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Episodic Past, Future, and counterfactual thinking in Relapsing-Remitting Multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a progressive disease characterized by widespread white matter lesions in the brain and spinal cord. In addition to well-characterized motor deficits, MS results in cognitive impairments in several domains, notably in episodic autobiographical memory. Recent studies have also revealed that patients with MS exhibit deficits in episodic future thinking, i.e., our capacity to imagine possible events that may occur in our personal future. Both episodic memory and episodic future thinking have been shown to share cognitive and neural mechanisms with a related kind of hypothetical simulation known as episodic counterfactual thinking: our capacity to imagine alternative ways in which past personal events could have occurred but did not. However, the extent to which episodic counterfactual thinking is affected in MS is still unknown. The current study sought to explore this issue by comparing performance in mental simulation tasks involving either past, future or counterfactual thoughts in relapsing-remitting MS. Diffusion weighted imaging (DWI) measures were also extracted to determine whether changes in structural pathways connecting the brain's default mode network (DMN) would be associated with group differences in task performance. Relative to controls, patients showed marked reductions in the number of internal details across all mental simulations, but no differences in the number of external and semantic-based details. It was also found that, relative to controls, patients with relapsing-remitting MS reported reduced composition ratings for episodic simulations depicting counterfactual events, but not so for actual past or possible future episodes. Additionally, three DWI measures of white matter integrity—fractional anisotropy, radial diffusivity and streamline counts—showed reliable differences between patients with relapsing-remitting MS and matched healthy controls. Importantly, DWI measures associated with reduced white matter integrity in three association tracts on the DMN—the right superior longitudinal fasciculus, the left hippocampal portion of the cingulum and the left inferior longitudinal fasciculus—predicted reductions in the number of internal details during episodic counterfactual simulations. Taken together, these results help to illuminate impairments in episodic simulation in relapsing-remitting MS and show, for the first time, a differential association between white matter integrity and deficits in episodic counterfactual thinking in individuals with relapsing-remitting MS.

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1. Introduction

Multiple sclerosis (MS) is a chronic dysimmune disorder of the central nervous system (Gross and Lublin, 2017) and one of the main causes of disability in young adults worldwide (Melcon et al., 2014). Currently, while there is no cure for MS, the available disease-modifying therapies focus on immune mechanisms of MS and have growing success in slowing the progression of associated disabilities, which can manifest through motor, sensory, and neuropsychiatric symptomatology. This associated neuropsychiatric symptomatology includes depression, anxiety and fatigue (Horng and Fabian, 2017), which in turn can have downstream effects on cognitive functions, including affecting processing speed and visual memory—although attention, working memory, executive functions, and long-term memory can be impaired too (Chiaravalloti and DeLuca, 2008; Sumowski, et al., 2018). In Latin America, it is estimated that 34.5% of MS patients present cognitive impairment, greatly affecting their quality of life (Vanotti and Caceres, 2017).

One of the least well understood aspects of cognitive decline in MS is its impact on autobiographical memory. An initial study employing the autobiographical memory interview (Kopelman et al, 1989) suggested that only personal semantic information from the patients' autobiographical memory (e.g., remembering the name of your elementary school) was affected in MS, and that the impairment was rather mild (Paul et al, 1997). However, a subsequent study with MS patients at advanced stages of the disease showed instead marked deficits in both autobiographical incidents (i.e., remembering precise episodes from one's personal past) and personal semantic information (Kenealy et al., 2000; 2002). These conflicting findings likely result from the fact that the notion of autobiographical memory is complex (Mace, 2019), and earlier instruments failed to recognize that a single autobiographical memory may involve both episodic and semantic components, as both episodic and semantic memory are profoundly intertwined when it comes to the encoding and retrieval of memories of past personal experiences (Renoult et al, 2019; De Brigard, Umanath and Irish, 2022).

To more carefully explore autobiographical memory deficits in MS, recent studies have employed alternative measures better suited to differentially quantify episodic and semantic components within a single autobiographical recollection (Levine et al, 2002). A consistent finding across these more recent studies is that patients with relapsing remitting MS (RRMS) present impairments in autobiographical memory, but these difficulties are confined to *episodic* autobiographical memory (EAM), that is, the mental reliving of past personal experiences, which occurred in specific spatiotemporal contexts, via the reinstatement of remembered episodic details, including sensory, affective and contextual (Tulving, 2002). Moreover, these difficulties have been associated with executive-related impairments in generating strategies to retrieve past episodic information (Ernst et al., 2013), which in turn have been associated with bilateral prefrontal lobe hyperactivation (Ernst et al., 2012; 2014). By contrast, *semantic* autobiographical memory, which refers to the factual and conceptual knowledge that helps to scaffold and structure memories of past personal events (Irish and Piguet, 2013), appears to be unscathed in RRMS (Ernst et al., 2014).

In the past two decades, a wealth of research has shown that EAM not only enables us to recall information from past personal episodes, but that it also supports *episodic future thinking* (EFT), i.e., our capacity to imagine personal events that could happen in the future (Schacter and Addis, 2007). To add to this evidence, recent studies have shown that RRMS patients also present parallel difficulties in EAM and EFT (Ernst et al., 2014; Ernst et al., 2015a). As with EAM in RRMS, this impairment in EFT, too, has been associated with bilateral prefrontal and hippocampal hyperactivation (Ernst et al., 2015b; Ernst et al., 2016). Such parallel impairments align with the finding that both EAM and EFT share common neurocognitive mechanisms (Schacter et al, 2012). To account for these findings, Schacter and Addis (2007) proposed the *constructive episodic simulation hypothesis*, according to which the mental simulation of EAM and EFT involves a common system that can flexibly recombine details from episodic memory to create a coherent simulation. The underlying neural structure associated with this common system has been identified with the brain's default mode network (DMN; Spreng and Grady, 2010). A fundamental resting-state brain network, the DMN integrates the anterior and posterior cingulate cortices, inferior parietal lobe, hippocampus, lateral temporal cortex, and precuneus (Greicius et al., 2003). The constituent nodes of the DMN are connected by multiple canonical fiber tracts, and many of the DMN tracts connecting medial temporal lobe (MTL) regions (e.g., the inferior longitudinal fasciculus or ILF) are especially associated with episodic memory function (Lockhart et al., 2012). Indeed, recent evidence has shown that the MTL—hippocampus included—and the inferior parietal portions of the DMN are critical for the recombination and construction processes inherit in the generation of episodic simulations (Andrews-Hanna et al., 2014; Benoit and Schacter, 2015).

More recently, it has been shown that the same core network of regions in the DMN that support EAM and EFT also underwrite our capacity to imagine alternative ways in which past events could have occurred but did not—a cognitive operation known as *episodic counterfactual thinking* (ECT; De Brigard and Giovanello, 2012; De Brigard et al, 2013). Like EFT, ECT involves the simulation of a personal hypothetical episode, but unlike EFT, the hypothetical episodes depicted in ECT are known to *not* have occurred and thus are bounded by remembered facts (De Brigard and Parikh, 2019). Thus, despite documented behavioral, phenomenological and neural similarities among EAM, EFT and ECT (Schacter et al, 2015), a handful of studies have reported neural differences too. For instance, ECT elicits greater activation of medial prefrontal cortex relative to EFT (Van Hoeck et al., 2013), while the perceived plausibility of the episodic simulation differentially recruits the hippocampus during EFT relative to ECT (Parikh et al., 2018). More relevant for our present purposes, a number of studies report parallel deficits in EAM, EFT and ECT in different populations, including older adults (De Brigard et al., 2016; 2017), schizophrenia (Hooker et al., 2000; Chen et al., 30), Parkinson's disease (McNamara et al., 2003; De Vito et al, 2012; Souchay and Smith, 2013), MTL amnesia (Mullally and Maguire, 2014; Rosenbaum et al., 2005), and patients with focal frontal lobe injuries (Irish et al, 2013; Beldarrain et al, 2005).

