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Research Articles

Neural underpinnings of memory encoding and retrieval: Validation of a novel ecologically valid fMRI paradigm

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ABSTRACT

Cognitive impairment is prevalent in affective disorders. Currently, there is a lack of effective treatment options, which is partly due to limited insight into their neural underpinnings and poor transfer to everyday life. Integrating neuroimaging measures in cognition trials to identify neurocircuitry biomarkers is crucial for treatment development. We pooled baseline data from two clinical trials to validate a novel functional magnetic resonance imaging (fMRI) paradigm simulating real-life verbal learning and memory tasks. Healthy participants with no psychiatric history (n = 34) underwent fMRI and an ecologically valid virtual reality-based verbal memory task. During fMRI, they performed an ecologically valid paradigm involving encoding and recognition of a grocery shopping list. Whole-brain analyses assessed task-related activation in key neural networks. Neural underpinnings of memory encoding involved the hippocampus, prefrontal, temporal, occipital, and parietal regions, and caudate. Recognition task activation encompassed a network of frontal, parietal, temporal, and occipital regions. Positive associations were found between encoding-related activity in the inferior temporal gyrus and lateral occipital cortex and the number of correctly recalled grocery items. This study introduces and validates a novel fMRI paradigm for assessing real-life verbal learning and memory abilities. The identified neural underpinnings highlight the involvement of diverse brain regions in encoding and recognition processes that may be implemented in future investigations of the neural correlates of memory impairment and improvement.

1. Introduction

Cognitive impairments across several domains are found in neuropsychiatric disorders. These can be detrimental to patients' daily functioning by rendering day-to-day chores, such as keeping a home clean or remembering a shopping list, unbearable tasks (Millan et al., 2012). Cognitive impairments thereby have a negative impact of patients' quality of life in addition to what is already caused by for example affective and psychotic symptoms. The underlying neurobiological mechanisms of cognitive impairments seen in for example Huntington's and Alzheimer's diseases ultimately can be explained by neurodegeneration (Braak and Braak, 1991), (Labbadia and Morimoto, 2013).

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However, within affective and psychotic disorders, the neurobiological foundations of cognitive impairment are much less understood, which constitutes a substantial obstacle in the development of possible pro-cognitive treatments.

Currently, no evidence-based treatment options for cognitive impairments in affective and psychotic disorders are in clinical use. This is despite immense research interest in novel pro-cognitive treatments over the past decade (McCleery and Nuechterlein, 2019), (Miskowiak and Petersen, 2019). Studies suggest potential benefits of cognitive remediation therapy, though its effect still seem to be varied as a large subgroup of patients experience no benefit from the treatment (Miskowiak et al., 2016a), (Miskowiak et al., 2016b), (Wykes et al., 2011). The limited success in treatment development is a result of several major methodological challenges in cognition intervention trials, including limited insight into the neural underpinnings of cognitive and functional impairment and improvement in affective disorders (Miskowiak et al., 2022a). Based on this, a key recommendation has been to include neuroimaging measures in cognition trials to identify neurocircuitry biomarkers of pro-cognitive effects that can be implemented to evaluate novel interventions targeting cognition and daily functioning (Carter et al., 2011), (Petersen and Miskowiak, 2021). Importantly, proof-of-concept studies validating these neuroimaging measures in healthy populations are initially crucial prior to implementation in cognition trials.

