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Planning in amnestic mild cognitive impairment: an fMRI study

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ABSTRACT

Introduction: The memory impairment that is characteristic of amnestic mild cognitive impairment (aMCI) is often accompanied by difficulties in executive functioning, including planning. Though planning deficits in aMCI are well documented, their neural correlates are largely unknown, and have not yet been investigated with functional magnetic resonance imaging (fMRI).
Objectives: The aim of this study was to: (1) identify differences in brain activity and connectivity during planning between people with aMCI and cognitively healthy older adults, and (2) find whether planning-related activity and connectivity are associated with cognitive performance and symptoms of apathy.
Methods: Twenty-five people with aMCI and 15 cognitively healthy older adults performed a visuospatial planning task (Tower of London; ToL) during fMRI. Task-related brain activation, spatial maps of task-related independent components, and seed-to-voxel functional connectivity were compared between the two groups and regressed against measures of executive functions (Trail Making Test difference score, TMT B-A; Digit Symbol Substitution Test, DSST), delayed recall (Rey Auditory Verbal Learning Test), and apathy (Apathy Evaluation Scale).
Results: People with aMCI scored lower on task-switching (TMT B-A), working memory (DSST), and planning (ToL). During planning, people with aMCI had less activation in the bilateral anterior calcarine sulcus/cuneus, the bilateral temporal cortices, the left precentral gyrus, the thalamus, and the right cerebellum. Across all participants, higher planning-related activity in the supplementary motor area, the retrosplenial cortex and surrounding areas, and the right temporal cortex was related to better delayed recall. There were no between-group differences in functional connectivity, nor were there any associations between connectivity and cognition. We also did not find any associations between brain activity or connectivity and apathy.
Conclusion: Impaired planning in people with aMCI appears to be accompanied by lower activation in a diffuse cortico-thalamic network. Across all participants, higher planning-related activity in parieto-occipital, temporal, and frontal areas was related to better memory performance. The results point to the relevance of planning deficits for understanding aMCI and extend its clinical and neurobiological signature.

1. Introduction

Older adults with amnestic mild cognitive impairment (aMCI) experience memory problems that are beyond those expected for their age, and are at an increased risk for developing dementia (Mitchell and Shiri-Feshki, 2009). Memory problems in aMCI are often accompanied by difficulties in executive functions, especially planning (Beversdorf et al., 2007; Brandt et al., 2009; da Costa Armentano et al., 2013; Espinosa et al., 2009; Johns et al., 2012; Sanders et al., 2014; Schmitter-Edgecombe et al., 2012; Werner et al., 2009; Zhang et al., 2007).

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Planning is a higher-order executive function that involves considering a series of possibilities and creating an optimal sequence of steps needed to reach a goal (Unterrainer and Owen, 2006). In everyday life, people with aMCI have problems planning tasks that are necessary to maintain independence and a high quality of life, such as trips to the grocery store or a day out (Jekel et al., 2015; Yeh et al., 2011). Though the prevalence and the burden of planning deficits in aMCI are well documented, their neural correlates remain largely unknown.

The most commonly used measure of visuospatial planning ability in neuroimaging research is the Tower of London (ToL) task in which participants plan a sequence of moves in order to rearrange a set of beads into a target configuration (Shallice, 1982). In younger and older healthy participants, the ToL task elicits activation in a fronto-striato-parietal network that includes the bilateral prefrontal cortices, supplementary motor areas, inferior parietal lobules, parts of the occipital gyri, the precuneus, the caudate, and the cerebellum (see Nitschke et al., 2017 for a meta-analysis). We were only able to identify one study that investigated the relationship between brain activity and planning in people with cognitive decline. Matías-Guiu et al. (2017) found that better ToL performance measured outside the scanner was related to higher metabolism in bilateral parietal and right frontal and temporal regions. However, to the best of our knowledge, no study to date has used functional neuroimaging to measure blood-oxygen-level dependent (BOLD) signal changes during planning in people with aMCI.

Diminished goal-directed behavior is one of the signs of apathy (Marin, 1996), which is a common neuropsychiatric symptom in all subtypes of MCI (Hwang et al., 2004; Ishii et al., 2009; Ma, 2020) and is associated with an increased risk of progression to dementia (Ma, 2020; Palmer et al., 2010; Richard et al., 2012; Teng et al., 2007; van Dalen et al., 2018). People with MCI who also display signs of apathy were found to score lower on tasks of memory and executive functions (Drijgers et al., 2011; Montoya-Murillo et al., 2019; Robert et al., 2006; Zahodne and Tremont, 2013), and were more functionally impaired (Zahodne and Tremont, 2013) than people with MCI without apathy. In MCI and Alzheimer's disease (AD), apathy has been associated with structural abnormalities in frontal brain areas, including the anterior cingulate cortex, the orbitofrontal cortex, and the dorsolateral prefrontal cortex (Kos et al., 2016; Raimo et al., 2019; Stella et al., 2014; Theleritis et al., 2014). Findings on functional correlates of apathy in aMCI are few and conflicting, as it has been associated with both lower (Munro et al., 2015) and higher (Joo et al., 2016) resting-state connectivity within the fronto-parietal control network.

The aim of this study was to investigate neural correlates of planning impairment in aMCI, and find how they relate to behavioral outcomes and apathy. To that end, we used functional magnetic resonance imaging (fMRI) while participants performed the ToL task to identify regions that show significantly different activation or connectivity in people with aMCI than in cognitively healthy older adults. We compared BOLD signal response, seed-to-voxel functional connectivity, and spatial maps of planning-related networks obtained with independent component analysis (ICA) between the two groups. Moreover, we investigated whether ToL-elicited activity and connectivity are related to cognitive performance or apathy measured outside the scanner. Thus, we tested the hypothesis whether fronto-striato-parietal network would be compromised in aMCI, implying that a focus on brain networks relevant for memory may be too narrow.

2. Methods

2.1. Participants

We used data of thirty-two people with aMCI and 20 cognitively healthy older adults who participated in a study on neural correlates of apathy in aMCI. Participants were recruited through advertisements in the community, and through neurologists at the University Medical Center Groningen. All participants had a diagnostic workup that included an assessment by a neurologist and a neuropsychologist. Diagnosis of aMCI was made using the criteria by Petersen et al. (1999) and the core clinical NIA-AA criteria (Albert et al., 2011). To be diagnosed with aMCI, participants had to have (1) a subjective memory complaint, (2) objective memory impairment, defined by scoring in the lowest 5% adjusted for age and education on the Rey Auditory Verbal Learning Test (RAVLT), (3) essentially preserved general cognitive function, (4) largely intact functional activities, and (5) no dementia. Twelve of the people with aMCI were diagnosed with apathy by a clinician and a neuropsychologist according to criteria described by Robert et al. (2009). All participants had to be aged between 60 and 80 years. Additional inclusion criteria for cognitively healthy older adults were (1) absence of subjective memory complaints, and (2) a score of at least 28 on the Mini Mental State Exam (MMSE). Exclusion criteria for all participants were (1) using medication that could affect experimental outcomes, (2) being diagnosed with a psychiatric condition (with the exception of depression), a neurological condition, or having problems with eyesight, (3) MRI contra-indications (metal implants or particles, red ink tattoos, claustrophobia), and (4) fulfilling NINCDS/ADRDA (McKhann et al., 1984) and DSM-IV criteria for AD, assessed by a clinician and a neuropsychologist. Cognitively healthy older adults were also excluded if they scored in the abnormal range on any neuropsychological test. The study was approved by the medical ethical board of the University Medical Center Groningen and was in accordance with the Declaration of Helsinki. All participants signed written informed consent before taking part in the study.