Given the fundamental role played by the DMN in supporting episodic simulation during EAM, EFT and ECT, and the likelihood that the white matter impairments associated with MS threaten the integrity of the DMN, it becomes critical to explore the impact of MS in episodic simulation, as well as the more specific hypothesis that MS patients with more resilient structural pathways in the DMN should show better performance in episodic simulation tasks. To our knowledge, no study to-date has focused on ECT in patients with RRMS, or has employed measures of white matter integrity to predict performance in these three kinds of episodic simulation tasks. Indeed, very little is known about ECT in general in RRMS. In the context of decision-making, for instance, Simioni et al. (2012) reported that individuals with RRMS experienced less disappointment and regret relative to controls in a gambling task involving counterfactual reasoning. Unfortunately, these kinds of tasks require little episodic simulation, and are largely independent of EAM processes. As a result, a main objective of the current work is to explore, for the first time, ECT in patients with RRMS and its relation to EAM and EFT employing both behavioral and structural neuroimaging measures. Given the critical role that ECT plays in allowing us to revise past actions to improve upon our decision-making and hedge future uncertainty (Roese and Epstude, 2017; De Brigard and Parikh, 2019), understanding the nature of ECT in RRMS, and its relationship to documented deficits in EAM and EFT, is critical to further advance our knowledge of the disease.

To that end, we compared the performance of 22 RRMS patients and 22 matched controls across EAM, ECT, and EFT, using both the Autobiographical Interview (AI; Levine et al., 2002) and the Memory Characteristics Questionnaire (MCQ; Johnson et al., 1988). Both measures

are well validated approaches to explore the experience of episodic simulations during EAM, EFT and ECT, and enable to measure differences in the amount of episodic (internal) and semantic (external) information individuals generate when engaging in these three kinds of mental simulation. Importantly, while both measures were developed to explore the phenomenological experience of episodic simulation, they do so by different means, as the AI requires intersubjective agreement among external coders, whereas the MCQ indexes subjective reports for detail-specific items in a questionnaire (e.g., colors, sounds, spatial arrangement of objects, feelings, thoughts, etc. See **Supplementary Materials** for the questionnaires). Additionally, structural connectivity data were collected from multiple canonical fiber tracts connecting nodes of the DMN in order to assess the relationship between white matter integrity of structures underlying the DMN and potential deficits in the three kinds of episodic simulations in RRMS. We focus on a number of well-characterized canonical tracts using diffusion-weighted imaging (DWI) techniques, because an accurate anatomical localization of these white matter tracts in conditions such as MS can contribute to a better understanding of symptomatology and disease evolution effects. Multiple DWI metrics have been shown to be an effective tool for measuring distinct components of white matter health (Davis et al, 2009) and were employed here as measures sensitive to axonal myelin sheath thickness (*Radial Diffusivity* or RD) as well as general white matter health (*Fractional Anisotropy* or FA and *Streamline Counts*). We therefore chose to use this canonical tract approach in the current study to estimate the structural architecture supporting potential differences in the experience of EAM, EFT and ECT, in an effort to bridge clinical and basic science approaches.

Building and expanding upon previous findings, our first hypothesis was that, relative to controls, individuals with RRMS will include fewer internal details in all three kinds of episodic simulations, with no differences in the number of external and semantic details. Previous studies employing both AI and MCQ in younger and older adults show that the reduction in internal details evidenced in the older group is paradoxically accompanied by higher scores in the perceived experience of sensory and composition factors of the episodic simulations (De Brigard et al, 2016; 2017). As such, a second hypothesis was that individuals with RRMS will show higher scores in the sensory and composition factors relative to healthy controls across all three kinds of episodic simulations. In terms of the brain data, our third hypothesis was that, relative to controls, behavioral declines in individuals with RRMS will be associated with decrements in DWI measures associated with myelin health (FA, RD) for tracts connecting posterior DMN and hippocampal regions, and that MS-related differences in these tracts, and not others, will be associated with differences in performance in episodic simulation tasks. Testing for this hypothesis is important because it can delineate whether the specific episodic simulation impairments in RRMS are better explained by damaged constructive processes that compromise the integration and binding of details into a coherent scene (depending on the hippocampus), or by difficulties in initiating a strategic extraction of details (depending on the prefrontal regions).

2. Methods

2.1. Participants.

104 patients diagnosed with RRMS were recruited from the neuropsychology service of the Hospital Universitario Nacional (HUN) and the MS program sponsored by the health service *Salud Total* in Bogotá, Colombia. All patients were diagnosed with the McDonald's revised criteria (Polman et al, 2011) and all presented relapsing remitting phenotype according to Lublin (2014). Exclusion criteria included a history of relapse or corticoid treatment in the three months prior to participating in the research, neurological diseases other than MS, traumatic brain injury, and history of alcohol or drug abuse. The study received approval from the local ethics committee and all of the participants gave their approval to participate in the study according to the declaration of Helsinki.

In an initial session, each patient completed a comprehensive neuropsychological assessment battery to assess depression levels, fatigue, and cognitive impairments in verbal learning, working memory and processing speed. As per our inclusion criteria, which followed closely prior work (Ernst et al, 2012; 2013), 49 patients were excluded for presenting a score greater than 13 in the Beck et al. (1996) depression inventory or for presenting a history of psychiatric disorders, 6 were excluded because they presented a history of neurological diseases additional to MS, and 27 for showing no sign of mild cognitive impairment, which is present in over half the population of MS patients in Colombia (Alarcon et al., 2020). Cognitive impairment was defined as patients obtaining a score −1.5 standard deviations below the mean in learning tasks (CVLT / BVMT-R) or executive function tests (PASAT and FAS) (Benedict, 2009). Of note, when this investigation took place all patients lived independent lives and required no additional help. The final sample included 22 patients and 22 healthy controls, all Spanish native speakers (See Table 1 for demographics).

2.2. Neuropsychological assessment.

In the initial neuropsychological assessment session, a battery of tests frequently used to identify cognitive deficits in MS was applied. The tests included the Free Coding Learning and Memory Test (PAMCL, for its Spanish acronym), which is the Colombian adaptation of the CVLT-I (Delis et al. 1987), and assesses verbal memory and learning (Alarcon et al, 2020); the Brief Visual Memory Test Revised (BVMT-R; Benedict, 1997), which assesses learning and visual memory; the Symbol Digits Modalities Test - Oral version (SDMT; Smith, 1982), which assesses visual scanning and processing speed; the Paced Auditory Serial Addition Test (PASAT; Vanotti et al., 2016), which assesses working memory and speed of processing; and the FAS word fluency test (Spreen and Benton, 1977) which is a measure of phonemic word fluency, adapted for Latin-American (Caceres et al., 2011). The PAMCL, BVMT-R and SDMT were scored using regression-based norms adjusted by age, sex, and years of schooling using the norms developed by Alarcon et al. (2020). Z-scores for the PASAT and FAS word fluency test were scored with normative data adjusted to the Argentine population developed by Caceres et al. (2011). We employed the Spanish translation of the Beck depression inventory (Caceres et al., 2014) to detect depression symptoms, and the Spanish adaptation of the Daily Fatigue Impact Scale (D-FIS) used to assess the perception of physical and mental fatigue (Fisk & Doble, 2002; Martinez-Martin et al., 2006). Z scores were transformed to percentiles and are presented in Table 1.

2.3. Experimental session.

For patients, the experimental session occurred between one week and six months after the initial neuropsychological session, whereas for controls it occurred between one and two weeks after the initial neuropsychological assessment. The MRI scan took place during the experimental session, which consisted of two parts. The first part began with the administration of the Possible Autobiographical Event Questionnaire (PAEQ; De Brigard et al., 2016), which contains 24 statements referring to common possible events—half of them positive and half negative. After each statement, participants answered whether or not the event had occurred to them in the last five years (i.e., past statement) and, if not, whether or not the event could have happened to them in the past five years (i.e., counterfactual statement), and whether or not the event could happen to them in the next five years (i.e., future statement). Additionally, they were asked to rate the likelihood of such an event occurring from 1 (unlikely) to 7 (likely). The experimenter monitored that there was at least one negative and one positive past statement, and one positive and one negative future and counterfactual statement that were perceived as likely—i.e., that received a likelihood rating of 5 or

Table 1
Neuropsychological Test Performance. Means and standard deviations (in parenthesis) for both controls and Relapsing Remitting Multiple Sclerosis (RRMS) patients, RRMS normative percentiles for the relevant patient population, *p*-values and effect sizes. EDSS = Median Expanded Disability Status Scale. GMV = Gray Matter Volume. WMV = White Matter Volume. WMLV = White Matter Lesion Volume BDI-II = Beck Depression Inventory II. D-FIS = Daily Fatigue Impact Scale. SDMT = Symbol Digit Modalities Test. PAMCL = Free Coding Learning and Memory Test. BVMT-R = Brief Visual Memory Test Revised. FAS = Word fluency test from the Controlled Oral Word Association Test (COWAT). PASAT = Paced Auditory Serial Addition Test.