Within affective disorders, patients' performance in attention and executive function are associated with interpersonal and occupational functioning (Cambridge et al., 2018), and verbal memory performance has been related to functional outcome (Solé et al., 2022). Indeed, impairments in verbal memory and executive function seem to be more strongly associated with occupational outcome than symptomatology (Tse et al., 2014). Together, this highlights executive function, verbal learning and memory and their neural underpinnings, as a key research priority to enhance functional recovery in affective disorders. At the neural level, functional magnetic resonance imaging (fMRI) studies of cognition in affective disorders point towards both task-related hypo- and hyper-activation in comparison to healthy populations. This aberrant activity is found especially in the dorsal prefrontal cortex (dPFC), coupled with hyper-activity in the default mode network (DMN), and is believed to be related to cognitive performance (Miskowiak and Petersen, 2019), (Petersen et al., 2022). Here, valid and robust fMRI paradigms are essential in order to further examine these differences of neural activation. Currently, however, the vast majority of extant fMRI paradigms tap into executive function and working memory using e.g. the N-back and Go/No-go tasks, whereas few fMRI studies explore learning and memory difficulties, leaving this domain relatively unexplored despite its large impact on daily life functioning (Miskowiak and Petersen, 2019). In line with this, existing fMRI paradigms of verbal learning and memory typically involve abstract cognitive tasks that do not correspond well to daily life cognitive challenges (Kassel et al., 2016), (Oertel-Knöchel et al., 2014), (Van Eijndhoven et al., 2013). For instance, employing a picture encoding paradigm to classify indoor vs. outdoor scenes followed by a free recall, revealed no task-relevant neural activity within expected cognitive control regions or the hippocampus in patients with affective disorders (Macoveanu et al., 2022), (Petersen et al., 2021). This may be partially attributed to poor alignment between the paradigm and real-life memory tasks, and thus insufficient capturing of neurocircuitry activity underlying patients' daily life memory impairments. Accordingly, a paradigm that employs a memory task of abstract figures, while producing relevant brain activation, does not necessarily simulate everyday memory abilities and hence may not capture potential improvements in patients' abilities in real life following pro-cognitive intervention (Oertel-Knöchel et al., 2014). Together, this highlights the need for novel fMRI paradigms that tap into more ecologically valid verbal learning and memory abilities in affective disorders. In line with this, it is crucial to first validate such a paradigm in a sample of healthy participants to ensure expected task-related activation (Miskowiak et al., 2017). Notably, prior studies of list-learning paradigms in healthy participants have shown task-related activity in areas of the cognitive control network (CCN), hippocampus, and the dorsal prefrontal cortex (dPFC) during encoding and recognition, although activation in the hippocampus during recognition is a point of disagreement (Spaniol et al., 2009), (Stark and Squire, 2000).

In the present study, we aimed to validate a newly designed fMRI paradigm that mimics real-life verbal learning and memory tasks by simulating the process of memorizing and recalling a grocery shopping list. For both the encoding and recognition tasks, we aimed to assess the task validity by examining activation in key task-relevant neural networks, CCN, hippocampus, and dPFC, in healthy individuals.

2. Methods

2.1. Participants and procedure

Participants were between 18 and 55 years, fluent in Danish, and had no current or prior psychiatric illness, which was confirmed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1990). Common exclusion criteria were current substance abuse, dyslexia, pregnancy, previous serious head trauma, neurological disorder, and use of sedative medication. Additionally, participants recruited from the ALTIBRAIN study had to be non-smokers and otherwise somatically healthy, and participants recruited from CAVIR were further free from first-degree family history of psychiatric illness. Further details on recruitment procedures and exclusion criteria for participants are available from ClinicalTrials.gov (ALTIBRAIN: NCT06121206; CAVIR: NCT06038955).

Both studies have been approved by the Danish Research Ethics Committee for the Capital Region of Denmark (CAVIR: H-22004153; ALTIBRAIN: H-22028111) and The Danish Data Protection Agency Capital Region of Denmark (CAVIR: P-2022-411; ALTIBRAIN: P-2022-354). The recommendations of the Declaration of Helsinki were followed, and written consent was obtained for all participants prior to study participation.

2.2. Measures

2.2.1. Demographics and verbal IQ

Baseline demographics (age, sex, and years of education) was collected for all participants. An estimate of verbal intelligence quotient (IQ) was further assessed with the Danish Adult Reading Task (DART) (Nelson and O'Connell, 1978).

2.2.2. Neurocognitive assessment

After inclusion into the study, participants underwent neuropsychological assessment of their memory performance with a virtual reality test of cognitive functioning (Cognition Assessment in Virtual Reality test (CAVIR)), which includes a subtask of memory learning and recognition (Miskowiak et al., 2022b). This subtask is a kitchen scenario, where participants are instructed to select ingredients that they have memorized from a given recipe.