Seven people with aMCI and five cognitively healthy older adults were excluded from analysis for the following reasons: (1) inability to perform the task during the scanning session (2 cognitively healthy older adults), or performing with $\leq$ 50% accuracy on easy ToL trials (1–3 steps) or with $\leq$ 70% accuracy on the counting task (7 aMCI, 1 cognitively healthy older adult), (2) excessive motion (1 cognitively healthy older adult), (3) unreliable fMRI signal (1 cognitively healthy older adult). Data of the remaining 25 people with aMCI and 15 cognitively healthy older adults was included in analyses.

2.2. Behavioral data

The following cognitive and behavioral tests were administered to all participants: (1) Mini Mental State Exam (MMSE; Folstein et al., 1975) for assessing general cognitive ability, (2) Global Deterioration Scale (Reisberg et al., 1982) for characterizing stages of dementia, (3) Geriatric Depression Scale (GDS; Yesavage et al., 1982), (4) Apathy Evaluation Scale – Clinician version (AES; Marin et al., 1993, 1991), (5) Middelheim Frontality Score (MFS; de Deyn et al., 2005) for assessing frontal lobe features, (6) Rey Auditory Verbal Learning Test (RAVLT; Lezak et al., 2004) of immediate and delayed recall, (7) digit span test (Lezak et al., 2004) of immediate recall and working memory, (8) Digit Symbol Substitution Test (DSST; Lezak et al., 2004) of attention span and working memory, (9) Trail Making Test parts A and B (TMT A/B; Lezak et al., 2004) to measure visual attention and task-switching, (10) Hayling test (Burgess and Shallice, 1997) and Stroop test (Lezak et al., 2004) of response inhibition, and (11) Boston Naming Test (BNT; Lezak et al., 2004) of word retrieval.

Because GDS includes questions on apathy, a concept that is also measured with the AES, we calculated a GDS non-apathy sub-score by leaving out items that were identified as the apathy component (items 2, 12, 19, 20, 21, and 28; Adams et al., 2004). To capture the cost of task-switching independent of processing speed, we subtracted the time needed to complete TMT part A from the time needed to complete part B (TMT B-A). Response inhibition measured by the Stroop task was quantified by calculating the interference score (time needed on part 3 divided by time needed on part 2).

2.3. Magnetic resonance imaging

2.3.1. Acquisition

MRI scans were acquired on a 3.0 T Phillips Intera scanner with a 32-channel SENSE head coil. The task was presented on a screen visible through a mirror on top of the head coil, and participants made their responses with an MRI-compatible response box. T2*-weighted gradient echo-planar images were acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 70°, field of view (FOV) = 224 mm × 129.5 mm × 224 mm, 37 axial slices, anterior-posterior preparation direction, and 3.5 mm × 3.6 mm × 3.5 mm voxels. A high-resolution 3D T1-weighted anatomical image was acquired for registration purposes (TR = 9 ms, TE = 3.6 ms, FA = 8°, FOV = 256 mm × 232 mm × 256 mm, 170 axial slices, anterior-posterior preparation direction, 1 mm isotropic voxels).

2.3.2. Experimental paradigm

The Tower of London (ToL; Fig. 1) task was based on Lazeron et al. (2000), and has been described previously by Lieburg et al. (2015). The task was presented using *E*-prime 2.0. During the planning condition, participants were shown two configurations of differently colored beads (red, blue, green) placed on three rods. They had to count the minimum number of steps needed to rearrange the beads in the upper configuration so it matched the lower configuration. Only the top bead on each rod could be moved, one at a time, and had to immediately be placed onto another rod. Possible numbers of steps ranged from 1 to 5. Trials with 1–3 steps were considered easy, and trials with 4 and 5 steps were considered hard. During the counting or control condition, participants were again shown two configurations of beads, and had to count the number of blue and red beads on the screen. During both conditions, two answer options were presented at the bottom of the screen, and participants were asked to select the correct one by a button press using either the index or the middle finger of their right hand (for the left and right option, respectively).

The task was presented in a block design, consisting of 5 blocks of each task condition. Trials within a block were self-paced, and each block was terminated after 60 s. Trials were separated by a 250 ms fixation cross, and task blocks by a 30 s fixation cross (resting blocks).

2.3.3. Preprocessing

Data was preprocessed with the Statistic Parametric Mapping toolbox (SPM12; FIL Wellcome Department of Imaging Neuroscience, London, UK) in Matlab R2015a (The Mathworks Inc., Natick, MA, USA). We first realigned functional volumes to the first volume and generated a resliced mean image, which was then coregistered to the T1-weighted structural image. The resulting coregistration parameters were also applied to functional volumes. Both functional and structural images were spatially normalized to the Montreal Neurological Image (MNI) T1 template. Each pair of functional and structural images was checked after coregistration and normalization. Functional images were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian smoothing kernel. Outlier functional volumes (volumes with framewise displacement above 0.9 mm or global BOLD signal changes above 5 SD) were detected with the ART-based scrubbing method implemented in the CONN toolbox version 20.b (www.nitrc.org/projects/conn, RRID: SCR_009550). One cognitively healthy older adult was excluded from analysis because 81% of volumes were flagged as outliers. Across remaining participants, outliers represented 5% of data (± 7%, range 0–29%). Outlier volumes were later scrubbed from the data by adding a binary regressor for each volume to the first-level model.

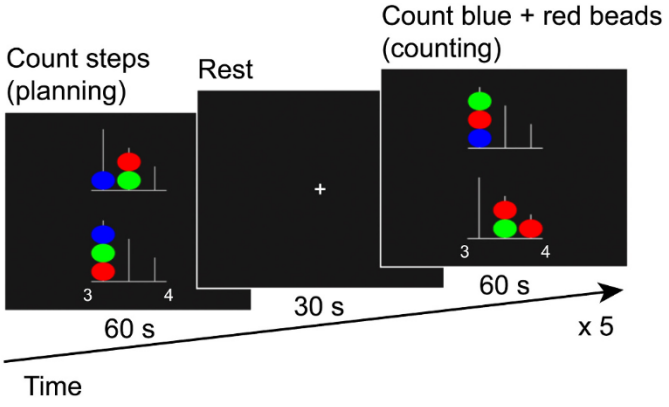

Fig. 1. Tower of London (ToL) task. The top drawing is the starting configuration and the bottom one is the target configuration of beads. Participants were instructed to either count the number of steps between the starting and the target configuration (in the planning condition) or to count the number of blue and red beads on the screen (in the counting condition).