Measure	Controls	RRMS	RRMS Normative percentiles	*p* value	Effect size (Cohen's d)
Sex (M−F)	14–8	14–8	–	–	–
Age	40.05 (10.93)	40.50 (10.76)	–	0.89	0.04
Years of education	15.86 (1.83)	15.64 (2.40)	–	0.72	0.11
Time since onset of symptoms	–	8.82 (5.17)	–	–	–
EDSS (Median: IQR)	–	(2: 2.38)	–	–	–
GMV (Corrected by total intracranial volume)	0.43 (0.02)	0.39 (0.03)	–	$p < 0.001$	1.42
WMV (Corrected by total intracranial volume)	0.37 (0.01)	0.35 (0.02)	–	$p < 0.001$	1.17
WMLV (Corrected by total intracranial volume)	1.7×10^{-5} (1.5×10^{-4})	4.99×10^{-3} (6.6×10^{-3})	–	$p = 0.01$	0.979
BDI-II	4.68 (3.85)	6.88 (4.07)	–	$p = 0.02$	0.69
D-FIS	3 (5.34)	12.38 (10.22)	–	$p < 0.001$	
SDMT	60.64 (11.79)	45.61 (16.24)	30.45 (30.7)	$p < 0.001$	1.07
PAMCL − 5 trials	58.45 (7.87)	46.61 (11.31)	40.18 (30.7)	$p < 0.001$	1.23
PAMCL - Delay free Rec.	13.18 (2.08)	10.33 (2.74)	–	$p < 0.001$	1.18
PAMCL - Delay cued Rec.	14.14 (1.70)	11.39 (2.66)	–	$p < 0.001$	1.25
BVMT-R 3 trials	28.09 (5.05)	20.78 (6.962)	24.64 (20.1)	$p < 0.001$	1.22
BVMT-R Delay Rec	11.09 (1.34)	8.78 (2.76)	–	$p < 0.01$	1.09
FAS (Phonology)	44.05 (8.76)	32.50 (10.35)	20.77 (25.1)	$p < 0.001$	1.09
PASAT 3 s	47.41 (8.98)	30.89 (13.54)	14.64 (23.7)	$p < 0.001$	1.21
PASAT 2 s	39.45 (8.93)	22.00 (10.88)	8.5 (17.7)	$p < 0.001$	1.46

more. A list of 30 additional possible events was available in case the experimenter needed additional statements.

After a 15 min distraction task (coloring a mandala), a second autobiographical memory test was administered, comprising 6 events chosen from the PAEQ administered in the first part, as follows: from each participant's answers, one positive and one negative past statement—i.e., statements depicting events participants had an actual autobiographical memory about—were selected for the *Memory* condition; one positive and one negative likely counterfactual statement—i.e., statements depicting events participants knew had not occurred in their life but could likely have occurred—were selected for the *Counterfactual* condition; and one positive and one negative future statement—i.e., statements depicting possible events participants thought could likely occur in their future—were selected for the *Future* condition. Three other statements—one past, one counterfactual and one future—were randomly selected for an initial practice trial. Thus, for the second part of the study, the 6 chosen events were presented to the participant for a total of six trials: past positive, past negative, counterfactual positive, counterfactual negative, future positive, and future negative. The order to presentation of the events was counterbalanced across valence and condition. All trials had the same structure: participants would see a screen with a heading indicating one of three conditions: "Remember when", for the Memory condition; "Imagine what would have happened if", for the Counterfactual condition; and "Imagine what would happen if", for the Future condition. Below the heading, participants they read the statement corresponding to the selected trial, and they were asked to verbally describe their mental simulation. Specifically, for the Memory trials, they were asked to remember the moment corresponding to the event and to describe their memory in as much detail as possible; for the Counterfactual trials, they were ask to imagine what would have happened had event occurred in their past and to describe their imagination with as much detail as possible; finally, for the Future trials, participants were asked to imagine what would happen if the event were to occur in their future and to describe their imagination with as much detail as possible. Participants described their mental simulations aloud for up to three minutes while being recorded, and received no prompting or interruption, unless their narrative ended within 30 s, in which case the investigator encouraged them to continue asking "Is there anything else that comes to mind? Finally, after each trial, participants completed the Phenomenological Characteristics Questionnaire (PCQ), which is an adaptation of the MCQ (Johnson et al., 1988) that includes both episodic future and counterfactual thinking in addition to episodic memory. The PCQ enabled participants to register subjective ratings for 21 phenomenological characteristics of their mental simulations. This modified version of the PCQ has been previously employed in English (De Brigard and Giovanello, 2012; De Brigard et al., 2016; Parikh et al., 2020) and was also recently translated and validated in Spanish (De Brigard et al., 2017).

2.4. Autobiographical interview scoring.

Each participant's tape-recorded description was transcribed and scored by three trained scorers, blind to group and hypothesis, and in accordance with the AI protocol (Levine et al., 2002). To aid with the scoring process and improve the precision of the detail count, scorers used the qualitative analysis software Atlas T.I. 8 Windows (ATLAS.ti Scientific Software Development GmbH), which allows manual categorization and automatic calculation of the frequency of a specific category in a given text. Each trial's scoring started by the identification of the main event. Scorers had access to the statement that cued each trial for each participant, so the main event was identified as the one that corresponded to the cue. All other episodes in the narrative were considered external events. The transcription was then divided into distinct segments or "details". Those that concerned episodic information pertaining to the main event were considered *internal* (e.g., details specific to time of day, objects, sensations, thoughts, etc.), whereas all other details were considered *external*. Thus, external details included not only information about episodes tangential to the main event, but also narrative elements such as metacognitive statements, semantic information and repetitions. For each trial, the number of internal and external details was tallied, and inter-rater reliability was evaluated by Cronbach's Alpha, observing an excellent agreement for both internal (patients $\alpha = 0.93$, controls $\alpha = 0.96$) and external details (patients $\alpha = 0.96$, controls $\alpha = 0.96$).

2.5. Behavioral analyses.

Demographic and neuropsychological data were analyzed using

Student's *t*-test implemented in R 4.03 (R Core Team, 2020) to interrogate for differences between groups. R was also used to model data from the AI as Repeated-measures ANOVA to interrogate for effects of group and condition; all post-hoc tests were Tukey-corrected. Results from the PCQ were first subject to a Confirmatory Factor Analysis (CFA), with a six-factor structure based on previous findings (De Brigard et al., 2016) using the Lavaan package for R. Diagonally weighted least squares was selected as extraction method, since this method is specifically designed for ordinal data and does not make assumptions about the distribution of the observed variables (Li, 2016). The values of the latent variables were calculated using the lavpredict function. Next, six linear mixed-effects models (LMEM) were performed using the afex package for R; Group (2), Condition (3), and Valence (2) were treated as fixed factors, and the variance due to random variation per subject was treated as a random effect. The maximum structure of random effects was included at the beginning of the process and each random effect was removed one by one until the model converged (see **Supplementary Material**). Finally, *p*-values were obtained using the Kenward-Roger Approximation (Kenward and Small, 1997; Singmann and Kellen, 2019). Because of an error in the recording, behavioral data from one patient was unavailable.

