Gazzaley et al., 2005; Mechelli et al., 2004) and by facilitating stimulus selection (Curtis and D'Esposito, 2003; Passingham and Sakai, 2004). These frontal areas also form functional networks with the basal ganglia that have been related to attention and executive function, which become impaired in old age (Buckner et al., 2006; Craik and Byrd, 1982; McDowd and Shaw, 2000; Verhaeghen and Cerella, 2002; Verhaeghen et al., 2003). As the memory set-size increases, the probe item must be retained longer, compared to more memory set items, and the results of the search must be maintained across repeated comparisons, even as the comparison items from the memory set-are switched in and out. All of these processes require either the executive functions of the frontal lobes (e.g., item-switching and maintaining early results against interference from later comparisons) or parietal functions modulated by the frontal lobes (e.g., the probe/item comparison itself). Decrease in the frontal component of the probe network could reasonably be expected to slow completion of these processes on an item-by-item basis, leading to the observed behavioral effects. These findings are consistent with a study demonstrating that, in the context of working memory, when cognitive demands increased beyond threshold in old compared to young samples the former showed reduced activations in pre-frontal regions along with poorer behavioral performance (Mattay et al., 2006). Age differences in capacity limitations were not observed previously using the same DIR task with letters (Zarahn et al., 2007). We suggest that because letters are extremely well rehearsed stimuli (for English speaking individuals) less attention and executive processes had to be recruited for task execution. Consequently, upper bounds for brain activation during the probe were not sufficiently increased to detect age differences.

3.2. Neural inefficiency

In the context of aging, the neural inefficiency model postulates that older adults' increased utilization of brain function be associated with poorer or equivalent behavioral outcome in comparison to young individuals. To support the neural inefficiency model brain and behavioral data should meet two criteria. First, young and old participants should use the same brain networks to accomplish a task or mental operation. Second, expression of the brain network in aging should increase relative to young participants, while performance remains constant or degrades. The data in the current study did not support this notion. While young and old participants shared single brain load-dependent and independent brain networks during stimulus presentation and probe presentation, expression of those networks was either unchanged by aging, or decreased in expression while behavior degraded, as discussed above. Because a number of studies showed that visual areas activate less in older adults compared to youngs (Cabeza et al., 2004; Iidaka et al., 2001;

Madden et al., 1996) it is not surprising that the neural inefficiency hypothesis was not supported by data specific to the memory set presentation phase of the DIR task either.

3.3. Neural compensation

Neural compensation predicts that age-specific brain activation pattern be present in old individuals to support performance (Stern et al., 2005; Stern, 2006). In this study an age-specific brain activation pattern was identified in the load dependent BOLD signal during the retention delay. This pattern occurred in addition to a more dominant pattern shared between young and old participants. Consistent with neural compensation, recruitment of brain networks to support the active maintenance of novel stimuli differed between the young and old participants as a function of increased number of items to be rehearsed. Previously, a second age-specific activation pattern during retention delay was reported for the rehearsal of letters during load-dependent processing (Zarahn et al., 2007). Hence, within the context of the DIR task there is converging evidence in support of neural compensation as a model explaining age-related effects on working memory when both familiar and novel items are rehearsed. Nonetheless, we acknowledge that, although not required by neural compensation theory, we did not find a significant association between the age-related activation pattern and behavioral performance. As such, our interpretation of the specific age-related brain activation during retention delay is admittedly speculative. We also recognize that the de-differentiation hypothesis can theoretically account for the second age-related brain activation pattern during retention delay as this pattern may represent decreased functional integration between brain regions recruited for task performance. Future studies should specifically address the issue of whether age specific brain activations that are not associated with improved cognitive performance are there to support existing function or merely represent dedifferentiated neural networks.