2.2.3. fMRI memory encoding and recognition paradigm

A strategic memory encoding fMRI task using grocery-related words was chosen to simulate the everyday cognitive task of remembering and recalling a grocery list. The paradigm was programmed in E-Prime 2.0 (Psychological Software Tools, Pittsburgh, PA, USA) using an event-related design and presented on a screen, which participants viewed using an angled mirror while lying in the scanner. Prior to the scan, participants were introduced to the task by a short visual presentation along with verbal instructions from a research assistant. Specifically, they were instructed to memorize a grocery shopping list. Once inside the scanner, the participants performed the encoding task, which was

followed by an immediate 2-min free recall test while participants were still lying in the scanner but with no current scanning sequence. After this, the word recognition task was conducted. In the encoding task, participants were shown both words of items commonly found in a grocery store (e.g., 'Pasta') and nonsense words with no meaning (control condition; e.g., 'Klerp'), and instructed to classify whether each word was a grocery item word or a nonsense word by pressing a button with their index or middle finger, respectively (see Fig. 1). Participants were further told to intently remember the grocery item words for which they were encouraged to use mnemonic strategies if they knew any. Thirty-five grocery item words were intermixed with 35 nonsense words, each presented for 1.5 s and separated by interstimulus intervals of 2–4 s (3 s on average), and every new word or nonsense word was preceded by a fixation cross presented for 0.5 s (350 s in total). In the second part of the fMRI paradigm after the free recall test (i.e., recognition task), participants were presented with a mixture of the 35 grocery item words previously shown (i.e., items from their 'grocery list') in addition to 35 new grocery item words not shown before, each presented for 1 s and separated by interstimulus intervals of 2–4 s (3 s in average) and every new or old word was preceded by a fixation cross presented for 0.5 s (325 s in total). Participants were instructed to classify, as quickly and accurately as possible, whether or not they had seen the words in the initial grocery list encoding task.

2.3. fMRI analysis

2.3.1. MRI acquisition

MRI data was collected at the University Hospital of Copenhagen, Denmark using a 3 T SIEMENS Prisma scanner and a 32-channel head-neck coil. Functional BOLD T2*2-weighted images were acquired using a multi-band multi-echo (MB3ME3) sequence with the following parameters: TR = 1300 ms, TEs = 15, 34, and 54 ms, flip angle = 70°, matrix size = 76 × 76, slices per volume = 48, slice thickness = 2.5 mm, voxel size 2.5 mm isotropic, and a 3x multiband acceleration factor. For the encoding task, 270 vol were acquired, and for the recognition task 243 vol

Structural T1-weighted images were also acquired and used to aid the registration of the functional images to a standard MNI template. The T1-weighted images used a standard Magnetization Prepared Rapid Gradient Eccho (MPRAGE) pulse sequence with TR = 2000 ms; TE = 2.58 ms; flip angle = 8°; matrix size = 256 × 256; slices per volume = 224; slice thickness = 0.9 mm, and voxel size 0.9 mm isotropic.

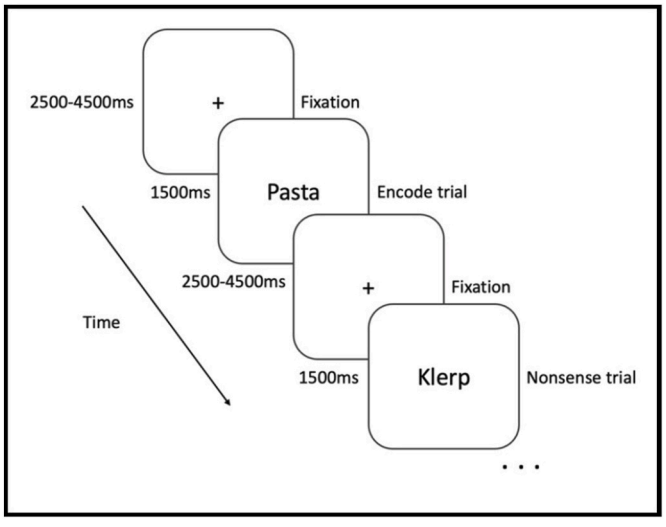


Fig. 1. Supermarket encoding fMRI paradigm. Visual presentation of the two conditions in the encoding fMRI task, showing a grocery item word (i.e., 'Pasta') followed by a fixation cross and then the nonsense word (i.e., 'Klerp').

