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Investigating the neural substrate of cognitive control in remitted depression with ACT-R and fMRI

Graduation Project
(Computational Cognitive Science)

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July 30, 2022

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Abstract

Rumination, a key component of depression, is linked to a lack of cognitive control, and still present in remitted depressed patients. Rumination and cognitive control are also associated with medial and lateral frontoparietal networks, respectively. The connection between these networks turns out to be disturbed in people with remitted depression, but is unclear whether this disturbance contributes to their lack of cognitive control. To investigate this issue, healthy controls and remitted depressed patients were scanned in an fMRI scanner during a verbal working memory task. Afterwards, we applied preventive cognitive therapy (PCT), which expectedly alleviates rumination, to some of the remitted patients. Three months later, all remitted depressed patients performed the task again in the scanner. PCT is known to prevent relapse risk, but the expectation that this prevention is caused by an alleviation of rumination has never been confirmed. To test this expectation, we created ACT-R models that did the same task with and without rumination, but due to a poor data fit, the results were inconclusive. The fMRI scans were compared cross-sectionally, and healthy controls were found to have increased left inferior parietal lobule activation. No differences were found between treated and untreated remitted depressed patients. Spatial independent component analyses provided no evidence for a change in the inter-network connection with treatment.

1 Introduction

Major depressive disorder (MDD, or simply 'depression') is a serious medical condition that generally involves a depressed mood or a loss of pleasure in daily activities, with additional symptoms including sleeping disorders, a diminished ability to concentrate, feelings of worthlessness, or even attempts at suicide (American Psychiatric Association, 2013). It is the second-leading cause of years lived with disability worldwide (Vos et al., 2015) and impacts patients both in their social (Kupferberg, Bicks, & Hasler, 2016) and cognitive functioning (McIntyre et al., 2013). Moreover, it has a highly recurrent nature (American Psychiatric Association, 2013), which makes the prevention of relapse an active area of research.

One of the key components of MDD is rumination, a process in which a person repeatedly thinks about their depressive symptoms as well as the consequences of those symptoms (Nolen-Hoeksema, 1991). This process might enhance the processing and memorisation of negatively valenced information, which can lead to a vicious cycle in which rumination and depressed mood strengthen each other (Blaney, 1986). The details of the mechanisms of rumination, however, are uncertain. A prominent hypothesis is that a lack of cognitive control, something that most MDD patients suffer from (Joormann & Tanovic, 2015), is one of the main contributors to rumination (Zareian, Wilson, & LeMoult, 2021).

Within the human brain, research has often associated cognitive control with a lateral frontoparietal network (lateral FPN) of brain regions (Uddin, Yeo, & Spreng, 2019). These regions include the lateral prefrontal cortex, anterior inferior parietal lobule, and dorsal anterior cingulate cortex (Niendam et al., 2012; Uddin et al., 2019). This network is involved in rule-based problem solving, decision making during goal-directed behaviour and maintenance and manipulation of items in working memory (WM) (Borst & Anderson, 2013; Menon, 2011). The lateral FPN shows increased connectivity with the medial frontoparietal network (medial FPN)[1] during tasks that require internally directed attention (Kam et al., 2019). On the other hand, the lateral FPN also has functional connections to the dorsal frontoparietal network (dorsal FPN)[2] (Murphy, Bertolero, Papadopoulos, Lydon-Staley, & Bassett, 2020). This dorsal FPN is believed to be activated during externally driven streams of thought (Smallwood, Brown, Baird, & Schooler, 2012).

As it turns out, rumination is strongly correlated with activity in the medial FPN core regions (Zhou et al., 2020), which, combined with the fact that the lateral FPN is more strongly connected to the medial FPN when attention is directed internally (Kam et al., 2019), could mean that something has gone awry in the communication between these two networks in individuals with a tendency to ruminate. Resting-state studies of (remitted) depressed patients have indeed found decreased connectivity between the lateral FPN and the posterior part of the medial FPN (Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015), while an n-back task, administered by Bartova et al. (2015), elicited increased connectivity between the lateral FPN and some anterior parts of the medial FPN. These findings indicate, at the very least, that the communication between the two networks has been disturbed, which might reflect a neural substrate of the loss of cognitive control. Whether this inter-network connection truly underlies cognitive control, however, is as of yet unclear.