Medial temporal and hippocampal areas are activated in maintenance of novel visual stimuli (Ranganath and D'Esposito, 2001; Ranganath and Blumenfeld, 2005; Stern et al., 2001). Consistent with these previous findings, examination of cortical areas that were activated during retention delay in the second latent patterns (see Table 2) suggests high, though not exclusive, involvement of hippocampal and medial temporal areas. These findings suggest that the recruitment of brain networks that have been identified as critical for the maintenance of novel material is age-dependent. It is important to note that the second spatial latent patterns during retention delay were different than zero in both the young and old groups but in the opposite direction. This is consistent with the notion of age-related re-organization of brain networks that appears to facilitate performance as suggested by the neural compensation hypothesis. While beyond the scope of the present paper we aimed to qualitatively address the implications of the second latent pattern identified during retention. This network represents regions that significantly differed in their load related activity between the two groups. Whereas, as a whole, the young group expressed this network in the positive direction the elder group expressed the network in the negative direction. The most significant regions

expressed in the positive direction were the right and left parahippocampal gyri. This finding may suggest that as the quantity of information to be retained increases, the elder participants demonstrated decreasing activity in the right and left parahippocampal gyri while activity increased in the young subjects in these areas. Investigation into the actual data that went in to the MLM analyses revealed a weak response for all load-dependent conditions for the young group but a strong decreasing response with increasing load in the elders. This suggests that the finding concerning the parahippocampal gyri is more specific to the elder group. Contributions to the second network that were in the negative direction included the left anterior cingulate and insula, where load-dependent activity decreased in the young but increased in the elder group. Further investigation demonstrated that activity in the left anterior cingulate and insula (within this network) was high for the elder group, but with minimal load effect, while there was a marked decrease with increasing load in the young group.

The limitations of this study should be considered. The samples were not randomly selected and consequently may not be considered representative of the population. Nonetheless, the number of subjects was relatively large for a single imaging study and the old and young subjects were carefully matched on demographic variables and estimated level of intellectual function. All subjects were in good health and free of dementia (McKhann et al., 1984) and mild cognitive impairment (Petersen et al., 1999). However, it has been established that Alzheimer's dementia pathology exists in cognitively normal older adults (Snowdon, 2003). Hence, the absence of an independent index of brain pathology in the current study is a limitation that should be addressed in future research.

In summary: the current study was designed to examine whether three competing models of cognitive aging were supported vis-à-vis working memory for novel visual material. Support for capacity limitation and neural compensation was process specific and evident in the probe presentation and retention delay phases of the DIR task, respectively. Of note is that the inefficiency model was not supported by the data in this study. The process specific support for the theories we examined is consistent with a large corpus of research showing that the substrates underlying the encoding, retention and probe phases are different. That is, cognitive aging theories can be specific to the neural networks/regions underlying the different phases of working memory. Delineating how these theories work in concert can increase knowledge of age-related effects on working memory.

4. Experimental procedures

4.1. Participants

Twenty-five older adults (n females=13), ages 65–84 years, and 25 younger adults (n females=13), ages 19–34 years, (all right-handed as determined by the Edinburgh Handedness Questionnaire) participated in the current study. The participants were community residents who were recruited from newspaper advertising and senior centers. All the participants were determined to be in good health and appropriate for this study on the basis of clinical interviews, structured questionnaires, medical examination and relevant structural imaging data. Specifically, the following served as exclusion criteria: uncontrolled high blood pressure (systolic blood pressure≥180 mmHg; or diastolic blood pressure ≥105 mmHg on two measures), current or recent (last 5 years) non-skin neoplastic disease or melanoma, active hepatic disease or primary renal disease requiring dialysis, primary untreated endocrine diseases, e.g., Cushing's disease or primary hypothalamic failure or insulin dependent diabetes (Type I or II), HIV infection, any history of psychosis, current or recent (past 5 years) Major Depressive Disorder, Bipolar Disorder, or Anxiety Disorder, history of ECT, current or recent (within past 12 months) alcohol or substance abuse or dependence, recent use (past month) of recreational drugs, brain disorders such as stroke, tumor, infection, epilepsy, multiple sclerosis, degenerative diseases, head injury (LOC>5 min), diagnosed learning disability, dyslexia, or ADHD, and mental retardation. In addition, any use of medications that target the central nervous system (e.g., neuroleptics, anticonvulsants, antidepressants, benzodiazepines) within the last month served as exclusion criteria as well. The old and young samples were comparable in terms of education [old: M(SD)years of education=15.6(3.0); young=14.92(2.3)] and estimated verbal IQ using the National Adult Reading Test [NART; (Nelson and Willison, 1991)]; old M(SD)standard IQ score=118(6.5); young M(SD)standard IQ score=114(6.6)]. The Dementia Rating Scale (DRS; (Mattis, 1988)) was used to rule out dementia and provide an estimate of current cognitive status. DRS performance of the old [M (SD) total score=139(3.9)] and young [M(SD) total score=141 (2.9)] was comparable and well above the suggested dementia cut score (123). Exclusionary criteria were medical and psychological history that might affect cognition (e.g., brain trauma, neurodegenerative diseases, and depression), medications known to have an effect on test performance, and history of learning disability. All participants provided informed consent, and all were compensated for their participation.