Fieldmap data was acquired with a gradient echo sequence (TR = 444,s; TE1 = 4.92 ms; TE2 = 7.38 ms; flip angle = 60°) and used to correct for geometric distortions due to B0 inhomogeneities. A fieldmap image was calculated based on the phase difference between two echoes using the FMRIB Software Library (FSL) version 6.0.5.2 (Jenkinson et al., 2012).

2.3.2. fMRI preprocessing

Preprocessing of the fMRI data was performed using the fMRIPrep 23.1.4 software package (Esteban et al., 2019). The pre-processing steps included generation of a BOLD reference volume by aligning and averaging 3 single-band references, estimation of head-motion parameters with respect to the BOLD reference, susceptibility distortion correction using the acquired fieldmap, slice-time correction, combination of the multi-echo times series, co-registration to the T-weighted image, resampling to the standard MNI152NLin6Asym space with 2 × 2 × 2 voxel size, spatial smoothing using a 5 mm full-width-half-maximum gaussian kernel, and high-pass temporal filtering using 100s cut-off. Each subject's registration to the MNI template was visually examined and head movement parameters plots calculated by fMRIprep were inspected to not exceed 0.25 mm mean framewise displacement.

2.3.3. Individual-level fMRI analyses

At the individual-level, we modelled the encoding and recognition tasks in the FMRI Expert Analysis Tool (FEAT) using two events: the grocery item words and nonsense words for the encoding task, and new grocery item words and old grocery item words for the recognition task. The events were convolved with a double-gamma hemodynamic response function. In addition, the subject-level GLM included basic movement regressors ($n = 6$) and temporal derivatives of task regressors to model slice-timing effects. One contrast of interest was calculated for each task: grocery item word vs nonsense word for the encoding task, and old grocery item word vs new grocery item word for the recognition tasks, respectively.

2.3.4. Group-level fMRI analyses

To examine whether the tasks successfully engage task-relevant neurocircuitries, we conducted whole-brain analyses in FEAT with FMRIB's Local Analysis of Mixed Effects (FLAME) as estimation method (Woolrich et al., 2004). The model included the contrasts of interest from the first-level analysis (encoding: grocery item word - nonsense word; recognition: old grocery item word – new grocery item word). Cluster significance was set at $p < 0.05$ and corrected for multiple comparisons using Gaussian Random Field (GRF) theory with a cluster-forming threshold at $Z = 3.1$ ($p = 0.001$). Mean percent signal change was extracted from clusters showing significant task-engagement during memory encoding or recognition and was used for illustrative purposes. To investigate potential effects of age on encoding- and recognition-related task activation, we also conducted a post hoc sensitivity analysis, adding age as a covariate to the analysis above.

2.3.5. Statistical analyses of behavioral data

Data normality distributions were explored using Shapiro-Wilk test of normality. A chi-square goodness-of-fit test was conducted to assess sex distributions within the sample.

For each subject, we calculated a memory score based on the CAVIR recognition subtest to estimate the participants' ability to discriminate between targets (i.e. correct hits) and foils (i.e. false positives). This 'CAVIR verbal memory P_r score', was determined by calculating a hit rate (0.5+number correct targets)/(1+number total targets) and a false alarm rate (0.5+number incorrect foils)/(1+number total foils), and subtracting the false alarm rate from the hit rate (Snodgrass and Corwin, 1988). Similarly, for the inside-scanner behavioral response during the recognition task, we calculated a 'grocery list recognition P_r score' using the same formula as above. For both P_r scores, a higher score constitutes a better memory performance. We used Statistical Package for Social

Sciences (SPSS) version 28 (IBM, Armonk, New York, United States) for statistical analyses with a significance level threshold set at $p \leq .05$ (two-tailed).