In the present study, we have investigated a treatment that has proven useful in preventing relapse, called preventive cognitive therapy (PCT; de Jonge et al., 2019). PCT is to be applied after remission and might lower relapse risk for up to ten years (Bockting et al., 2015). The mechanisms by which the protective effect of PCT is obtained are not yet known (van Kleef et al., 2019), but applying cognitive therapy in the acute phase of MDD has been shown to lower ruminative tendencies (Jones, Siegle, & Thase, 2008), which might be associated with increased cognitive control (Visted, Vøllestad, Nielsen, & Schanche, 2018). We suspected that PCT would have a similar effect, and hypothesised that the neural basis for these changes would include a reversal of the abnormal connectivity between lateral and medial FPN as described above. If PCT would truly target rumination and, at the same time, restore a normal inter-network connectivity pattern, then we would consider this a strong argument for the relationship between cognitive control and the lateral-medial FPN connectivity.

Our hypothesis was tested with a verbal working memory (VWM) task, which required participants to maintain and manipulate information in working memory, just like the n-back task used by Bartova et al. (2015). The VWM task was adapted from an earlier version designed by Jolles, Grol, Buchem, Rombouts, and Crone (2010), who showed that it elicited much activation in the lateral FPN, making it a suitable task for demonstrating interactions between task-

[1] Also known as the default mode network.

[2] Also known as the dorsal attention network.

related, lateral FPN and rumination-related, medial FPN regions. Highly recurrent, remitted MDD (rrMDD) patients were recruited for this study and divided into two groups: One that received eight sessions of PCT over the course of three months, and one that was placed on a waiting list for the same duration. Both before and after those three months, the patients performed the VWM task in a functional magnetic resonance imaging (fMRI) scanner. In addition, a number of healthy controls (HCs) did the same task in the scanner as a baseline measurement (without the treatment and the follow-up fMRI measurement). This allowed us to assess the initial differences between HCs and rrMDD patients and then determine whether PCT would be able to erase any residual abnormalities that remitted depressed patients might suffer from. We expected to find differences in the lateral-medial FPN connectivity between the HC and rrMDD group, and since we believed PCT might reverse the abnormal connectivity pattern previously found in remitted patients, we also expected to find this same difference in connectivity between the treatment and waiting list groups.

However, since our suspicion that PCT achieves its protective effect through the alleviation of rumination has not yet been confirmed, we also scored the remitted patients according to the Leuven Adaptation of the Rumination on Sadness Scale (LARSS; Raes, Hermans, Williams, Bijttebier, and Eelen, 2008), both before and after treatment. In this way, we could examine whether treatment indeed caused any change in rumination. Additionally, to consolidate the argument that PCT targets rumination and cognitive control, as well as to investigate how rumination affects our VWM task exactly, we developed a cognitive model capable of performing the task. This model was built within the Adaptive Control of Thought-Rational (ACT-R) architecture (Anderson, 2007) and featured a control deficiency that would lead to rumination, similar in spirit to a different rumination model by van Vugt et al. (2018). This 'depressed' model was contrasted with a 'healthy' model that did not feature this lack of cognitive control. The behavioural data of both versions were compared with the human data, in order to ascertain whether the behavioural effects of treatment coincided with the effects of removing rumination from the model.

2 Methods

2.1 Participants

Our study is based on a broader initiative called the Neurocognitive Working Mechanisms of the Prevention of Relapse In Depression (NEWPRIDE; van Kleef et al., 2019) study. For that study, 25 healthy controls (HCs) and 80 highly recurrent, remitted major depressive disorder (rrMDD) patients were recruited. All participants were aged between 18 and 60 years, had no DSM-IV diagnosis, no current depressive symptomatology (a score of 13 or less on the Inventory of Depressive Symptomatology), and no past or present alcohol or drug dependency. For the rrMDD group specifically, participants were required to meet the lifetime criteria of a DSM-IV MDD diagnosis, be in a remission of a major depressive episode (MDE) for at least two months and at most two years, and have had at least two MDEs in the past five years. In addition, they were not allowed to have used psychotropic medication for at least four weeks, ought not to have received cognitive (behavioural) therapy for the last MDE, and could not have suffered any past or present psychotic or (hypo)manic episode. Healthy controls, on the other hand, were not allowed to have a lifetime diagnosis of any DSM-IV disorder.