2.3.4. Planning-related brain activity

Task-related differences in brain activity were investigated with a general linear model in SPM12. Smoothed functional images were entered into first-level analysis. For each participant, regressors were modelled in a block design and convolved with a hemodynamic response function (HRF). Regressors of interest were planning and counting blocks. As regressors of no interest, we included planning trials that were not responded to (trials at the end of the block), instructions, six realignment parameters, and one regressor for each outlier volume. Resting blocks were assumed to represent baseline activity. The following contrasts were created for each participant: (1) counting > rest, (2) planning > rest, and (3) planning > counting. The first two contrasts were intended to check whether the tasks successfully modulated brain activity, and the third to find regions that support planning performance. One participant was excluded from further analysis because neither the counting nor the planning task engaged expected brain regions (e.g. the visual cortex) at $p < 0.001$ (uncorrected). This participant's activation maps showed that no voxels survived the counting > rest contrast, and that only few small clusters, dispersed mainly in the white matter and around the ventricles, survived the planning > rest contrast. Because previous studies showed that planning-related brain activity is modulated by task complexity (Nitschke et al., 2017), we created a second model where easy (1–3 steps) and hard (4 and 5 steps) trials were modelled with two separate regressors, with all other regressors remaining the same. Here we created two contrasts per participant: (1) hard > easy, and (2) easy > hard. To ensure our analyses were limited to gray matter voxels, a group mask was created by smoothing the mean normalized gray matter image with an 8 mm full-width half maximum (FWHM) Gaussian smoothing kernel, and thresholding it at i1 > 0.2.

2.3.5. Planning-related brain connectivity

2.3.5.1. Independent component analysis. Twenty independent components (ICs) were extracted using the Infomax algorithm implemented in the Group ICA of fMRI toolbox version 3.0c (GIFT; Calhoun, 2004). We used multiple regression to compare time courses of each IC to the task time course, and identified two components that were related to planning. Subject-specific spatial maps of these components were entered into statistical analyses.

2.3.5.2. Seed-to-voxel functional connectivity. Planning-related seed-to-voxel functional connectivity was assessed using the CONN toolbox version 20.b (www.nitrc.org/projects/conn, RRID:SCR_009550). First-level models created to investigate planning-related brain activity were imported into CONN. Each participant's preprocessed functional data was denoised with CONN's default denoising pipeline. Denoising included linearly regressing out noise components from white matter and cerebrospinal fluid, six realignment parameters, outlier scans

(scrubbing), and task effects, and temporally filtering the BOLD signal to remove frequencies below 0.008 Hz. Seed regions for seed-to-voxel connectivity analyses were defined based on peak activation of the group. Relevant clusters that showed greater activation during planning than during counting ($p_{FWE} < 0.05$) were selected with xjView toolbox (https://www.alivelearn.net/xjview) and used as seed regions. Location, size, and composition (according to the AAL atlas implemented in xjView toolbox) of the six seed regions was as follows: (1,2) two regions in the left frontal cortex (number of voxels (k) = 28, 93% of voxels in middle frontal gyrus; k = 46, 72% of voxels in middle frontal gyrus, 22% of voxels in inferior frontal gyrus), (3) right frontal cortex (k = 72, 65% of voxels in middle frontal gyrus, 32% of voxels in superior frontal gyrus), (4) left lateral parietal cortex (k = 262, 33% of voxels in angular gyrus, 31% of voxels in inferior parietal lobule, 27% of voxels in middle occipital gyrus, 8% of voxels in middle temporal gyrus), (5) right lateral parietal cortex (k = 361, 34% of voxels in angular gyrus, 25% of voxels in inferior parietal lobule, 14% of voxels in middle occipital gyrus, 10% of voxels in superior parietal lobule, 8% of voxels in supramarginal gyrus, 7% of voxels in middle temporal gyrus), and (6) the precuneus (k = 485, 52% of voxels in right precuneus, 41% of voxels in left precuneus).

2.4. Statistical analysis

Demographic and behavioral data of the two groups were compared with one-way ANOVAs, Mann-Whitney *U* tests, or chi-squared tests using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). To control the false discovery rate (FDR), we used the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995). For analyses where cognitive performance was used as a regressor, missing scores on DSST, TMT B-A, and GDS non-apathy were replaced by the mean value of the group.

The main effect of planning and the effect of task complexity across all participants were investigated with one-sample *t*-tests. Results for the main effect of planning were thresholded at a stringent FWE-corrected $p < 0.05$ at peak-level, and for the main effect of complexity at a more lenient FWE-corrected $p < 0.05$ at cluster-level. For both analyses, the initial cluster-defining threshold was set at $p < 0.001$ (uncorrected). Peak-level correction only retained clusters in which the activity of at least one voxel was high enough to be significant at $p < 0.05$. Cluster-level correction only retained clusters that were large enough to be significant at $p < 0.05$. Though correction at cluster-level is less spatially precise, it is more sensitive, and is therefore appropriate for smaller effects, such as the effects of task complexity and between-group differences, as opposed to larger effects, such as the main effect of planning. Between-group differences in (1) planning-related brain activity, (2) complexity-related brain activity, (3) spatial maps of planning-related ICA networks, and (4) seed-to-voxel functional connectivity were investigated with separate two-sample *t*-tests. Since nine of the 25 participants with aMCI were diagnosed with apathy, which is characterized by diminished goal-directed behavior, and our primary interest was to investigate differences between people with aMCI and cognitively healthy older adults, the AES score was added as a control variable in all between-group analyses. Associations between measures of brain function (planning-related brain activity, spatial maps of planning-related ICA networks, seed-to-voxel functional connectivity) and cognitive performance (DSST, TMT B-A, RAVLT delayed recall) were investigated with separate multiple regression analyses, again controlling for the AES score. We also checked whether planning-related brain activity, spatial maps of planning-related ICA networks, and seed-to-voxel functional connectivity were related to apathy, using GDS non-apathy and sex as control variables. Sex was added as a control variable because it was shown that neural correlates of apathy can differ between males and females (Spalletta et al., 2013). Because performance on the ToL task differed between the two groups ($F = 7.7$, $p = 0.005$), we checked whether any of the significant results were independent of task performance by repeating the analyses adding ToL accuracy as a control variable. Results of analyses on planning-related brain activity, complexity-related brain activity, and spatial maps of planning-related ICA networks were thresholded at FWE-corrected $p < 0.05$ at cluster-level, using an initial threshold of $p < 0.001$ (uncorrected). For seed-to-voxel functional connectivity analyses, we controlled for family-wise error by using permutation/randomization analysis with 1000 iterations. Results were thresholded at FDR-corrected $p < 0.05$ at cluster-level with an initial threshold of $p < 0.01$ (uncorrected).