2.3.6. Associations between neural activity and memory performance

To identify regions showing a significant association between task-related BOLD response and behavioral performance, we set up whole brain GLM models in FEAT, using the memory performance scores as covariates and the same statistical thresholds as described above. Specifically, for the encoding task, we investigated associations with 1) inside-scanner number of correctly recalled grocery item words and 2) outside-scanner 'CAVIR verbal memory P_r score' as an ecologically valid measure of memory performance in daily life. For the recognition task, we further associated mean percent BOLD signal change with 1) inside-scanner 'grocery list recognition P_r score' in addition to 2) the outside-scanner 'CAVIR verbal memory P_r score'.

3. Results

3.1. Demographic, clinical, and memory performance comparisons

Thirty-four participants were included in this study (demographics and cognitive scores are presented in Table 1). The sample consisted of healthy, young adults (age distribution = 19–31 years old, mean age = 24 [SD = 3]), with both sexes being equally represented (female: 59%, $p = 0.39$). Participants had a median of 13 educational years (IQR = 3) and an average verbal IQ score of 109 (SD = 4) (Table 1).

3.2. Neural underpinnings of memory encoding

Whole-brain analysis of neural response during encoding revealed significant task-related activations in the following frontal areas: left and right superior frontal gyrus (BA = 3, BA = 7); left frontal orbital cortex (BA = 42); medial paracingulate gyrus (BA = 25); medial frontal medial cortex (BA = 11); right frontal pole (BA = 11), as well as temporal areas: right lateral occipital cortex, superior division (BA = 28); left middle temporal gyrus, temporal-occipital part (BA = 37); left and right temporal fusiform cortex, posterior division (BA = 37, BA = 20); right inferior temporal gyrus, temporal-occipital part (BA = 20); right parahippocampal gyrus, anterior division (BA = 20); left middle temporal gyrus, posterior division (BA = 20), and the following occipital areas: left lateral occipital cortex, superior division (BA = 28); medial occipital pole (BA = 17); left occipital fusiform gyrus (BA = 18), and parietal areas: medial precuneus cortex (BA = 26); medial cingulate gyrus, posterior division (BA = 5). Finally, encoding activated the right and left caudate (Fig. 2 illustrates this encoding-related neural network; see Table 2 for cluster size, peak MNI coordinates, and p-values). The results remained similar after adjusting for age (see Supplementary Table S1).

Table 1
Demographic and clinical characteristics in HCs for validation of the paradigm.

	HC ($N = 34$)	p-value
Demographics		
Gender (F/M%)	59%/41%	0.39
Age in years, mean (SD)	24 (3)	
Educational years, median (IQR)	13 (3)	
Verbal IQ, mean (SD)	109 (4)	
HDRS-17, median (IQR)	0 (1)	
YMRS, median (IQR)	0 (1)	
Cognition and functioning		
Grocery list, correctly recalled words, mean (SD)	12 (5)	
Grocery list, false positive words, median (IQR)	1 (2)	
Grocery list recognition P_r score, median (IQR)	0.9 (0.1)	
CAVIR verbal memory P_r score, median (IQR)	0.8 (0.2)	

Notes: HC=Healthy controls. M = mean. SD = standard deviation. IQ = intelligence quotient. HDRS-17 = Hamilton Depression Rating Scale 17-items version. YMRS=Young Mania Rating Scale. FAST=Functioning Assessment Short Test. CAVIR = Cognitive Assessment and training in Virtual Reality. Chi-square for categorical variables, Mann-Whitney for non-parametric data (median (IQR)), independent t-tests for normally distributed data (mean (SD)).

3.3. Neural underpinnings of recognition

For the recognition task, one participant had to be excluded due to excessive movement, thereby yielding a subsample of n = 33 participants. Whole-brain analysis revealed significant activation during recognition in the following frontal areas: left and right frontal pole (BA = 10, BA = 11), left middle frontal gyrus (BA = 44); left paracingulate gyrus (BA = 32), in addition to parietal areas: left angular gyrus (BA = 39); left precuneus cortex (BA=N/A). Recognition also activated the right lateral occipital cortex, superior division (BA = 19); left middle temporal gyrus, posterior division (BA = 20); right insular cortex (BA = 48) (Fig. 3 illustrates the recognition-related neural network; see Table 3 for cluster size, peak MNI coordinates, and p-values). Finally, adjusting for age did not change the results (see Supplementary Table S2).