4.2. Behavioral task

The DIR task (see Fig. 4 for schematic presentation) is a nonverbal adaptation of the Sternberg task (Rypma et al., 1999; Sternberg, 1966, 1969).

Task parameters and training procedures were identical to those reported in our previous studies (Zarahn et al., 2007, 2005). In brief, each trial of the DIR task consisted of set presentation, retention delay and probe presentation. Based on pilot studies stimulus set size ranged from 1 to 3 shapes and was varied pseudo-randomly across trials via a random-without-replacement scheme. The non-verbal stimuli consisted of 450 different computer-generated closed-curve shapes. Each shape was presented only once in the testing conditions of each participant. This presented an advantage in that both the novelty and appearance of the shapes maximized visual demands and limited the extent of phonologic processing (for further details see (Holtzer et al., 2004). There were three experimental blocks each consisting of 10 trials with 5 true positive and 5 true negative probes per set size yielding a total of 30 trials per block and 90 trials for the entire task per participant. Blank trials (presentation of a blank
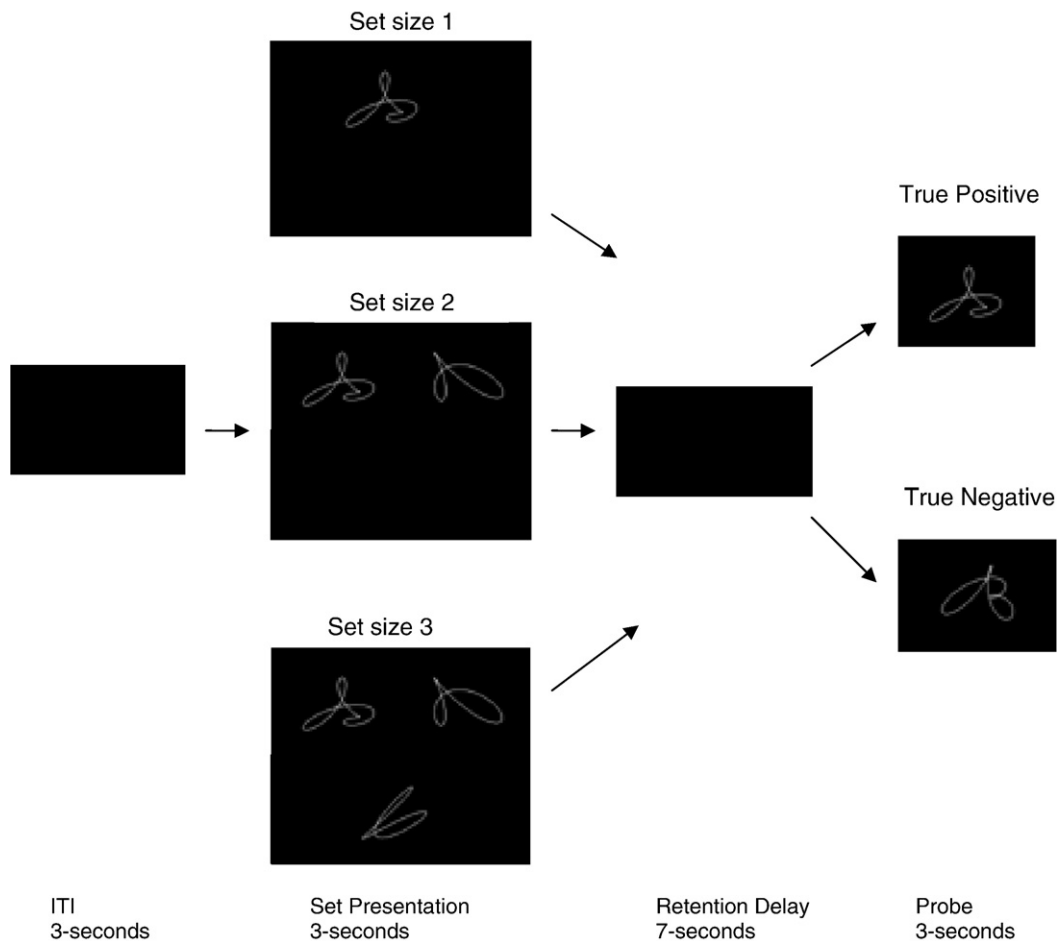
Fig. 4 – Schematic presentation of the DIR task. *Shapes are not drawn to scale.