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics of the sample are given in Table 1. People with aMCI and cognitively healthy older adults were comparable in age, sex, education, and handedness. People with aMCI had higher GDS total ($U = 60.5$, $p < 0.001$) and GDS non-apathy scores ($U = 60.0$, $p < 0.001$), and higher AES scores ($U = 116.0$, $p = 0.045$) than cognitively healthy older adults. As expected, people with aMCI

Table 1
Sample characteristics.

Variable	People with aMCI (mean (SD))	Cognitively healthy older adults (mean (SD))	Significance
n	25	15	
Age (years)	67.6 (5.2)	66.2 (3.8)	n. s.[d]
Sex (% male)	76%	67%	n. s.[e]
Level of education (Verhage score)	5.5 (1.1)	5.7 (0.8)	n. s.[f]
Self-reported handedness (% right-handed)	88%	100%	n. s.[e]
MMSE	28.8 (1.1)	28.9 (1.2)	n. s.[f]
GDS total[a]	8.7 (6.4)	2.5 (3.9)	$U = 60.5$, $p < 0.001$*
GDS non-apathy[a]	6.3 (4.8)	1.6 (2.8)	$U = 60.0$, $p < 0.001$*
AES	32.0 (10.6)	25.2 (4.8)	$U = 116.0$, $p = 0.045$
RAVLT			
Immediate recall	31.7 (6.5)	40.3 (9.0)	$F = 12.2$, $p = 0.001$*
Delayed recall	5.3 (2.2)	8.5 (2.9)	$F = 16.5$, $p < 0.001$*
Digit span			
Forward	5.7 (1.3)	6.3 (1.3)	n. s.[f]
Backward	4.7 (0.8)	4.8 (1.2)	n. s.[f]
DSST[b]	46.3 (6.8)	51.8 (6.6)	$F = 6.2$, $p = 0.018$*
TMT B—A[c] (s)	47.7 (27.6)	30.6 (16.3)	$U = 98.0$, $p = 0.033$
Hayling test	13.8 (3.7)	14.7 (4.3)	n. s.[d]
Stroop test interference score (part 3/part 2)	1.8 (0.5)	1.7 (0.2)	n. s.[f]
BNT	27.4 (2.2)	27.0 (2.1)	n. s.[f]
Tower of London (% correct)			
Counting	95.3 (3.9)	96.0 (2.0)	n. s.[f]
Total ToL trials	63.0 (12.4)	73.3 (9.1)	$F = 7.7$, $p = 0.005$*
Easy ToL trials (1–3 steps)	70.9 (13.3)	82.2 (13.4)	$F = 6.7$, $p = 0.014$*
Hard ToL trials (4 and 5 steps)	54.6 (17.1)	62.9 (12.7)	n. s.[d]

[a] Score for one person with aMCI was missing.
[b] Scores for two people with aMCI were missing.
[c] Scores on TMT B were missing for one person with aMCI and one cognitively healthy older adult.
[d] Compared with one-way ANOVA.
[e] Compared with chi-squared test.
[f] Compared with Mann-Whitney *U* test.
* Survives FDR correction for multiple comparisons.

had poorer immediate (F = 12.2, p = 0.001) and delayed recall (F = 16.5, p < 0.001). In addition, people with aMCI scored worse on two measures of executive functioning, the DSST (F = 6.2, p = 0.018) and the TMT B-A (U = 98.0, p = 0.033), though the latter did not survive correction for multiple comparisons.

Compared to cognitively healthy older adults, people with aMCI were less accurate on the ToL task (F = 7.7, p = 0.005; Fig. 2). This effect was mostly driven by the easy trials (F = 6.7, p = 0.014), as it was not significant for hard trials. On hard trials, 40% of people with aMCI and 20% of cognitively healthy older adults performed below or at chance level (50% accuracy).

3.2. Planning-related brain activity

Areas that were more active during planning than during counting across all participants are shown in Table 2 and Fig. 3. There were no effects of task complexity, meaning brain activity did not differ significantly between easy and hard trials.

During planning, people with aMCI had less activity in the bilateral anterior calcarine sulcus and cuneus, the bilateral thalamus, bilateral temporal cortices, the left temporo-occipital cortex, the left precentral gyrus (Brodmann area 6), and the right cerebellum (Table 3, Fig. 4). Clusters in the calcarine sulcus/the cuneus and the thalamus remained significant after controlling for ToL accuracy (calcarine sulcus/cuneus: k = 117, Z = 4.62; thalamus: k = 69, Z = 3.86). There were no regions where people with aMCI had more activity than cognitively healthy older adults.

Across all participants, better scores on delayed recall measured with the RAVLT were associated with higher activity in three clusters (Fig. 5). The first cluster (k = 425, Z = 4.82) covered the bilateral supplementary motor area (28% of voxels), precuneus (17% of voxels), paracentral lobule (17% of voxels), superior frontal gyrus (11% of voxels), precentral gyrus (11% of voxels), and postcentral gyrus (7% of voxels). 27% of voxels in this cluster were in Brodmann area 6. The second cluster (k = 385, Z = 4.38) was in the bilateral calcarine sulcus (36% of voxels), precuneus (14% of voxels), and cuneus (10% of voxels), as well as the right lingual gyrus (12% of voxels). 11% of voxels were in the retrosplenial cortex (Brodmann areas 29 and 30). The final cluster (k = 88, Z = 3.90) was in the right superior temporal gyrus (55% of voxels), middle temporal gyrus (16% of voxels), and Rolandic operculum (15% of

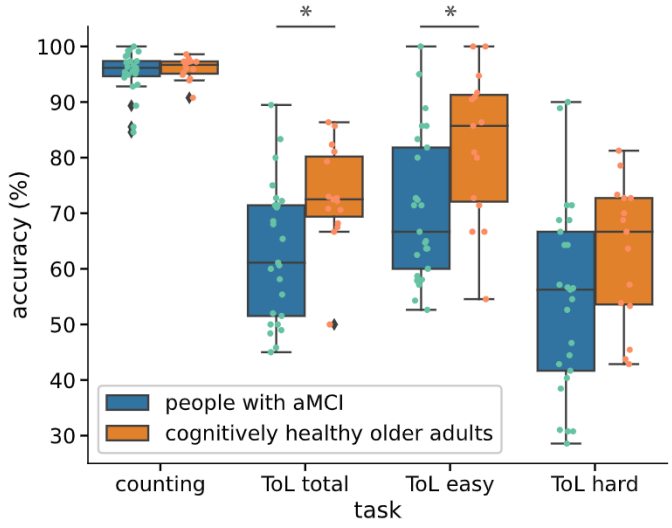

Fig. 2. Accuracy (% of correct responses) on counting and planning (ToL) trials. People with aMCI (shown in blue) were less accurate than cognitively healthy older adults (shown in orange) on total planning trials, and on easy trials (1–3 steps). Dots represent individual data points, and asterisks significance at p_{FDR} < 0.05.