2.6. MRI acquisition & structural connectivity Analysis.

Participants were scanned during the experimental session on a Philips Multiva 1.5 T gradient-echo scanner, equipped with a 16-channel head coil. A high-resolution SPGR series (1-mm sections covering whole brain, interscan spacing = 0, matrix = 256^2, flip angle = 30, TR = 22 ms, TE = minimum full (3–6 ms), FOV = 19.2 cm) was collected. Finally, DWI data were collected using a single-shot echo-planar imaging sequence (TR = 1700 ms, slices = 50, thickness = 2.0 mm, FOV = 256 × 256 mm^2, matrix size 128 × 128, voxel size = 2 mm^3, b value = 1000 s/mm^2, diffusion-sensitizing directions = 25, total scan time = 18 min), with one unweighted (b = 0) image. The anatomical MRI was acquired using a 3D T1-weighted echo-planar sequence (matrix = 2562, TR = 12 ms, TE = 5 ms, FOV = 24 cm, slices = 68, slice thickness = 1.9 mm, sections = 248). Scanner noise was reduced with ear plugs, and head motion was minimized with foam pads. Total scan time, including breaks and structural scans, was approximately 22 min. The breaks did not occur during the diffusion sequence, but rather in between scan types. Participants remained in the scanner during the entire session and there were no interruptions during the diffusion sequences. Two RRMS patients did not undergo MRI due to dental work that would have created artifacts in the imaging data. Information on the structural connectivity analysis and the construction of connectivity metrics for canonical tract groups are detailed in the **Supplementary Material**. Briefly, we follow the estimation of connectivity between pairs of regions comprising canonical fiber systems, i.e., Canonical Tract Groups (CTG), as outlined in Davis et al. (2018). This CTG algorithm summarizes connectivity in canonical, well-characterized fiber systems. Streamline connectivity between regions of interest (ROIs) of a subparcellated version of the Harvard-Oxford Atlas (Tzourio-Mazoyer et al., 2002), defined originally in MNI space, and used previously in our work (Beynel et al., 2020; Davis et al., 2017) and others (Hall et al. 2021). One disadvantage of this standard atlas is that the ROIs could have different sizes. This issue was addressed by the sub-parcellation into 471 ROIs (Fornito et al., 2010), which produces nearly isometric volume across all ROIs, which reduces bias in DWI tractography and CTG estimation. For each canonical fiber tract (estimated from the JHU tract atlas, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), if any two atlas ROIs A and B overlap with that tract, we consider that region pair to be part of that particular canonical fiber system. This operation is performed in an iterative, automated manner, free of individual rater bias, as is suggested by deterministic, seed-target-ROI tractography techniques used elsewhere (Davis et al., 2009). Essentially, this approach is "connectome-based", in that it attempts to bring some anatomical validity to the widespread use of automated structural connectivity techniques so widely used today. To assess MS-related changes to these CTGs, a basic Student's *t*-test was also run through R Studio to compare the three diffusion parameters of interest (RD, FA, and STR) for fiber pathways between RRMS patients and healthy controls (see Table 3).

2.7. Defining canonical tract groups

We examined only region pairs that are connected by canonical fiber systems, i.e., CTG (Davis et al., 2018). This algorithm summarizes connectivity in canonical, well-characterized fiber systems. As outlined above, the DMN connects many disparate regions of cortex: the anterior and posterior cingulate cortices, inferior parietal lobe, hippocampus, lateral temporal cortex, and precuneus (Alves et al., 2019). Given our focus on the DMN, seven targeted tracts (Fig. 1) defined by the Johns Hopkins University white matter tractography atlas (Hua et al., 2008) were included in the present analysis: the dorsal (CING) and ventral cingulate (CINGhipp) tracts, connecting cingulate and hippocampal cortices, respectively; the forceps minor (FMin) of the corpus callosum (connecting left and right anterior cingulate regions); the inferior longitudinal fasciculus (ILF), which connects lateral temporal cortex with occipital cortex; and the superior longitudinal fasciculus (SLF), connecting the inferior parietal lobule and precuneus. We also included two fiber tracts which are not in the DMN but nonetheless often found to mediate mnemonic function (Von Der Heide et al., 2013), to examine the specificity of behavior—brain connectivity relationships studied herein: the uncinate fasciculus (UF), connecting inferior frontal and anterior temporal cortices, and the inferior fronto-occipital fasciculus (IFOF), which connects inferior frontal and occipital cortices. Based on the deterministic streamlines traversed by these tracts, fractional anisotropy (FA) and radial diffusivity (RD) values are averaged over the course of all streamlines in a tract. Both FA and RD have been widely interpreted as measures that are sensitive to myelin density; the logic of this interpretation is that while the principal direction of diffusion (i.e., $\lambda 1$, also known as axial diffusivity or AD) orients the fiber tract, the two transverse diffusivities ($\lambda 2 + \lambda 3/2$ = RD) reflect the amount of diffusion perpendicular to the main axis of the fiber tract. Thus, greater RD would reflect less restriction of water movement and may reflect myelin damage, as has been widely observed in MS (Klawiter et al., 2011). These values represent inputs to later regression models described below; the normalized grey matter volume (adjusted for total intracranial volume) was also included in these models as covariates of no interest (for calculation see **Supplementary Material**).

2.8. Robust regression analyses.

To assess whether differences in tractography measures predicted behavioral differences between groups, robust regressions were performed using the function lmrobM from the package robstatTM implemented in R. An efficiency of 0.85 was used as well as the "mopt" function, which computes the tuning constant that yields an MM-regression estimator with a desired asymptotic efficiency. Robust regressions were chosen because they generate more reliable estimates for outliers by systematically downweighing them (Greco et al., 2019). Grey matter volume and total intracranial volume were measured via the SPM toolbox CAT12 (https://www.neuro.uni-jena.de/cat/). The CAT12 toolbox segments data into different tissue classes by using a local intensity transformation. The tissue segments as a last step are then normalized to a common spatial reference using DARTEL (Ashburner, 2007).

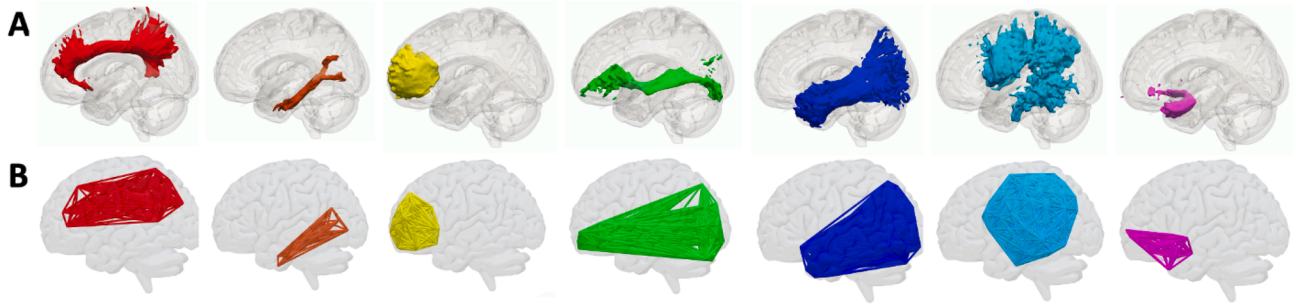

Fig. 1. Canonical fiber tracts. Assessments of canonical fiber tracts derived from diffusion-weighted tractography (**A**) can be readily assessed via structural connectomes filtered to only (**B**). Tracts include cingulum cingulate gyrus L (red), cingulum hippocampus L (orange), forceps minor (yellow), inferior fronto-occipital fasciculus L (green), inferior longitudinal fasciculus L (blue), superior longitudinal fasciculus L (turquoise), and the uncinate fasciculus L (pink). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Neuropsychological Assessments.

Demographic and neuropsychological data are summarized in Table 1. Controls and RRMS patients were matched for age and years of education, and sex was equally distributed between the two groups. RRMS patients completed the Beck Depression Inventory, with scores within normal range. However, RRMS patients were impaired on all neuropsychological tests, with effect sizes >1.0.

3.2. Autobiographical interview.

Scores for internal and external details were modelled as two independent mixed-design 2 × 2 × 3 ANOVAs, with Group (RRMS, control) as a between-subjects factor, and Valence (positive, negative) and Condition (Memory, Counterfactual, Future) as within-subjects factors. For *internal details* (Fig. 2**A**) this analysis revealed an effect of Group, $F(1,41) = 15.0$, $p < 0.001$, $\eta_p^2 = 0.268$ indicating that controls generated on average more internal details than RRMS patients. This effect remained significant when including as co-variates depression, $F(1,40) = 15.45$, $p < 0.001$, $\eta_p^2 = 0.279$, fatigue, $F(1,40) = 12.795$, $p < 0.001$, $\eta_p^2 = 0.242$, and verbal fluency (FAS), $F(1,40) = 10.51$, $p = .002$, $\eta_p^2 = 0.208$. To further evaluate the potential influence of executive function deficits in the effect of Group, we ran linear models for each of the following neuropsychological tests as predictor variables, PAMCL, BVMT-R, PASAT, SDMT, and FAS, and the number of internal details as the predicted variable, but none of these scores predicted group performance in internal details (see **Supplementary Material**). There was also an effect of Condition, $F(2,82) = 4.547$, $p = 0.013$, $\eta_p^2 = 0.100$. Post-hoc comparisons revealed that participants, regardless of group, generated fewer internal details in the future relative to the memory condition, $t(82) = 3.01$, $p^{tukey} = 0.010$. This effect remained significant when including depression as a co-variate, $F(2,80) = 3.332$, $p = 0.041$, $\eta_p^2 = 0.077$, but not so with fatigue, $p = 0.294$.