Both healthy controls and rrMDD patients were scanned during a baseline scanning session. During the following three months, 55 patients received eight sessions of preventive cognitive therapy (PCT), while 25 were placed on a waiting list. After those three months, the rrMDD patients were scanned again in a follow-up session. For the baseline measurements, five patients had their behavioural data missing due to data collection issues. Three HCs and 14 patients had missing or corrupted MRI scans. During the course of the study, 11 patients dropped out, preventing any follow-up measurements. As for the patients that did do a follow-up measurement, nine had their behavioural data files missing or corrupted, and eight patients suffered from missing scans. In total, 22 HC and 66 patient baseline scans were submitted to the preprocessing pipeline, while 61 follow-up scans made it to preprocessing.

Because the fMRI scanner that we started out with had to be replaced during the course of the study, two scanners were used to collect the scans. One of those scanners, the Siemens scanner, produced artefacts which required us to adjust our preprocessing pipeline. This meant that we had a default and an adjusted pipeline. From the default pipeline, only 16 (64%) HC, 27 (36%) patient baseline, and 33 (44%; 15 treatment, 18 waiting list) patient follow-up scans were submitted to the second-level analysis because of poor preprocessing and first-level results. On the other hand, the adjusted pipeline eventually allowed 15 (60%) HC, 38 (50.67%) patient baseline, and 39 (52%; 24 treatment, 15 waiting list) patient follow-up scans to be analysed.

For the baseline comparisons of the behavioural data, we started out with 25 HCs and 75 remitted depressed patients. Before further behavioural analysis, we excluded any participants that did not perform significantly better than chance, as assessed with binomial tests. This meant that four HCs and nine remitted patients were excluded, so 21 (84%) HCs and 66 (82.5%) patients were submitted to the baseline analysis. For the second behavioural analysis, we excluded 8 out of 80 rrMDD patients because of poor task performance. Additionally, we required patients that had data for both the baseline and follow-up measurement, in order to determine how their behavioural data changed over time with treatment. Due to relatively high drop-out rates, 51 out of the remaining 72 patients had data for both time points. In total, 20 (80%) waiting list and 31 (56.36%) treatment patients were included in the analysis.

2.2 Clinical measures

To determine whether PCT influenced rumination at all, we administered the Leuven Adaptation of the Rumination on Sadness Scale (LARSS; Raes et al., 2008) to both rrMDD groups before and after treatment. A linear mixed-effects (LME) regression model (Baayen, 2008) was used to test for a significant effect of treatment on the LARSS scores.

2.3 Verbal working memory task

Because previous work had found the disturbed connection between lateral and medial FPNs during a task that relied heavily on working memory (Bartova et al., 2015), we used data from the verbal working memory (VWM) task of the NEWPRIDE study. This task, based on work by Jolles et al. (2010), consisted of several trials in which participants were shown a series of pictures. An example of such a trial is shown in Figure 2.1. The pictures contained only emotionally neutral content and were retrieved from the Max Planck Institute's picture dataset.[3] The number of pictures shown on each trial (also referred to as the 'load') could be three, four, or five. That number was presented as a cue at the start of every trial for 500 ms, after which participants saw the pictures themselves. Each one appeared for 850 ms, interleaved with a mask consisting of three asterisks for the duration of 250 ms.

Afterwards, participants received a 500 ms instruction to remember the pictures either in the order in which they were presented (forwards condition), or in the reverse order (backwards condition). For the example in Figure 2.1, which specifies the instruction as "FORWARDS", the items are supposed to be remembered as 'broom - glass - harp'. If the instruction were "BACKWARDS" instead, the items should have been remembered in the sequence 'harp - glass - broom'. The forwards condition corresponded to the *maintenance* of information in WM, while the backwards condition required the *manipulation* of such information. At the start of the experiment, the participants were told to do all of the rehearsals subvocally.