Table 2
Main effect of planning on brain activity.

Regions (AAL)	BA	k	MNI coordinates			Z
			x	y	z	
L angular gyrus, inferior parietal lobule, middle occipital gyrus, middle temporal gyrus	39, 40, 19	262	−37.5	−77	35	7.17
R and L precuneus, superior parietal lobule, R angular gyrus, inferior parietal lobule, middle occipital gyrus, supramarginal gyrus, middle temporal gyrus	7, 40, 39, 31	860	8	−63	52.5	6.84
L middle temporal gyrus	/	30	−55	−63	−3.5	6.50
L cerebellum crus 1, cerebellum crus 2	/	79	−30.5	−66.5	−31.5	5.96
L middle frontal gyrus, inferior frontal gyrus	10	46	−34	49	7	5.86
R cerebellum crus 1	/	76	29	−66.5	−38.5	5.85
L cuneus	/	19	−20	−59.5	17.5	5.66
R middle frontal gyrus, superior frontal gyrus	8	72	22	10.5	49	5.56
L middle frontal gyrus	/	28	−37.5	7	56	5.17

Results were thresholded at p_{FWE} < 0.05 (peak-level). The table shows regions and BAs with at least 10 voxels, except for the cluster in the left cuneus, where the highest number of voxels in one region was 7. AAL = automated anatomical labeling atlas, BA = Brodmann area, L = left, R = right, k = number of voxels.

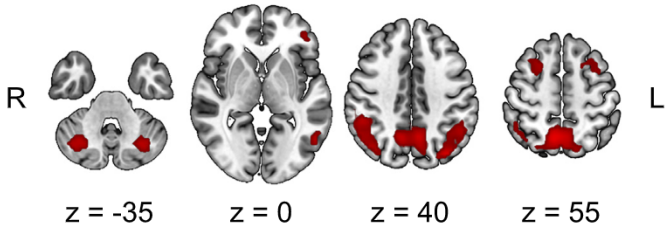

Fig. 3. Main effect of planning on brain activity. Results were thresholded at p_{FWE} < 0.05 (peak-level). Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 3
Brain areas where planning-related activity was lower in people with aMCI.

Regions (AAL)	BA	k	MNI coordinates			Z
			x	y	z	
L and R calcarine sulcus, cuneus, L superior occipital gyrus, lingual gyrus, R precuneus	31, 23, 30, 18, 17, 7	498	−16.5	−70	17.5	5.17
R middle temporal gyrus, superior temporal gyrus, Rolandic operculum, Heschl's gyrus, supramarginal gyrus	22, 39, 13, 40, 41, 43, 42	473	57	−63	14	5.02
L and R thalamus	/	114	−6	−17.5	7	4.24
R cerebellum crus 2	/	48	18.5	−73.5	−38.5	4.07
L precentral gyrus, superior frontal gyrus	6	64	−27	−17.5	70	4.06
L inferior occipital gyrus, fusiform gyrus, middle temporal gyrus, cerebellum 6	19	71	−41	−73.5	−3.5	4.05
L superior temporal gyrus	41	46	−48	−21	10.5	3.62

Results were thresholded at p_{FWE} < 0.05 (cluster-level). The table shows regions and BAs with at least 10 voxels. AAL = automated anatomical labeling atlas, BA = Brodmann area, L = left, R = right, k = number of voxels.

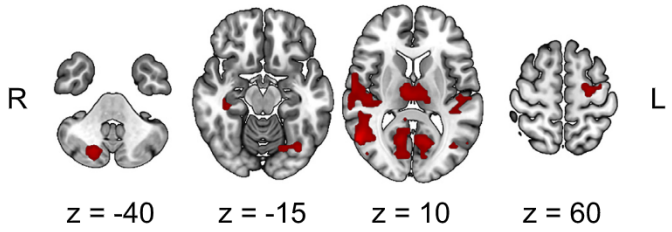

Fig. 4. Brain areas where planning-related activity was lower in people with aMCI. Results were thresholded at $p_{FWE} < 0.05$ (cluster-level). Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

voxels). Results remained similar after controlling for planning accuracy, though the third cluster was no longer significant (the first cluster was split into two: k = 123, Z = 4.52 and k = 53, Z = 4.41; the second cluster: k = 114, Z = 4.11).

There were no significant associations between planning-related brain activity and scores on the DSST and the TMT B-A, or between planning-related brain activity and apathy.

3.3. Planning-related brain connectivity

3.3.1. Independent component analysis

We identified two planning-related components ($R^2 = 0.273$ for IC6 and $R^2 = 0.136$ for IC11; Fig. 6). There were no significant differences in the spatial maps of these components between people with aMCI and cognitively healthy older adults, nor were there any significant associations with cognitive performance nor apathy.

3.3.2. Seed-to-voxel functional connectivity

There were no significant differences in connectivity of any of the seed regions between people with aMCI and cognitively healthy older adults. There were also no significant associations between connectivity and cognitive performance, or between connectivity and apathy.

4. Discussion

The aim of this study was (1) to compare planning-related brain activity and connectivity between people with aMCI and cognitively healthy older adults, and (2) to find whether planning-related activity and connectivity were related to performance on cognitive tests and symptoms of apathy. We found between-group differences in brain activity, but not connectivity. People with aMCI had less activity in the calcarine sulcus/cuneus, bilateral temporal cortices, the left premotor cortex, the thalamus, and the right cerebellum (see Fig. 4). In addition, we found a positive association between delayed recall measured by the Rey Auditory Verbal Learning Test (RAVLT) and planning-related activity in Brodmann area 6, the retrosplenial cortex and surrounding areas, and the right temporal cortex (see Fig. 5). There were no associations between apathy and brain activity or connectivity.