For *external details* (Fig. 2**B**), there was an effect of valence, $F(1,41) = 22.03$, $p < 0.001$, $\eta_p^2 = 0.286$, indicating that, regardless of group, narratives with negative valence across all conditions included fewer external details relative to narratives with positive valence. There was also an effect of Condition, $F(2,82) = 4.247$, $p = 0.018$, $\eta_p^2 = 0.094$, which post-hoc analyses revealed to be driven by a higher amount of details in the memory relative to the future, $t(82) = 2.825$, $p^{tukey} = 0.016$, condition. These effects remain significant when including fatigue as co-variate, Condition: $F(2,82) = 4.137$, $p = 0.020$, $\eta_p^2 = 0.094$; Valence: $F(1,41) = 8.299$, $p = 0.006$, $\eta_p^2 = 0.172$, but not so with depression, Condition: $p = 0.597$; Valence: $p = 0.176$. Importantly, there was no effect of group, $p = 0.431$.

3.3. Phenomenological characteristics

The CFA fit a model with the following six-factor structure: (1) *Visual Sensory*, which included ratings of clarity, color, visual details, vivacity, and overall sense of feeling; (2) *Non-visual Sensory*, which included ratings of sound, smell, taste, and touch; (3) *Composition*, which included ratings of composition, clarity of location, spatial arrangement of objects, spatial arrangement of people, and time of day; (4) *Emotional Valence*, which included ratings of emotion during the event and emotion during the simulation; (5) *Intensity of Emotion During the Event* and (6) *Intensity of emotion during simulation*. The model showed an adequate fit $\chi^2 = 147.6$, $df = 122$, $p = .057$, TLI = 0.991, CFI = 0.993, RMSEA = 0.029, and values for the resultant latent variables are depicted in Table 2.

Visual Sensory factor. The LMEM revealed a significant main effect of Condition, $F(2, 40) = 22.16$, $p < 0.001$. Holm corrected pairwise contrasts indicated that future $t(41) = -6.048$, $p < 0.001$ and counterfactual simulations, $t(41) = -5.618$, $p < 0.001$, had lower visual sensory ratings relative to memories. This main effect was modified by a Condition × Valence interaction, $F(2, 82) = 9.87$, $p < 0.001$. Holm corrected pairwise contrasts indicated that negative memories, $t(118) = -2.532$, $p = 0.032$, and negative future simulations, $t(118) = -2.313$, $p = .032$, received lower visual sensory ratings than positive memories and positive future simulations. Also, negative counterfactuals received higher visual sensory ratings than positive counterfactuals, $t(118) = 2.588$, $p = 0.032$.

Non-Visual Sensory factor. The LMEM revealed a significant main effect of condition $F(2, 205) = 8.04$, $p < 0.001$. Holm corrected pairwise contrast indicated that future simulations received lower non-visual sensory ratings than memories, $t(205) = -4.006$, $p < 0.001$. There was also a main effect of valence, $F(1, 205) = 7.04$, $p = 0.017$. Holm corrected pairwise contrast indicated that negative simulations received lower non-visual sensory ratings than positive ones, $t(205) = -2.397$, $p = 0.0174$.

Composition factor. The LMEM revealed a significant main effect of Condition $F(2, 164) = 20.62$, $p \leq 0.001$. Holm corrected pairwise contrasts showed that counterfactual, $t(164) = -5.338$, $p < 0.001$, and future simulations, $t(164) = -5.761$, $p < 0.001$, had lower ratings of composition than memories. This effect was modified by a Group × Condition interaction, $F(2, 164) = 3.95$, $p \leq 0.021$. Holm corrected pairwise contrasts indicated that, relative to controls, RRMS patients gave lower ratings of composition to counterfactual simulations, $t(69.7) = -2.707$, $p = 0.025$.

Emotional valence. The LMEM revealed a significant main effect of Valence, $F(1, 41) = 92.96$, $p \leq 0.001$, with no interactions. Holm corrected pairwise contrasts indicated that regardless of condition and group, negative simulations were rated more negatively than positive simulations, $t(41) = -9.642$, $p \leq 0.001$.

Intensity of emotion during the simulated event. The LMEM revealed a

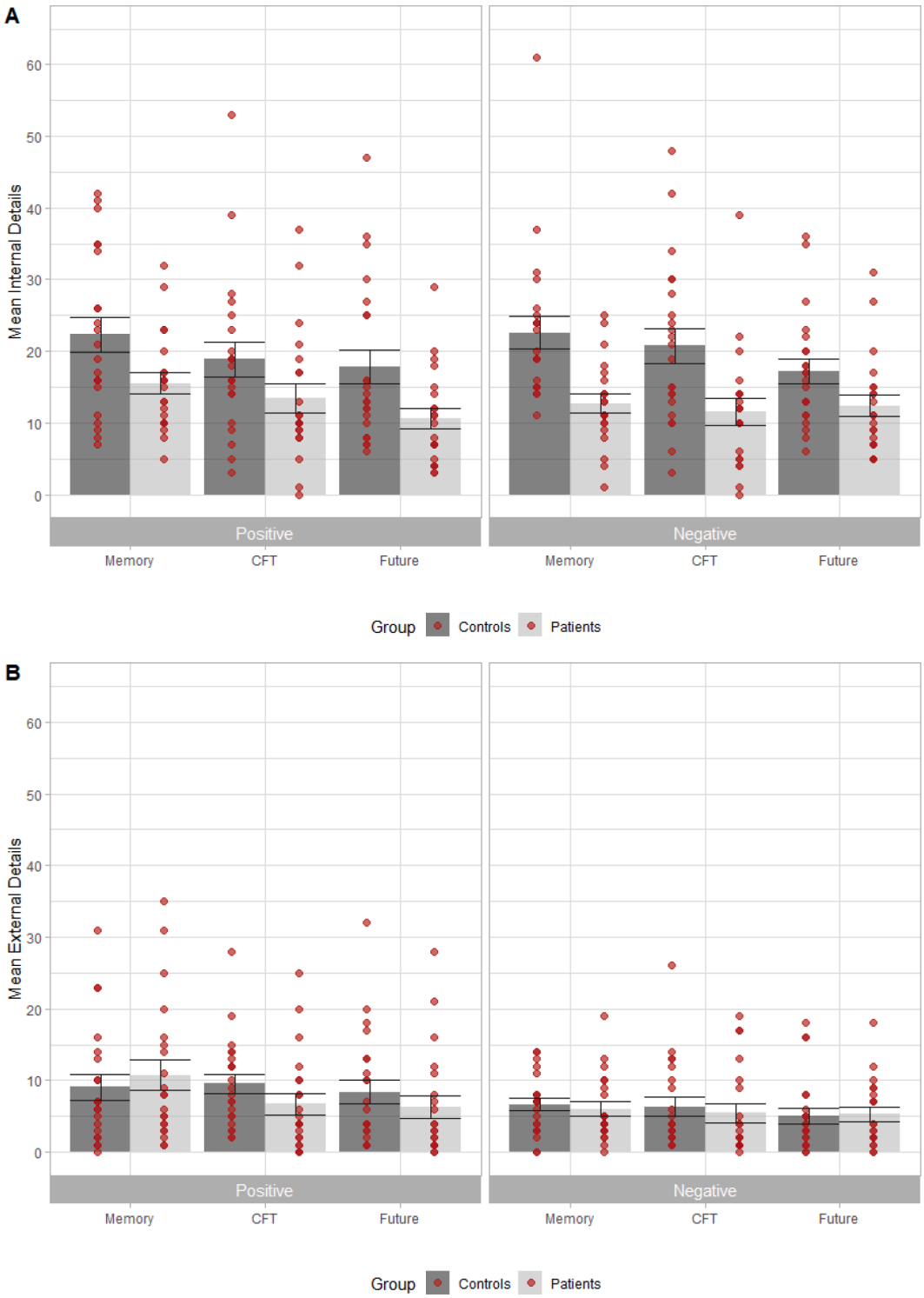

Fig. 2. Results from the Autobiographical Interview. Average number of internal (**A**) and external (**B**) details between conditions in RRMS patients and controls. CFT = Counterfactual. Error bars indicate standard error of the mean. Individual data points are also plotted to better visualize the spread and distribution of the data.