After the forwards/backwards instruction and a rehearsal delay of 6 s, participants were confronted with two pictures from the picture sequence of that trial, along with a question that asked which picture appeared on position p in the forwards/backwards list, where p could range from 1 to the trial load. In the example of Figure 2.1, the item that came second was the glass, so the button corresponding to the right item would be the correct one. (It should be noted that this response scheme differs from that used by Jolles et al. (2010), who presented just one picture to the participant and required them to answer at which position in the forwards/backwards list this picture resided.) After a response or, if no response was recorded, a timeout duration of 5 s, the experiment continued to the inter-trial interval, which was jittered from 1 to just over 7 seconds.

[3] https://www.mpi.nl

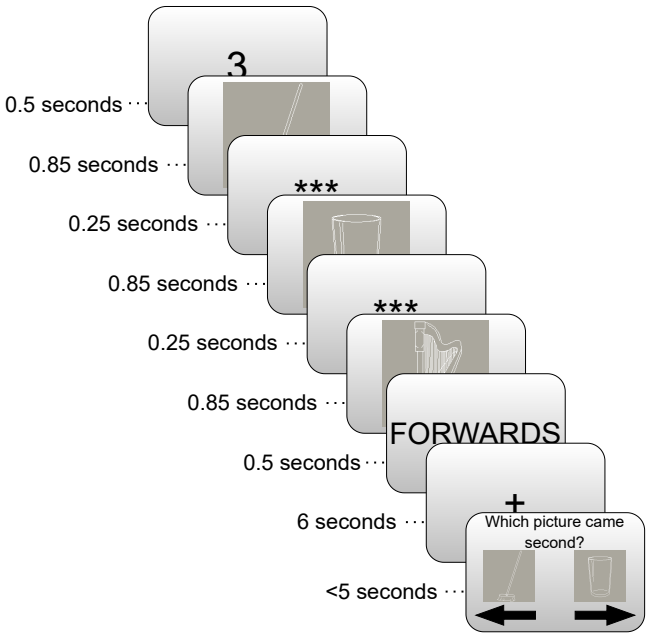

Figure 2.1: Illustration of a task trial, which starts with presenting the cue that indicates the trial load. Pictures of a broom, a glass and a harp are then shown interleaved with masking screens (marked as "***"). Afterwards, the participant is instructed to rehearse the items in the presented order (forwards) during the delay period (marked as "+"). Finally, the participant can indicate with a button press which of the two items on the response screen came second in the forwards item list.

The task consisted of 60 trials, with load and maintenance/manipulation distributed evenly among the trials (i.e. 20 load three trials, 20 load four trials, 20 load five trials; 30 forwards trials, 30 backwards trials). Pictures could occur more than once over the course of the task, but never twice or more in the same trial. In addition, before the experiment started, participants were shown and required to shortly describe all the pictures of the task, so the pictures were familiar to them. The same version of the task was administered at both the baseline and follow-up scanning sessions. The complete task lasted about 15 minutes, depending on participant pace.

2.4 Behavioural analysis

To determine which patterns were significant in the behavioural data, we have constructed linear models for both the accuracy and reaction time (RT) data gathered during the experiment. For the accuracy data, we have employed a binomial generalised linear model, while for the RT data, we have applied a log transform (to ensure the reaction times were close to normal) before estimating a regular linear model. Since this study includes repeated measures from the same participants, we used linear mixed-effects regression for both

types of data. This allowed us to deal with the repeated-measures design by including participants as a random effect (Baayen, 2008).

The fixed effects differed depending on whether we were comparing rrMDD and HC participants (baseline comparison) or rrMDD treatment and rrMDD waiting list participants (treatment comparison). As far as the first comparison is concerned, participant group (rrMDD versus HC), trial type (forwards versus backwards), and load (number of items to remember), as well as their interactions, were included as possible fixed effects. The LME model for the treatment comparison, meanwhile, included the participant group (treatment versus waiting list), trial type, load, time of measurement (baseline versus follow-up), and also their interactions as its fixed effects.

Finally, for both models, a forwards-fitting model comparison scheme was used to assess whether the random effects contribute significantly to the model quality. After that, backwards-fitting was used to determine how many fixed effects could be removed before the model quality started to decline significantly.

2.5 Image acquisition

The 25 HCs and first 54 rrMDD patients were scanned on a Philips Intera 3 Tesla MR scanner (32-channel receiver head coil) in the Neuroimaging Center of the University Medical Center Groningen (UMCG). Because the Philips scanner had to be replaced at some point during this study, the final 26 rrMDD patients were scanned on a Siemens 3 Tesla Magneton Prisma MR scanner (64-channel receiver head coil) in the Radiology Department of the UMCG.