screen for two seconds, requiring no behavioral output) were pseudo-randomly interspersed between delayed item recognition trials to both provide a baseline condition for positive control purposes and reduce the likelihood of neurophysiological responses predictive of the beginning of trials. The pseudo-randomization of these blank trials was via a random-without-replacement scheme (thus, more than one blank trial could occur sequentially, leading to an effectively jittered inter-trial interval), with a total of 70 blank trials per block. The participants indicated whether the probe item was included in the initial set by a differential button press (left hand=no, right hand=yes). The participants were instructed to respond as quickly as possible.

4.3. fMRI data acquisition

During the performance of each block of the delayed item recognition task, 207 T2*-weighted images, which are BOLD images (Kwong et al., 1992; Ogawa et al., 1993), were acquired with an Intera 1.5 T Phillips MR scanner equipped with a standard quadrature head coil, using a gradient echo echo-planar (GE-EPI) sequence [TE/TR=50 ms/3000 ms; flip angle=90 degrees; 64×64 matrix, in-plane voxel size=3.124 mm×3.124 mm; slice thickness=8 mm (no gap); 17 trans-axial slices per volume]. Four additional GE-EPI excitations were performed before the

task began, at the beginning of each run, to allow transverse magnetization immediately after radio-frequency excitation to approach its steady-state value; the image data for these excitations were discarded. A T2-weighted, fast spin echo image was also acquired from each subject for spatial normalization purposes [TE/TR=100 ms/2000 ms; flip angle=90°, 256×256 matrix; in-plane voxel size=.781 mm×.781 mm; slice thickness=8 mm (no gap); 17 trans-axial slices per volume].

Task stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Subjects viewed the screen via a mirror system located in the head coil. Responses were made on a LUMItouch response system (Photon Control Company). Task onset was electronically synchronized with the MRI acquisition computer. Task administration and data collection (RT and accuracy) were controlled using PsyScope (Cohen et al., 1993).

4.4. Behavioral data analysis

Repeated measures General Linear Model (GLM) assessed the effect of group (young vs. old) stimulus set size (1–3) and group×set size interaction on behavioral performance on the DIR task. Dependent measures were discriminability (dL; Snodgrass and Corwin, 1988) and median reaction time. Analyses collapsed over probe type. Slopes (across set size)

for RT and discriminability were calculated using linear regression analyses for each participant and then subjected to between group analyses.

4.5. fMRI data pre-processing

All image pre-processing and analysis were implemented using the SPM99 program (Wellcome Department of Cognitive Neurology) and other code written in MATLAB 5.3 (Mathworks, Natick MA). The following steps were implemented for each subject's GE-EPI dataset: data were temporally shifted to correct for the order of slice acquisition, using the first slice acquired in the TR as the reference. All GE-EPI images were realigned to the first volume of the first session. The T2-weighted (structural) image was then co-registered to the first EPI volume using the mutual information co-registration algorithm implemented in SPM99. This co-registered high-resolution image was then used to determine parameters ($7 \times 8 \times 7$ non-linear basis functions) for transformation into a Talairach standard space (Talairach and Tournoux, 1988) defined by the Montreal Neurologic Institute (MNI) template brain supplied with SPM99. This transformation was then applied to the GE-EPI data, which were re-sliced using sinc-interpolation to 2 mm×2 mm×2 mm. All statistical analysis was implemented using the SPM99 program and other code written in MATLAB5.3 (Mathworks, Natick MA). The fMRI data analysis comprised two levels of voxel-wise GLMs (Friston et al., 2005).