significant main effect of Valence, $F(1, 41) = 6.42$, $p < 0.015$. Holm corrected pairwise contrasts revealed that negative events received lower ratings of emotional intensity during the simulated event than positive ones, $t(41) = -2.533$, $p = 0.0152$. This effect was modified by a Valence × Condition interaction, $F(2, 164) = 4.80$, $p = 0.009$. Holm corrected pairwise comparisons revealed that negative future simulations received lower ratings of emotional intensity during the simulated event relative to positive future ones, $t(155) = -2.617$, $p = 0.0195$ and that negative memories received lower ratings of emotional intensity during the simulated event relative to positive ones, $t(155) = -3.024$, $p = 0.008$.

Intensity of emotion during simulation. The LMEM revealed a significant main effect of Valence, $F(1, 41) = 12.21$, $p = 0.001$. Holm corrected pairwise contrasts indicated that regardless of group and condition, and relative to positive simulation, negative simulations received lower ratings of emotional intensity during simulation, $t(41) = -3.494$, $p =$

Table 2
Phenomenological characteristics. Means and standard deviations for latent variables scores. CFT = Counterfactual.

Factor	Positive			Negative		
	Memory	CFT	Future	Memory	CFT	Future
Visual						
Controls	0.583 (0.673)	−0.221 (0.926)	0.050 (0.979)	0.206 (0.879)	0.198 (0.689)	−0.180 (0.903)
Patients	0.578 (0.858)	−0.627 (1.150)	−0.093 (1.070)	0.229 (1.070)	−0.305 (1.230)	−0.525 (1.140)
Non-Visual						
Controls	0.159 (0.923)	0.23 (1.080)	−0.051 (1.260)	0.122 (1.110)	−0.075 (0.776)	−0.262 (1.080)
Patients	0.586 (1.220)	−0.079 (1.150)	−0.115 (1.240)	0.105 (1.120)	−0.067 (1.180)	−0.292 (1.170)
Composition						
Controls	0.871 (0.777)	0.066 (1.100)	−0.076 (1.220)	0.345 (1.140)	0.346 (0.979)	−0.295 (1.150)
Patients	0.606 (1.250)	−0.771 (1.370)	−0.187 (1.550)	0.251 (1.440)	−0.648 (1.800)	−0.693 (1.510)
Emotional Valence						
Controls	0.666 (1.140)	0.611 (0.802)	0.643 (1.040)	−0.597 (1.240)	−1.040 (1.280)	−0.835 (1.200)
Patients	0.915 (1.330)	0.801 (1.400)	1.040 (0.872)	−0.768 (1.620)	−0.798 (1.810)	−0.887 (1.630)
Emotional Intensity Then						
Controls	0.295 (1.050)	−0.705 (1.560)	0.659 (0.666)	−0.614 (1.610)	0.159 (1.310)	−0.114 (1.590)
Patients	0.726 (0.814)	0.060 (1.540)	0.298 (1.530)	−0.083 (1.490)	−0.417 (2.010)	−0.417 (1.770)
Emotional Intensity Now						
Controls	0.360 (1.140)	0.314 (1.210)	0.178 (1.530)	−1.050 (1.790)	−0.413 (1.760)	−0.595 (1.790)
Patients	0.949 (1.360)	−0.385 (2.110)	0.472 (1.540)	0.234 (1.580)	−0.337 (1.960)	−0.004 (1.970)

0.001. Additionally, the Group × Condition interaction was significant, $F(2, 164) = 4.78$, $p = 0.01$. Holm corrected pairwise contrasts indicated that, contrary to controls, RRMS patients reported higher emotional intensity during memory relative to counterfactual simulation, $t(164) = -3.277$, $p = 0.007$.

3.4. Structural tractography

Group comparisons for key structural tractography measurements are summarized in Table 3. Visualizations of the seven canonical fiber tracks supporting association pathways in the brain's DMN are displayed in Fig. 1. Healthy controls (n = 22) show lower mean RD values than RRMS patients (n = 20) for bilateral cingulum tracts (both covering the cingulate gyrus and hippocampus), bilateral inferior fronto-occipital fasciculus, bilateral inferior and superior longitudinal fasciculus, and bilateral uncinate fasciculi. Similarly, healthy controls showed higher mean FA values than RRMS patients for all tracts. Notably, these findings validate previous findings describing disease-related declines in white matter health using DWI information[59] Lastly, in order to test whether these differences in qualitative measures (FA and RD) were not driven by differences in the underlying presence of fiber pathways, we evaluated streamline counts across our canonical tracts of interest. Differences in streamline counts between groups were low, such that healthy controls showed lower mean values than RMMS patients for bilateral hippocampal tracts in the cingulum and forceps minor, $t(36.16) = -2.35$, $p < 0.05$. Nonetheless, the overall lack of differences between groups suggests that our observations were driven by qualitative features (e.g., fiber organization or myelin content) of canonical tracts in the cerebrum, rather than by the presence or absence of the tracts themselves.

3.5. Behavior-Tractography relations

To evaluate whether differences in structural tractography measures could predict group differences in the performance on the AI, robust regressions for each Group, Condition and tractography measure were conducted, with the mean number of internal details as the dependent variable and each canonical tract of interest as a predictor variable. Gray matter volume was also included as a covariate in the models. These analyses revealed that, for healthy controls, as RD values in the right superior longitudinal fasciculus were higher, the number of internal details in the counterfactual condition were lower, $R^2 = 0.322$, $\beta = -0.864$, $p_{bonf} = 0.001$. No such correlation was evident for the memory and future conditions, once corrected for multiple comparisons. By contrast, for RRMS patients, as FA values in the left hippocampal portion of the cingulum and the left inferior longitudinal fasciculus were higher, so did the mean number of internal details in the counterfactual condition, $R^2 = 0.230$, $\beta = 0.497$, $p_{bonf} = 0.027$ and $R^2 = 0.204$, $\beta = 0.549$, $p_{bonf} = 0.049$, respectively (Fig. 3). Once again, no such correlation was found for the memory or future conditions (full regression results in **Supplementary Material**). Furthermore, we found no behavioral associations with either FA or RD values for two CTGs connecting mnemonic regions outside the DMN (UF and IFOF).

4. Discussion

The current study explored differences in the experience of mentally simulating EAM, EFT and ECT in RRMS patients and matched controls. To that end, we employed two behavioral measures—the AI and a modified version of the MCQ—and measures based on structural DWI tractography—RD, FA, and streamline counts—that describe the effective patterns of white matter integrity connecting disparate regions of cortex, with a particular focus on canonical tracts underlying the brain's DMN, which has been associated with all three forms of episodic simulation. Our analyses tested three hypotheses and yielded three main findings. First, we found that, compared to controls, RRMS patients included fewer internal details across all three kinds of episodic simulations, whereas differences in the number of external and semantic details between both groups were non-significant. This result not only replicates previous documented reductions in internal details during EAM and EFT in RRMS (Ernst et al., 2014; 216), but extends them to show that this reduction also affects ECT. These results also help to solve an open question left by prior findings, namely that the reduction in internal details during EFT may have to do with the reluctance to envision a possible future in light of the uncertainty surrounding the evolution of the disease (Ernst et al., 2014) rather than a cognitive

Table 3
Structural tractography measurements from DWI in healthy controls compared to RRMS patients.