3.4. Associations between encoding- and recognition-related activity and memory performance

For the encoding task, there were two clusters showing positive correlations between neural response and inside-scanner number of correctly recalled grocery items: left inferior temporal gyrus, temporooccipital part (BA 37; voxel size = 184, peak MNI coordinates: x = −46, y = −54, z = −18, peak Z-value = 4.52, p = 0.00012) and left lateral occipital cortex, superior division (BA 7; voxel size = 121, peak MNI coordinates: x = −30, y = −68, z = 46, peak Z-value = 4.12, p = 0.013). There were no clusters showing significant correlations between brain activity and CAVIR P_r scores for the encoding task nor for the recognition task and both behavioral measures.

4. Discussion

In this study, we examined the validity of a newly designed ecologically valid fMRI 'grocery list' paradigm of verbal learning and memory in healthy individuals. In line with our hypotheses, we found that both encoding and recognition of the grocery list activated dorsal prefrontal and parietal nodes of the CCN, while the hippocampus was selectively engaged in the encoding phase. Accordingly, the number of correctly recalled grocery words was positively associated with encoding-related activation in left inferior temporal gyrus and left lateral occipital cortex.

The neural networks activated by the current grocery list paradigm align closely with previous research on the neural foundations of verbal encoding and recognition, both in general and in patients with affective disorders. Specifically, studies have consistently shown activation across frontal, parietal, and hippocampal areas during memory encoding,

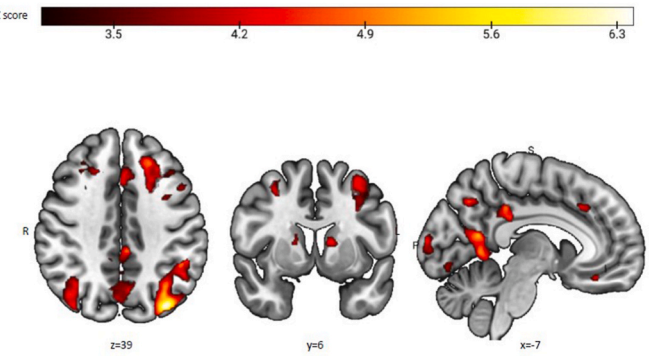


Fig. 2. Task-relevant neural network activated during the supermarket encoding task in healthy participants. Activity is seen in 20 different clusters, as listed in Table 2.

Table 2
Brain activation during the encoding task.

Anatomical region	BA	MNI			No. of voxels	*p*-value
		x	y	z		
L superior frontal gyrus	3	−26	16	62	3423	<0.001
L lateral occipital cortex superior division	19	−34	−80	40	2142	<0.001
M precuneus cortex	26	−4	−58	16	1064	<0.001
M cingulate gyrus posterior division	5	−6	−36	38	1060	<0.001
R superior frontal gyrus	7	20	28	34	1002	<0.001
R lateral occipital cortex superior division	28	46	−70	46	741	<0.001
L middle temporal gyrus, temporal-occipital part	37	−62	−50	−10	488	<0.001
L frontal orbital cortex	42	−30	36	−16	446	<0.001
L temporal fusiform cortex, posterior division	37	−28	−34	−22	421	<0.001
R caudate	3	14	16	−2	305	<0.001
L caudate	N/A	−12	0	16	285	<0.001
M paracingulate gyrus	25	−4	26	36	241	<0.001
R inferior temporal gyrus, temporal-occipital part	20	60	−46	−14	214	<0.001
M occipital pole	17	−10	−98	10	211	<0.001
M frontal medial cortex	11	−6	36	−18	183	0.001
L occipital fusiform gyrus	18	−18	−76	−16	167	0.002
R frontal pole	11	18	38	−20	149	0.005
R temporal fusiform cortex, posterior division	20	34	−26	−24	97	0.038
R parahippocampal gyrus, anterior division	20	32	−10	−34	95	0.041
L middle temporal gyrus, posterior division	20	−56	−16	−14	93	0.045

Abbreviations: BA=Brodmann area; No. = number; M = medial; R = right; L = left.