We found that people with aMCI showed impairments not only in memory, but also in several executive functions (see Table 1). They scored lower on tests of working memory (DSST), task-switching (TMT B-A), and planning (ToL). In contrast to some previous studies that also reported deficits in inhibitory control (Andres and van der Linden, 2000; Johns et al., 2012; Traykov et al., 2007), we did not find differences in performance on the Hayling test or the Stroop test. Though a recent meta-analysis confirmed inhibition deficits in people with aMCI, results of individual studies were often non-significant, especially when participants were drawn from the community (Rabi et al., 2020). Deficits in planning have been reported across different stages of cognitive decline, and were found in cognitively healthy older adults (Andres and van der Linden, 2000; Kaller et al., 2015; Köstering et al., 2016; Robbins et al., 1998; Zook et al., 2006), people with MCI (Beversdorf et al., 2007; Brandt et al., 2009) and people with AD (Coubard et al., 2011; Franceschi et al., 2007; Huang et al., 2017; Marchegiani et al., 2010; Rainville et al., 2002; Satler et al., 2017). We were unable to identify any studies that reported accuracy on the ToL task in people with aMCI, but accuracy of cognitively healthy older adults was comparable to previously reported values (Kaller et al., 2015; Köstering et al., 2016; Spreng and Schacter, 2012). Interestingly, the difference between the two groups was not significant when hard ToL trials were considered separately, presumably due to a floor effect. Given that all included participants performed above chance level on easy trials, we can assume they understood and were able to perform the task. Regardless, a fifth of cognitively healthy older adults performed below chance level on hard

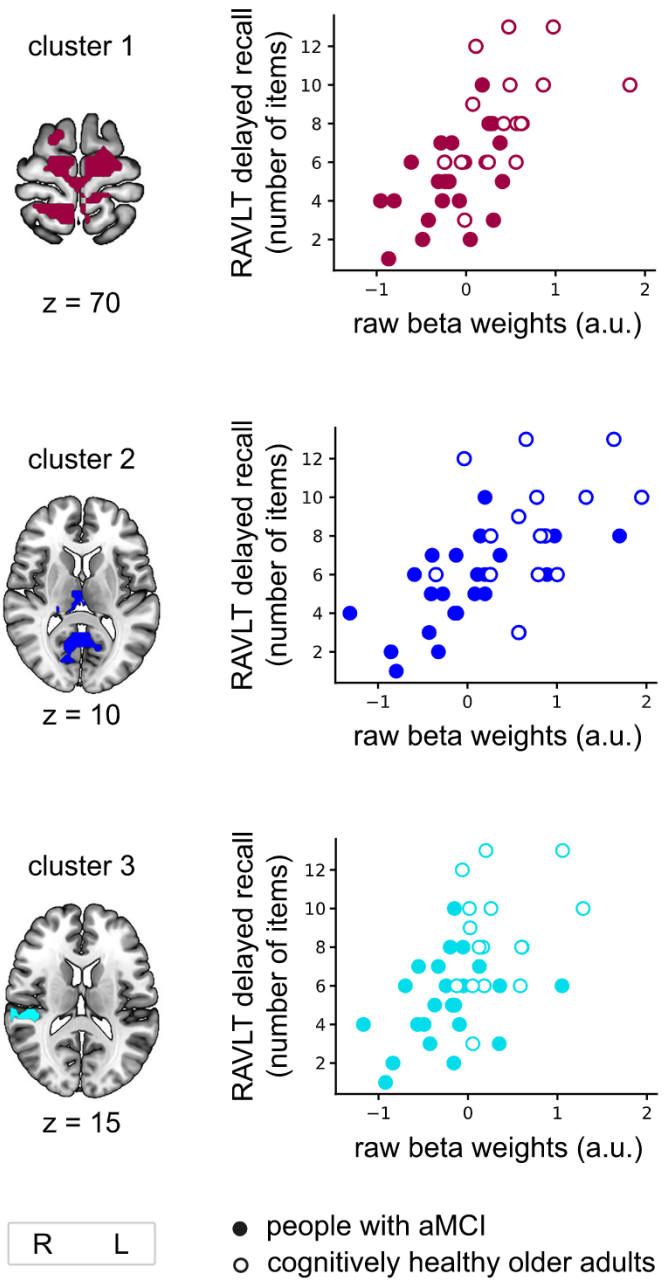

Fig. 5. Left: Three clusters where higher planning-related activity was related to better delayed recall. Results were thresholded at $p_{FWE} < 0.05$ (cluster-level). Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image. Right: Scatter plots of raw beta weights from the three clusters plotted against performance on the Rey Auditory Verbal Learning Test (RAVLT) of delayed recall.

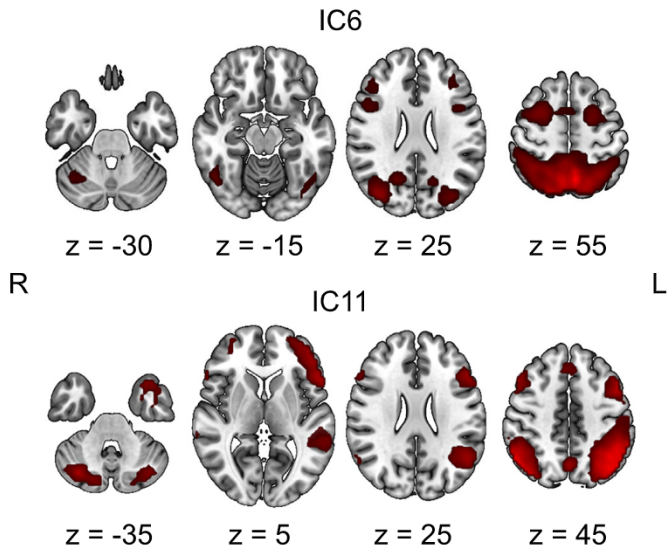

Fig. 6. Two planning-related components. Images are thresholded at $p_{FWE} < 0.05$ (peak-level) and are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

trials, with several more participants performing just above chance level. Our results indicate that trials that require planning 4 or more steps ahead can present a challenge even for cognitively healthy older adults, and may therefore not be able to separate between those with and without cognitive impairment.

Lower ToL performance in people with aMCI was accompanied by lower activation in several brain regions (see Fig. 4) that have previously been associated with visuospatial planning, spatial imagery, and object representation. Lateral Brodmann area 6, or the premotor cortex, has been implicated in previous studies using the ToL task (Baker et al., 1996; Beauchamp et al., 2003; Dagher et al., 1999; Nitschke et al., 2017; Schall et al., 2003; van den Heuvel et al., 2003; Wagner et al., 2006), and has been associated with updating spatial representations, sequence planning, and integrating visual cues with planned motor responses (Chouinard and Paus, 2006; Hoshi and Tanji, 2007, 2006; Schubotz and von Cramon, 2003; Tanaka et al., 2005). Similarly, activity in the cerebellum has often been observed during visuospatial planning (Beauchamp et al., 2003; Dagher et al., 1999; Nitschke et al., 2017; Schall et al., 2003), and has been associated with a series of cognitive functions that go beyond movement preparation (Ito, 2008; Stoodley, 2012). Though fewer studies reported planning-related activation in the thalamus (Owen et al., 1996; Wagner et al., 2006), this area has recently been suggested to play a role in maintaining and updating mental representations (Wolff and Vann, 2019). People with aMCI also had less planning-related activity in both temporal cortices, and in the left inferior occipital and fusiform gyri. Middle and superior temporal gyri have been associated with perceiving and imagining graspable objects (Creem-Regehr and Lee, 2005), maintaining visuospatial and object-based information in working memory (Park et al., 2011; Ren et al., 2019), and monitoring action outcomes (van Kemenade et al., 2019). Though the inferior occipital and fusiform gyri are most known for their involvement in facial recognition, they have also been implicated in spatial imagery (Cona and Scarpazza, 2019; Spagna et al., 2021).