Canonical tract group	RD values	FA values	STR values
Cingulum (cingulate gyrus) LPatients		0.43	992
Mean	5.64×10^{-4}	(0.04)	(381)
(SD)Healthy Mean	(7.24×10^{-5})	0.46	938
(SD)	5.14×10^{-4}	(0.03)	(112)
T-Value	(4.51×10^{-5})	3.13**	−0.61
	−2.62*		
Cingulum (cingulate gyrus) RPatients		0.41	855
Mean	5.70×10^{-4}	(0.04)	(332)
(SD)Healthy Mean	(7.53×10^{-5})	0.45	813
(SD)	5.14×10^{-4}	(0.02)	(93)
T-Value	(3.71×10^{-5})	3.67***	−0.54
	−3.03**		
Cingulum (hippocampus) LPatients		0.37	1675
Mean	6.50×10^{-4}	(0.05)	(548)
(SD)Healthy Mean	(7.82×10^{-5})	0.41	1337
(SD)	5.85×10^{-4}	(0.04)	(191)
T-Value	(8.65×10^{-5})	3.08***	−2.62*
	−2.58*		
Cingulum (hippocampus) RPatients		0.37	1458
Mean	6.44×10^{-4}	(0.04)	(643)
(SD)Healthy Mean	(7.09×10^{-5})	0.40	1108
(SD)	5.84×10^{-4}	(0.03)	(162)
T-Value	(5.86×10^{-5})	3.14***	−2.37*
	−3.02***		
Forceps minorPatients Mean		0.39	477
(SD)Healthy Mean	5.84×10^{-4}	(0.04)	(68)432
(SD)	(1.39×10^{-4})	0.43	(54)
T-Value	5.32×10^{-4}	(0.03)	−2.35*
	(4.24×10^{-5})	3.54***	
	−1.60		
Inferior fronto-occipital fasciculus L		0.37	880
Patients Mean (SD)Healthy Mean	6.42×10^{-4}	(0.03)	(654)
(SD)	(6.72×10^{-5})	0.40	717
T-Value	5.61×10^{-4}(4.37 ×	(0.02)	(92)
	10^{-5})	4.32***	−1.11
	−4.68***		
Inferior fronto-occipital fasciculus		0.38	820
RPatients Mean	6.30×10^{-4}	(0.03)	(744)
(SD)Healthy Mean	(6.67×10^{-5})	0.41	610
(SD)	5.63×10^{-4}	(0.02)	(49)
T-Value	(3.52×10^{-5})	3.76***	−1.26
	−4.08***		
Inferior longitudinal fasciculus		0.38	583
LPatients Mean	6.47×10^{-4}(7.18 ×	(0.04)	(299)
(SD)Healthy Mean	10^{-5})	0.42	487
(SD)		(0.02)	(44)
T-Value	5.65×10^{-4}	4.51***	−1.41
	(4.45×10^{-5})		
	−4.41***		
Inferior longitudinal fasciculus		0.36	640
RPatients Mean	6.60×10^{-4}	(0.04)	(262)
(SD)Healthy Mean	(6.57×10^{-5})	0.41	580
(SD)	5.71×10^{-4}	(0.02)	(49)
T-Value	(6.88×10^{-5})	4.87***	−1.01
	−4.34***		
Superior longitudinal fasciculus		0.40	475
LPatients Mean	6.15×10^{-4}	(0.04)	(112)
(SD)Healthy Mean	(6.83×10^{-5})	0.43	486
(SD)	5.51×10^{-4}	(0.03)	(33)
T-Value	(3.91×10^{-4})	3.34***	0.43
	−3.65		
Superior longitudinal fasciculus		0.40	371
RPatients Mean	6.15×10^{-4}	(0.04)	(83)385
(SD)Healthy Mean	(8.16×10^{-5})	0.43	(21)
(SD)	5.49×10^{-4}	(0.02)	0.71
T-Value	(5.89×10^{-5})	3.04***	
	−3.00***		
Uncinate fasciculus LPatients Mean		0.35	1665
(SD)Healthy Mean	6.45×10^{-4}	(0.03)	(1291)
(SD)	(7.36×10^{-5})	0.38	1149
T-Value	5.80×10^{-4}		
	(3.71×10^{-5})	(0.02)	(170)
	−3.60***	2.45*	−1.77
Uncinate fasciculus RPatients Mean		0.34	1404
(SD)Healthy Mean	6.46×10^{-4}	(0.03)	(1952)
(SD)	(8.29×10^{-5})	0.37	750
T-Value	5.94×10^{-4}	(0.02)	(102)
	(3.97×10^{-5})	3.29**	−1.50
	−2.59*		

Note: RD = Radial Diffusivity; FA = Fractional Anisotropy; SRT = Streamline Count. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.005$.

deficit with the retrieval and recombination of episodic details into hypothetical mental simulations. Since ECT involves the generation of an imagined situation that could have occurred in the past, but did not, the future uncertainty component of the hypothetical situation is removed—counterfactuals are, as their name implies, contrary to what actually occurred. As such, the current findings may lend credence to the claim that the reduction in internal details is due to deficits in the recombination of episodic components, rather than the psychological effects of future uncertainty associated with the evolution of the disease.

These findings also corroborate previous results showing no deficits in the external and semantic aspects of episodic simulations in individuals with RRMS (Ernst et al., 2013). As mentioned, earlier explorations of autobiographical memory in individuals with MS yielded mixed results, with some studies showing deficits in both episodic and semantic aspects of autobiographical recollection (Paul et al., 1997) while others showing a preserved semantic dimension (Kenealy et al., 2002). However, as remarked by Ernst and colleagues (2013), these initial studies employed the Autobiographical Memory Interview (Kopelman et al, 1989), an older instrument that has been shown to have poorer sensitivity to disentangle episodic and semantic aspects of autobiographical memories (McKinnon et al., 2006). Additionally, these initial studies failed to distinguish subtypes of MS, including participants at various stages of disease severity. Since our sample only includes a carefully curated set of RRMS, our results help to lend further support to the claim that the semantic dimension of episodic simulations in RRMS appears to be preserved, not only for EAM and EFT (Ernst et al., 2014; Ernst et al, 2015; Ernst et al., 2016), but also for ECT.

Extant studies comparing EAM to EFT in RRMS have employed the AI (Levine et al, 2002), which is based on the coding of transcribed narratives by external coders. However, little is known about the phenomenological characteristics of these kinds of simulations as measured by introspective self-reports. As such, a second aim of the current study was to explore, for the first time, the phenomenological characteristics of EAM, EFT and ECT in patients with RRMS. Building upon previous studies documenting an inverse relation between the number of internal details in the AI and the ratings of sensory, composition, vivacity, and intensity in older relative to younger adults across these three kinds of episodic simulations (De Brigard et al., 2016; 2017), we hypothesized that the same inverse relation may be present in RRMS relative to healthy controls, given the expected reduction in internal details. Our results, however, do not support this hypothesis, as we found no effect of group on the sensory, emotional and intensity factors. Surprisingly, although no effect of group was identified, we did find a condition by group interaction for ECT in the opposite direction, namely with RRMS reporting lower composition ratings relative to healthy control. It may be possible, then, that at least for ECT, RRMS introspective awareness of their imaginative experiences is more tuned to the episodic than the semantic components of their mental simulations.

Moving on to the brain data findings, we anticipated that individuals with RRMS will show decreases in white matter integrity (higher RD, lower FA) relative to controls. Our results are consistent with this hypothesis, as we see widespread effects in most canonical fiber systems for