For both scanners, the same scanning procedures were used. During the VWM task, BOLD images were acquired with echo planar imaging (TR: 2000 ms, TE: 30 ms, flip angle: 90°, voxel size: $3.5 \times 3.5 \times 3.5$ mm). The first two images were used as dummy scans and therefore discarded. In addition, a T1-weighted structural scan was acquired for anatomical reference (TR: 9 ms, TE: 3.5 ms, flip angle: 8°, voxel size: 1 mm^3).

2.6 Image preprocessing

Images have been preprocessed using the SPM12 (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) MATLAB (The MathWorks, Inc., Natick, Massachusetts, USA) package. The preprocessing procedure consisted of manual reorientation of both anatomical and functional images, realignment (but not reslicing) of the functional images, coregistration, normalisation and smoothing (Gaussian smoothing kernel FWHM: 8 mm^3). Additionally, because the scans of the Philips scanner contained some artefacts, all scans underwent an additional artefact removal step after the reorientation step. Scans were manually checked for aberrant realignment or coregistration.

Unfortunately, the scans of the Siemens scanner suffered from a strong inhomogeneity effect, probably because of the inactivity of one of the frontal coils. This meant that the functional scans had an intensity gradient running roughly along the anterior-posterior axis, which was accompanied by a change in variance: Frontal brain parts had weaker average signals and less signal variance. Analysing the Siemens scans with the default pipeline would run the risk of jeopardising the second-level analyses to be described below. We therefore created an additional preprocessing pipeline that included a log transform of all scans (including the Philips scans) before applying the default preprocessing pipeline. Log transforming the images made the range of possible voxel intensities less extreme and allowed SPM to more easily create masks for the first-level analysis.

2.7 fMRI analysis

Analyses of the fMRI data were conducted within MATLAB. We used a first-level (within-subjects) analysis with a canonical haemodynamic response function (HRF) and its temporal and dispersion derivatives. All task stages, i.e. the cue, item presentation (modelled as one block from the first up to and including the last item), instruction, rehearsal, and response stages, were modelled separately for forwards and backwards trials. Item presentation, rehearsal delay, and the response stage were further modelled separately for the trial load (three, four, or five). We expected our main effects within subjects to be concentrated in the rehearsal delay, as that was the point where participants were more likely to be focused exclusively on WM operations. However, we found that whole-brain activations were generally stronger if we also included data from the response stage, so our contrasts included data from the start of the rehearsal stage up to the response given by the participant. The contrasts we used were similar to the ones used by Jolles et al. (2010):

1. rehearsal+response $>$ fixation;
2. rehearsal+response forwards $>$ fixation;
3. rehearsal+response backwards $>$ fixation;
4. rehearsal+response backwards $>$ rehearsal+response forwards;

where contrast 1 was specified for all loads combined. Contrasts 2, 3, and 4, on the other hand, were specified both for each load separately and all loads combined. Although our fMRI analysis was mostly concerned with between-subject differences, specifying these within-subject contrasts for all trial types allowed us to also carry out the between-subject comparisons per trial type. This was helpful because Jolles et al. (2010) found the most lateral FPN activation in backwards trials and trials with high load, so we expected to more easily find any disturbances to the lateral-medial FPN connection in those trials as well.

Our second-level analysis used the results of the first-level analysis to determine the difference between the HC and rrMDD groups (baseline comparison) and the treatment and waiting list groups of the rrMDD patients (follow-up comparison). For the Philips data that were preprocessed using the

default pipeline, regular two-sample t-tests were conducted within SPM. These tests were conducted for the whole brain, as well as for a masked area with small volume correction. This (inclusive) mask consisted of a union between the regions associated with the lateral and medial FPNs according to Uddin et al. (2019).

As for the log-transformed data, the assumptions for a regular second-level analysis in SPM no longer held. For that reason, we conducted non-parametric permutation tests with the SnPM toolbox, using 10,000 permutations.

For both types of data, effects were considered significant at $p < 0.05$, after family-wise error correction.