The largest cluster of under-activation in people with aMCI covered the anterior calcarine sulcus, the anterior cuneus, and the superior occipital gyrus, and extended into the right precuneus. Structural, functional, and metabolic changes in the precuneus and the adjacent posterior cingulate cortex (PCC) have consistently been observed in MCI and early AD (see Jacobs et al., 2012 for a review). Given that the precuneus and the PCC are also involved in planning (Nitschke et al., 2017), changes in these areas could explain the high occurrence of planning deficits in MCI. Besides being involved in externally-oriented cognition, the precuneus and the PCC are also part of the default model network (DMN) that supports internally-oriented cognition (Leech and Sharp, 2014; Utevsky et al., 2014). Since the precuneus and the PCC are associated with both resting and task states, it can be hypothesized that they are involved in switching between the two. Interestingly, a recent meta-analysis found that the anterior portions of the cuneus and the precuneus are consistently recruited by older, but not younger adults during tasks of executive functions (Heckner et al., 2020). The authors suggested that this over-activation could serve to compensate for difficulties in inhibition and shifting between internally and externally directed attention. Lower planning-related activation in parietal areas could therefore indicate that this compensatory mechanism breaks down in aMCI, leading to more pronounced difficulties in executive functioning.

Because some of the between-group differences in brain activity were no longer significant after controlling for task performance, it remains unknown whether under-activation in people with aMCI is a feature of MCI or of planning deficits irrespective of MCI. Structural and functional alterations in some of the regions where under-activation was not independent of planning performance, namely temporal cortices and the cerebellum, have previously been reported in neurodegeneration. A meta-analysis found that people with aMCI have lower resting state activity in the right middle temporal gyrus, and higher resting state activity in the left middle temporal gyrus (Lau et al., 2016). Moreover, lower volume and cerebral blood flow in the left middle temporal gyrus has been related to conversion from aMCI to AD (Hirao et al., 2005; Karas et al., 2008). Changes in cerebellar volume and functional connectivity have also been reported in both MCI and AD (see Jacobs et al., 2018 for a review). The high prevalence of planning dysfunction in people with all subtypes of MCI (Brandt et al., 2009), together with our finding that people with aMCI were impaired even on easier ToL trials, might mean that deficits in this domain are an intrinsic part of aMCI. The focus on the "amnestic" component of MCI might therefore be too narrow, and though memory problems may be the characteristic symptom of aMCI, deficits in other domains should not be overlooked.

In line with the idea that memory and executive dysfunction in aMCI are closely related, we also found that better memory was related to higher planning-related brain activity in frontal, parietal, and temporal areas. Similarly, previous studies found that people with aMCI who have better preserved executive functions also have better memory performance, and that memory performance is related to functional connectivity and cortical thickness of brain areas that support executive functioning (Chang et al., 2010; Yuan et al., 2016). It could be that difficulties in planning and verbal memory have a common origin in impaired sequence processing, which could lead to suboptimal memorization or encoding strategies. We found that better delayed recall was related to higher activation in Brodmann area 6, mainly in the supplementary motor area (SMA; see Fig. 5). Despite its name, the SMA is also involved in processing of sequences outside the motor domain, such as verbal working memory (Cona and Semenza, 2017), and was shown to play a causal role in the updating of serial verbal representations (Tanaka et al., 2005). Parts of Brodmann area 6 have also been associated with the use of semantic encoding strategies during word list learning in older adults (Balardin et al., 2015). It has been found that successful performance on the RAVLT is achieved when people use semantic-based learning strategies (Cremona et al., 2020), which are used less often by older people and people with aMCI (Fernandes and Grady, 2008; Ribeiro et al., 2007). It might be that older adults with worse memory performance have difficulty manipulating the information in working memory into semantic clusters that would aid recall.

It should be noted that processing of non-motor sequences is usually ascribed to the anterior portion of the SMA, the pre-SMA, whereas our effects were mostly in the more posterior part, the SMA-proper, which is more commonly associated with motor processing (Balardin et al., 2015; Cona and Semenza, 2017; Tanaka et al., 2005). It has been suggested

that the SMA-proper is involved not only in the motor control of speech, but also in inner speech, and in verbal working memory associated with inner speech (Hertrich et al., 2016). Similar functions have been ascribed to the right superior temporal gyrus, which we also found to be related to delayed recall. The right superior temporal gyrus has been associated with visuospatial working memory (Park et al., 2011), as well as with the rate of inner speech production (Shergill et al., 2002), and was found to be active during encoding of a word list in a group of older adults with and without AD (Peters et al., 2009). Moreover, metabolism in the right lateral temporal cortex was also related with acquisition of a word list in people with MCI who later developed AD (Genon et al., 2013). One could hypothesize that the under-activation of the SMA and the right temporal cortex could lead to less efficient semantic encoding strategies and/or articulatory rehearsal, and therefore poorer recall. Future studies should elucidate the contribution of pre-SMA and SMA-proper to memory performance in older adults, as this might point towards the mechanisms behind memory impairment.

Better delayed recall was also associated with higher planning-related activity in the bilateral retrosplenial cortex (Brodmann areas 29 and 30), extending into the precuneus, the calcarine fissure and the lingual gyrus. The retrosplenial cortex and the precuneus are involved in episodic memory, scene construction, and visuospatial imagery (Cavanna and Trimble, 2006; Fletcher et al., 1995; Vann et al., 2009). Hypometabolism in these two areas is apparent in aMCI and early AD (Bailly et al., 2015; Brown et al., 2014; Minoshima et al., 1997; Nestor et al., 2003), and is related to episodic memory impairment in AD (Desgranges et al., 2002). There is evidence suggesting that damage to the retrosplenial cortex can impair verbal memory and the use of encoding strategies such as semantic and category clustering (Kim et al., 2007; McDonald et al., 2001). On the other hand, the retrosplenial cortex belongs to the DMN, which is normally deactivated during demanding cognitive tasks such as the ToL task (Anticevic et al., 2012). Previous studies have found that the deactivation of the DMN during cognitive tasks decreases from healthy aging to MCI to AD (Hafkemeijer et al., 2012). This is in contrast with our results, where people who showed more activation of the retrosplenial cortex during the ToL task were less impaired in delayed recall. Though the retrosplenial cortex would expectedly be involved in episodic memory performance, it remains unclear why activation during planning would be beneficial.

In contrast to previously published studies, there was no effect of task complexity on brain activity, which could be due to already high neural engagement for easier trials. Previous studies found that more complex ToL trials evoke stronger activation in regions that support planning performance, namely the bilateral dorsolateral prefrontal cortex (DLPFC) and frontal eye fields, the SMA, the inferior parietal lobule, the precuneus, the caudate, and the left anterior insula and the rostrolateral prefrontal cortex (see Nitschke et al., 2017 for a meta-analysis). The fact that we did not find an effect of task complexity could be due to at least two reasons. First, participants who found the hard trials too challenging may have disengaged from the task. Another possibility is that older adults already engage all available resources when solving easy trials, and have no room for further increase in activity for hard trials. Compared to younger adults, older adults were found to have higher brain activity when performing tasks of executive functions, especially in regions and networks involved in cognitive control (Di et al., 2014; Li et al., 2015), which could reflect compensatory mechanisms or reduced neural efficiency.