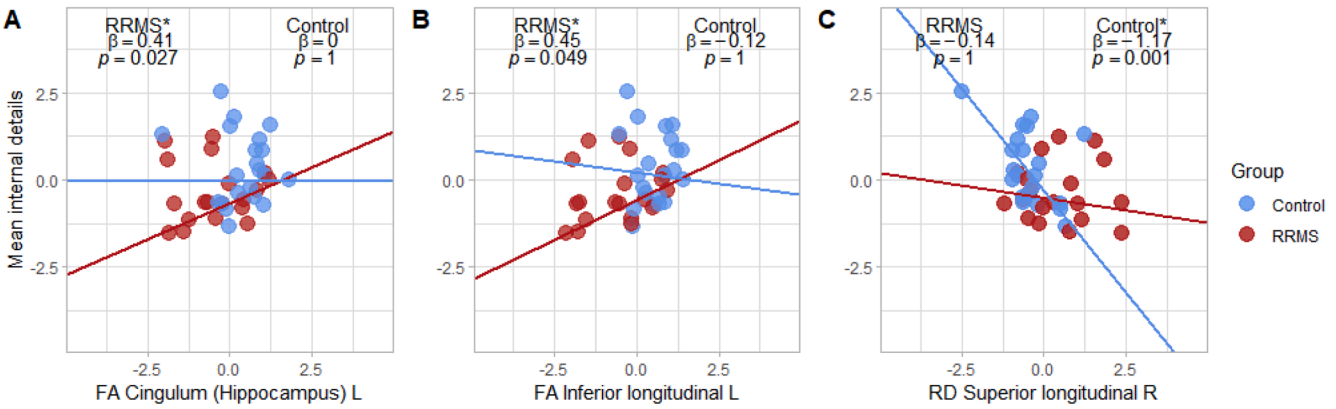

Fig. 3. Robust regressions. Results showing tractography measures associated with group differences in the number of internal details during counterfactual simulations. **A.** Left Inferior longitudinal fasciculus. **B.** Left hippocampal portion of the cingulum. **C.** Right superior longitudinal fasciculus. Patients in red; Controls in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

both FA and RD (Table 3). This may suggest generalized damage to white matter, instead of damage restricted to myelin, as is supposed in some models of RD (Davis et al, 2009); alternatively, FA is a derived measure which (by design) has a more normal distribution of values, and as such may be more sensitive to group differences. Intriguingly, we found the strongest group differences in tracts connecting regions strongly implicated in autobiographical memory, including the IFOF, the nearby ILF, and the temporal section of the cingulum connecting to the hippocampus. ILF has been shown to have lower FA in MS patients and is implicated in consolidation of visual memories and enhancement of processing visual stimuli (Roosendaal and Barkhof, 2015). Cingulum hippocampus has also been implicated in item and source memory performance in healthy aging (Henson et al., 2016; Ezzati et al, 2016) and this structure also may distinguish between normal and Alzheimer's disease-related groups (Nir et al., 2013). Functional neuroimaging studies have also demonstrated that left cingulate gyrus activation is more involved with language-based tasks (Zago et al., 2008). Since our memory tasks were all verbal memory paradigms, the laterality seen in our results may be explained by preponderance of the left hemisphere and specifically MTL structures in language-based tasks.

Finally, we explored whether differences in either of these DWI measures in tracts underlying the DMN—which has been reliably associated with our capacity to generate episodic simulations (Benoit and Schacter, 2015)—could predict behavioral differences in AI between individuals with RRMS and healthy controls. Two of our findings speak to these predictions. First, we found that in healthy controls, as the RD values were higher in the right superior longitudinal fasciculus, the number of internal details in the counterfactual condition decreased, suggesting that as the integrity of the myelin sheath is reduced in this tract (greater RD suggests more diffusion perpendicular to the fiber, and therefore a breakdown of myelin integrity), so is the episodic richness of ECT. Second, our findings also revealed that in RRMS, but not in healthy controls, higher FA values in the left hippocampal portion of the cingulum and the left ILF were associated with larger numbers of internal details in ECT, suggesting that the healthier the white matter/myelin sheath in these tracts, the more internal details are included in ECT. These canonical white matter fibers connect key parts of the DMN (hippocampus, PCC), lending further support to the observation that CFT rely on common DMN structures as EAM and EFT. It is important to note, too, that previous neuroimaging studies have shown that increased activity in the left hippocampus scales with increased perceived plausibility and vividness of episodic counterfactual thinking (De Brigard et al., 2013; Parikh et al., 2018). Likewise, studies with amnesic individuals with damage in the hippocampus have shown impairments in the generation and composition of spatial aspects of counterfactual simulations (Mullally and Maguire, 2014). As such, our findings are consistent with the observation that a healthy hippocampus and hippocampal tracts may be required to generate vivid and spatially coherent ECT (Palombo et al., 2018; Thakral et al., 2017).

It is important to acknowledge some limitations of the present work. Likely, a larger and even more balanced sample of RRMS patients and age-matched controls could have improved the strength of the evidence for some of the inferences we draw concerning the role of DMN connectivity in promoting ECT. As such, it is important to further corroborate these findings with other populations to make sure that our results generalize. That said, when considered as a sample of our relevant population, it is important to remark that Colombia is a country with low to moderate risk of developing the disease, and that approximately 10% of the total available population with MS in the city (Bogota) was included in this research (see, ***Participants***, above). A second limitation is that the AI was conducted between 1 week and 6 months after the neuropsychological tests and the depression scale were completed, so it is possible that in some cases the neuropsychological tests did not reflect the cognitive status of the patients at the time the AI was conducted. However, it is important to note that all patients had at least one follow-up visit with the medical team, and no patient presented new relapses, no changes were noted in the EDSS during that period, and none has been diagnosed with depression.

Lastly, there are also important theoretical limitations that need to be acknowledged. First, to establish the functional relevance of the structural disconnections examined here, it would be critical to relate structural connectivity in RRMS with functional connectivity, preferably collected during tasks involving EAM, EFT and ECT. A central premise in our work is that a system that can flexibly recombine details from episodic memory to create coherent mental simulations is supported by activity of the DMN, and this claim is supported by both functional and structural connectivity studies of EFT and CFT (Martin et al, 2011; Schacter et al., 2015; Faul et al, 2020). Functional connectivity during both EFT and ECT—isolated along the same pathways investigated here—may help to reveal a more complete picture of how episodic simulation changes in MS. Such task-related connectivity would also be instrumental in showing how RRMS patients may perhaps capitalize on alternative network connections to maintain successful performance. A second, theoretical limitation, is that we are interpreting our results in light of the constructive episodic simulation hypothesis (Schacter and Addis, 2007), according to which EAM, ECT and EFT show similar neural and cognitive effects because they share common episodic constructive processes. However, there are other alternative views in the offing, such as the scene construction hypothesis (Hassabis and Maguire, 2007), that are also compatible with our results. As such, these findings should not be interpreted as ruling out alternative explanations that need not appeal to episodic reconstructive processes (see De Brigard and

Gessell, 2016, for further discussion). Moreover, even if the constructive episodic simulation hypothesis is correct, it is still possible that other cognitive processes are also involved in our capacity to generate episodic simulations and, thus, could potentially explain some of our findings. To try to account for this possibility, we made sure to include linear models with relevant neuropsychological tests to investigate whether cognitive impairments in working memory, fluency, and the like, could predict the observed differences in task performance (see **Supplementary Material**). While no associations were found between neuropsychological scores and task performance, it remains a question for future research to explore how, for instance, impairments in working memory or executive function could potentially influence episodic simulation both in RRMS as well as healthy controls. Finally, a third theoretical limitation pertains to recent proposals suggesting more nuanced interpretations of the nature of external details in the AI (Strikwerda-Brown et al., 2018; Strikwerda-Brown and Irish, 2021) As such, caution is warranted when interpreting the lack of group differences in external details during these three kinds of episodic simulations, as further research will be needed to fully assess the different elements that compose the external details associated with the narratives of episodic simulations in patients with RRMS.

In sum, the current study reports the first examination of ECT in patients with RRMS, using (objective and subjective) behavioral and structural connectivity measures, and in comparison to EAM and EFT. Consistent with and extending previous reports, we found reduced levels of internal details across all episodic simulations in RRMS relative to matched controls, and identified reductions in composition ratings for ECT, but not in EAM and EFT, in RRMS. Additionally, our results show, for the first time, an association between white matter integrity in core tracts of the DMN and reductions in internal details in ECT in RRMS. These findings suggest that disease-related changes in ECT are related to the integrity of structural connectivity between regions of the DMN. Our results therefore add to a large body of literature showing parallel deficits in episodic past, future and counterfactual thinking in different populations—including older adults (De Brigard et al., 2016), schizophrenia (Hooker et al., 2000), Parkinson's disease (McNamara et al, 2003), MTL amnesia (Mullally and Maguire, 2014), Huntington's disease (Solca et al., 2015), and patients with focal frontal lobe injuries (Beldarrain et al., 2005)—but also to a wider set of results showing specific deficits in episodic mental simulation in RRMS (Ernst et al., 2014; Ernst et al., 2015). Given how important ECT is for emotion-regulation, decision-making and behavioral modification (Roese and Epstude, 2017), further examination of the influence of MS on this critical cognitive process may help to further illuminate the nature of the cognitive consequences of the disease and help to improve existing treatments.

Declaration of Competing Interest

The 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.nicl.2022.103033.

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