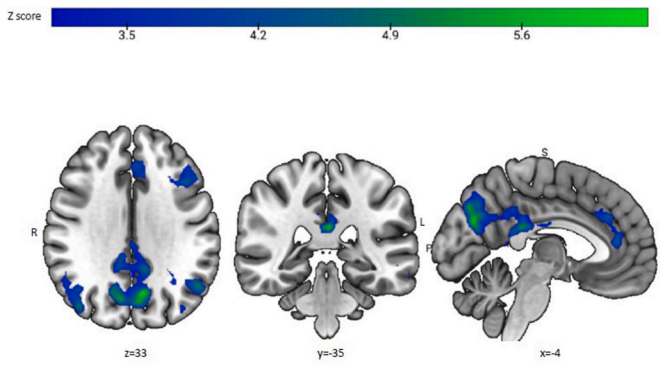


Fig. 3. Task-relevant neural network activated during supermarket recognition task in healthy participants. Activity is seen in nine different clusters, as listed in Table 3.

whereas recognition primarily engages frontal and parietal areas, with only occasional observations of hippocampal activation (Oertel-Knöchel et al., 2014), (Spaniol et al., 2009), (Oertel-Knöchel et al., 2013), (Glahn et al., 2010). In line with this, the PFC has further been associated with executive top-down encoding processes, and the hippocampus and PFC constitute parts of an essential neurocircuitry subserving episodic memory (Reber et al., 2002), (Eichenbaum, 2017). Furthermore, brain activity during grocery list encoding and recognition was generally left lateralized, as would be expected in *verbal* (as opposed to spatial) memory tasks (Grady et al., 1998). This suggests that the two tasks employed in the grocery list paradigm engage both verbal encoding and recognition-specific neural networks. More specifically the encoding task tapped into brain regions underlying *strategic* aspects of memory encoding as evident from the observed task-engagement within the

Table 3
Brain activation during the recognition task.

Anatomical region	BA	MNI			No. of voxels	*p*-value
		x	y	z		
L precuneous cortex	N/A	−10	−68	26	2879	<0.001
L angular gyrus	39	−42	−60	42	1653	<0.001
R lateral occipital cortex, superior division	19	40	−76	40	1276	<0.001
L middle frontal gyrus	44	−36	20	34	559	<0.001
L paracingulate gyrus	32	−8	34	32	532	<0.001
L frontal pole	10	−36	56	6	298	<0.001
L middle temporal gyrus, posterior division	20	−60	−24	−12	185	0.001
R frontal pole	11	26	52	6	154	0.004
R insular cortex	48	32	18	−12	97	0.037

Abbreviations: BA,=Brodmann area; No. = number; M = medial; R = right; L = left.

dPFC and hippocampal areas. Notably, this contrasts to our previous picture encoding paradigm, which failed to show the expected encoding-related dPFC and hippocampal engagement (Petersen et al., 2021). This is likely due to the different designs of the memory paradigms. Specifically, remembering a grocery list might be a task that is a lot more relatable and thereby more engaging than simply classifying indoor vs outdoor pictures, which is a task that may seem arbitrary. Taken together, the findings suggest that this newly developed grocery list memory paradigm taps into neural networks underlying more real-life like strategic memory encoding and recognition in healthy individuals.

The positive association between encoding-related activity in the inferior temporal gyrus and lateral occipital cortex and number of correctly recalled words was notable. The inferior temporal gyrus is involved in a range of higher-cognitive processes, including complex visual perception, lexical and phonological decisions, and word recognition, and it is hereby probably involved in the discrimination between word and non-words in the encoding task (Philipose et al., 2007), (Buckley et al., 1997), (Lin et al., 2020). Further, the association between correctly recalled words and activity in the lateral occipital cortex might be due to the participants using a visual imagery strategy, which is in the literature found to be an effective strategy to improve memory encoding and, hence, subsequent recall (Lee, 1973).