Surprisingly, we did not observe any between-group differences in functional connectivity, nor did we find any associations between connectivity and cognition. This is somewhat unexpected because functional connectivity is thought to reflect local fluctuations in cerebral blood flow (CBF), cerebral blood volume, and brain metabolism, all of which are affected in aMCI (Anchisi et al., 2005; Xu et al., 2007; Zimny et al., 2011). However, the relationship between these parameters and functional connectivity may change with aging. It has been found that age-related hypometabolism was not related to changes in functional connectivity, and that the correlation between CBF and functional connectivity was lower in older than younger adults (Chételat et al., 2013; Galiano et al., 2020). On the other hand, previous studies also reported altered functional connectivity in people with MCI in the resting state (Bai et al., 2009a; Cai et al., 2017; Sorg et al., 2007), as well as during task performance (Bai et al., 2009b; Bokde et al., 2006; Hird et al., 2018). Cai et al. (2017) found that people with aMCI had altered resting state functional connectivity within several networks, including the default mode, the sensorimotor, and the visual network. Though we investigated some of the similar regions of interest (the SMA, the inferior parietal lobule, and the middle occipital gyrus), we did not find between-group differences in connectivity. This could be because we analyzed task-based data, or because we had a smaller sample size. Whereas the correlation between resting state and task-based functional connectivity is generally high, it is significantly lower in older than in younger adults (Hughes et al., 2020), meaning we cannot draw direct comparisons between the two. Older adults may also have higher inter-individual differences in resting state connectivity compared to younger adults (Chen et al., 2021). If the same holds true for planning-related connectivity, it could be that our sample was simply too small to detect between-group differences in the presence of high inter-individual variation. The discrepancy between our findings and previous work could therefore be due to age-related dissociation between the measured parameters, and due to differences in experimental design.

It is also possible that by limiting our analysis to the six planning-related regions, we missed between-group differences in functional connectivity in other brain areas, such as the prefrontal cortex. This could also explain why we did not find any associations between brain activity or connectivity and apathy. Previous studies have shown that apathy in AD and MCI is related mostly to gray matter abnormalities in prefrontal areas, namely the anterior cingulate cortex, the DLPFC, and the orbitofrontal cortex, as well as the striatum and the insula (Jeong et al., 2018; Kos et al., 2016; Raimo et al., 2019; Starkstein and Brockman, 2018; Stella et al., 2014). We were only able to identify one study that measured functional connectivity during planning, and it showed that connectivity between the DLPFC and the superior parietal cortex was positively related to task complexity (Newman et al., 2003). Though the DLPFC is commonly implicated in planning (Nitschke et al., 2017), it was not activated in our sample. In healthy younger adults, superior performance on the ToL task, defined as performance with more than 70% accuracy, was associated with more extensive activation of the left DLPFC (Cazalis et al., 2003). It could be hypothesized that the relatively low performance in our sample meant that prefrontal areas were not sufficiently engaged, masking any differences that might have been observed there otherwise.

4.1. *Limitations and future directions*

Main limitations of this study are the rather limited sample size and relatively low task performance. Seven participants with aMCI and three cognitively healthy older adults had to be excluded from analysis due to poor performance on the ToL task. The task also did not evoke activity in prefrontal regions, which have consistently been associated with apathy in MCI and AD. Future studies should use a modified version of the task, or a task that is easier to perform for older adults and people with aMCI. This would allow for less participants to be excluded due to poor performance, and might also reduce the amount of noise in the data. Of the 25 people with aMCI, only nine were diagnosed with apathy. Having a larger number of participants with clinically-relevant levels of apathy could have enabled us to observe differences between people with aMCI with and without apathy. Lastly, given that we found a potential association between planning and memory deficits, future studies would benefit from including tests of episodic memory that are able to measure differences in learning strategies, such as the California Verbal Learning Test (Delis et al., 1988).

Given the importance of planning for daily functioning, it is

necessary to not only identify the brain areas associated with planning deficits, but to also devise effective interventions. Possible interventions range from cognitive training, to exercise, medication, or non-invasive brain stimulation. Strategy-based cognitive training programs for people with MCI that teach goal-setting, planning, and sequencing were found to have positive effects not only on planning abilities, but also on memory and daily functioning (Fukuta and Mori, 2019; Schmitter-Edgecombe and Dyck, 2014). There is also some evidence suggesting that physical exercise can improve executive functioning in MCI (see Öhman et al., 2014 for a review), and that at least in younger adults, aerobic exercise can lead to improved performance on the ToL task (Chang et al., 2011). Though findings on the benefits of cholinesterase inhibitors in MCI are mixed, a study found that visuospatial problem solving was improved in people that recently started donepezil (Beversdorf et al., 2021). Lastly, the effects of cognitive training could potentially be maximized by transcranial stimulation of brain areas involved in planning (Martin et al., 2014). In a study on healthy younger adults, non-invasive brain stimulation delivered while participants performed the ToL task resulted in better planning performance (Dockery et al., 2009). Though findings of individual studies can be promising, there are currently no interventions that are routinely used to improve cognition in people with MCI. Preserved planning abilities can help people maintain their independence, and may also make them more likely to benefit from strategy-based interventions that aim to minimize the effect of memory impairment on daily life through goal-setting and planning. Identifying neural underpinnings of planning deficits and how they relate to other cognitive domains can hopefully uncover new treatment targets and lead to effective interventions with transferrable benefits.

5. Conclusion

In conclusion, we found that planning deficits in people with aMCI were related to lower activity in a diffuse network of regions in parieto-occipital, temporal, and frontal cortices, as well as the thalamus and the cerebellum. Moreover, planning-related activity in the supplementary motor area, the retrosplenial cortex and adjacent areas, and the right temporal cortex was related to better memory performance across all participants. The results point to the relevance of planning deficits for understanding aMCI and extend its clinical and neurobiological signature. Future studies should investigate the role of planning deficits in memory impairment, and the impact planning deficits might have on learning strategies in people with cognitive decline.

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CRediT authorship contribution statement

Nena Lejko: Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Shankar Tumati:** Conceptualization, Investigation. **Esther M. Opmeer:** Conceptualization, Investigation. **Jan-Bernard C. Marsman:** Methodology. **Fransje E. Reesink:** Conceptualization, Investigation. **Peter P. De Deyn:** Conceptualization, Investigation. **André Aleman:** Conceptualization, Supervision. **Branislava Ćurčić-Blake:** Supervision.

Declaration of competing interest

None.

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