4.6. fMRI time-series modeling

At the first-level GLM, the GE-EPI time-series were modeled with regressors that represented the expected BOLD fMRI response (relative to the blank intervals) to the three DIR trial components of memory set presentation, retention delay, and probe presentation, separately for set size (1–3) and probe type (true positive/true negative). DIR trials without motor responses from the subject during the probe period were modeled separately, and were not included at the second-level GLM analysis. Two rectangular functions (and hence, two regressors) were used for the trial components of memory set presentation and probe presentation: one modeling a relatively brief (400 ms) neural response at the beginning of that trial component, and another modeling a neural response lasting throughout that entire component (3000 ms); a single rectangular function of 7000 ms duration was used for the retention delay. Contrasts were estimated for each load level, trial phase and probe type and were carried forward to the second-level group analyses.

The second-level, voxel-wise GLM that modeled the 18 repeated measures per subject per voxel, with a design matrix representing one between-subjects factor (age) and three repeated measure factors (trial component, set size, and probe type). Contrasts from this second level group analysis were calculated and subjected to the multivariate sequential latent root testing. The covariance matrix of this repeated measures second-level analysis was estimated at each voxel and spatially averaged to approximate the known observation error covariance matrix ($\sum$ in Worsley et al., 1997) used in the multivariate analyses.

4.7. Sequential latent root testing

In this version of CVA, often referred to as Multivariate Linear Modeling (MLM; Worsley et al., 1997), a singular value decomposition (SVD) was performed on the spatially whitened effects of interest to identify covariance patterns. Sequential latent root testing was subsequently used to assess the number of significant latent spatial patterns (with α controlled at a 0.05). The effects of interest for this study were the load-dependent working memory neural responses during the different phases of the experiment. These comprised three combinations of slopes of subject specific contrast maps with respect to set size (1–3) during the three trial components, each of which was computed separately for the old and young participants. Effects of interest were averaged over the probe type factor, thus making the effective number of trials per subject per set size equal to 30. Significant latent spatial patterns are presented for descriptive purposes scaled by their singular values (analogous to SPM{t} images (Worsley et al., 1997), thresholded for descriptive purposes at a t value corresponding to $p < 0.001$ uncorrected for multiple comparisons and a cluster size of 50 voxels. This threshold does not control map-wise statistical significance at $\alpha = 0.05$ (Friston et al., 1996; Worsley, 1994), but does provide a condensed description of the significant latent spatial patterns. Once identified, the spatial patterns were multiplied voxel by voxel with the subject specific contrast maps that were entered into the MLM analysis, and then summed to calculate each subject network expressions (see Fig. 5 for graphic illustration). Possible outcomes for the MLM analyses are 0, 1, or 2 latent patterns. By design, the first latent pattern is indicative of common activation pattern between groups (old vs. young in this case). In contrast, the second latent pattern, if identified, suggests group differences in brain activation.

The signs of the voxel values in a latent spatial pattern and its corresponding expression across subjects (or groups) are only meaningful in their product (i.e., the signs of each in isolation may be thought of as completely arbitrary). One multiplies a particular latent spatial pattern by its predicted expression to yield the predicted contribution from that latent pattern to the effects of interest (Worsley et al., 1997).
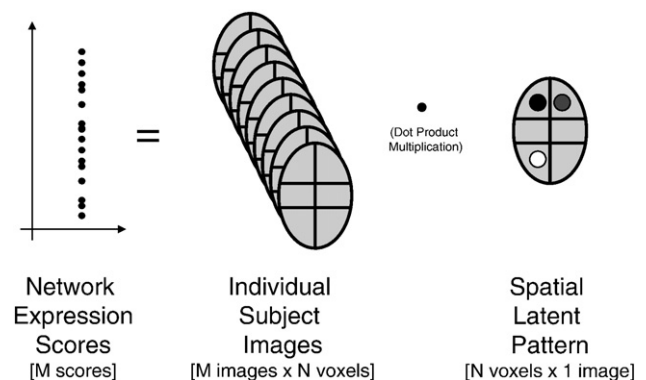

Fig. 5 – Graphic illustration: derivation of network expression scores.

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