In contrast, we found no correlation between task-related brain activity and the out of scanner virtual reality memory performance. This was surprising given that the virtual reality task is considered an ecologically valid assessment of memory encoding and recognition abilities (Miskowiak et al., 2022b). In this virtual reality task taking place in a kitchen scenario, participants were instructed to select ingredients that they had to memorize from a given recipe. Although this is similar to the grocery list paradigm, the virtual reality task is based on cross-modal recognition (i.e., recognition of visual objects from a verbal list of memorized words), which might engage slightly different neurocircuitries than the purely verbal grocery list encoding and recognition fMRI tasks.

Overall, this newly designed paradigm can be considered as a valid measure of verbal memory, as it showed robust task-activation in the expected encoding and retrieval-related neural networks in healthy participants. The paradigm is thus a relevant tool for examining neurocircuitries involved in verbal encoding and recognition processes. Accordingly, it has the potential to detect the effects of pro-cognitive treatments on neurocircuitries underlying verbal learning and memory abilities (Miskowiak and Petersen, 2019). Further, the grocery list paradigm was designed in an ecologically valid way, so that it more directly engages neurocircuitry activity that occur during patients' real-life cognitive challenges such as grocery shopping. Of the two (inter-related) tasks – encoding and recognition of grocery list items - the

encoding task seems to be most relevant for further testing, as it engaged the hippocampus in addition to dorsal PFC. Future studies should further investigate if this paradigm can detect subtle known aberrancies in brain activation in clinical populations as well as potential neurocircuitry changes following pro-cognitive interventions.

A key strength of this study is the fMRI task design, which involves memorizing and recalling a grocery list - a common cognitive challenge in daily life. This design enhances the ecological validity and relevance of the paradigm. Another strength was the association of both inside- and outside-scanner behavior with task-related BOLD response. Limitations include the relatively small sample size ($n = 34$), as a bigger sample might have led to more robust results and correlations, especially considering the general issues with BOLD response reliability (Holiga et al., 2018). Additional studies aiming to replicate the findings in a larger sample are therefore warranted to further validate the paradigm. Nevertheless, we identified two task-related neural networks in line with our hypotheses based on the current sample. Another limitation was that while participants were encouraged to use mnemonic strategies, we did not assess if they had used any and which they used, impeding investigations into the potential effects of mnemonic strategies on their neural response. Further, the extensive somatic exclusion criteria for the participants may also limit the generalizability of our results. Especially the subgroup of six healthy controls recruited through blood banks might be a poor representation of the general population due to the 'healthy donor effect' (a selection bias caused by the health criteria blood donors must meet) (Brodersen et al., 2023). Finally, while participants were fluent in Danish, it was not a requirement for them to have Danish as a first language, which might have impacted their verbal encoding and recognition performance.

5. Conclusion

In this present study employing a novel and ecologically valid memory fMRI paradigm, we observed task-relevant activation in neural networks associated with strategic memory encoding and recognition in healthy individuals. The paradigm presents a promising ecologically valid tool for assessing the neural correlates of daily life memory impairments across different patient populations as well as the effectiveness of pro-cognitive interventions.

Author contributions

KKT, JM, JM, VD, AEJ and KWM planned and conducted the behavioral analyses. JM and VD conducted the fMRI analyses. KKT created the first draft of the manuscript, which was then revised by VD, MBJ and KWM. JM and ATYN developed the fMRI paradigm. VD, JM, AEJ, CM, MD and SRO were involved in participant recruitment. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

KWM has received honoraria from Lundbeck, Janssen-Cilag, Angelini and Gedeon Richter in the past three years. The remaining authors declare no conflict of interest.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Kamilla Woznica Miskowiak reports a relationship with Janssen-Cilag that includes: speaker honoraria. Kamilla Woznica Miskowiak reports a relationship with Angelini SpA that includes: speaker honoraria and consultancy fees. Kamilla Woznica Miskowiak reports a relationship with Gedeon Richter Plc that includes: consultancy fees. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nsa.2024.104084.

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