2.7.1 Connectivity analysis Because the data suffered from multiple artefacts and showed few effects after the second-level analyses described above, we opted for a more exploratory connectivity analysis. More specifically, we ran spatial independent component analyses (SICAs) separately for both the baseline and the follow-up data, using GIFTv3.0b. Of specific interest would be components that included voxels from lateral and medial FPN regions, but also components with voxels concentrated in visual areas were included. Components for which the most activated voxels lied in irrelevant regions (i.e. motor cortex, auditory cortex, cerebellum, and cerebrospinal fluid) were excluded from this analysis. In addition, the voxels of some components formed thin, horizontal slices that cut indiscriminately through cortex and subcortical areas. These components clearly represented scanner artefacts and were removed after visual inspection. To assess differences in connectivity between groups, the back-reconstructed component maps were compared with second-level t-tests both for the baseline (HCs versus rrMDD) and the follow-up (treatment versus waiting list) data.

In addition, to determine whether components were more activated in specific task stages for one group than the other, per-subject linear regressions were conducted between an individual's component time course and their design matrix. The resulting beta coefficients were compared between groups using t-tests. Within every stage, Bonferroni correction was applied to account for the multiple comparisons problem.

2.8 Model

We have used a cognitive architecture to model both treated and untreated rrMDD patients doing this task, namely Adaptive Control of Thought-Rational (ACT-R; Anderson, 2007). A cognitive architecture is a framework for developing computational, cognitive models that aims to provide a task-general, complete description of how humans execute their tasks, from perception to motor actions (Anderson, 2007). Such a framework comes with a set of constraints inspired by neuroscientific literature that it imposes on every model developed within it; examples include how long it takes before a visual change is available to other cognitive processes, how often WM can be updated within a given time frame, and what factors influence the forgetting of items in declarative memory.

The advantage of casting our behavioural and fMRI results into an ACT-R model is that this allows us to integrate those results into a system that has already proven its merit in many other studies (Borst & Anderson, 2013; Gonzalez, Lerch, & Lebiere, 2003; Salvucci, 2006; Salvucci & Taatgen, 2008; van Vugt, Taatgen, Sackur, & Bastian, 2015). In addition, using a pre-existing cognitive architecture prevents us from only modelling a small part of the human cognitive system, which could tempt us to gloss over other parts that are currently not in our primary area of interest, but that might nonetheless be important for integrating our results with other results from the neuroscientific literature (Newell, 1973).

2.8.1 ACT-R design ACT-R is designed around a set of modules, each of which is matched to a specific area of the brain (Anderson, 2007; Borst & Anderson, 2013). These modules include the vision module (occipital cortex), the motor module (motor cortex), the imaginal module (used for storing and manipulating short-term information; parietal cortex), the declarative module (long-term information storage; prefrontal cortex), and the procedural module (controls communication between modules; anterior cingulate cortex). Every module (except the procedural module) has a buffer, which the modules can use to both send information to and receive it from other modules. Information is organised in chunks: Packages of relatively few, semantically related symbols (G. A. Miller, 1956). These symbols are assigned to the so-called *slots* of a chunk. Every module buffer has room for only one chunk.

The exchange of these chunks between buffers is governed by the procedural module, which uses a series of if-then rules (production rules) that require a certain configuration of module states and buffer contents to activate (fire), and cause a slightly different configuration in response. The procedural module will only fire a production rule with a minimum interval of 50 ms. All modules can work in parallel, but all information that needs to be communicated to other modules has to pass through the procedural module, effectively creating a central processing bottleneck that ACT-R imposes on all the cognitive models that can be created within it.

Another source of processing latencies is the time cost associated with a chunk retrieval from the declarative module. The amount of time required to perform such a retrieval, as well as whether such a retrieval is successful at all, is dependent on the activation of a chunk. This activation is determined by a number of factors, among which are a noise component and the recency and frequency with which a chunk has been retrieved: Chunks that have been retrieved recently and/or often have higher activations. The lower a chunk's activation, the longer it will take to retrieve that chunk. In fact, if the activation is lower than the retrieval threshold, the retrieval will fail after a fixed amount of time. When specifying a retrieval request, it is possible to only make a partial specification to target a range of chunks, rather than a single one.

If that happens, the chunk with the highest activation out of all the eligible chunks will be retrieved.

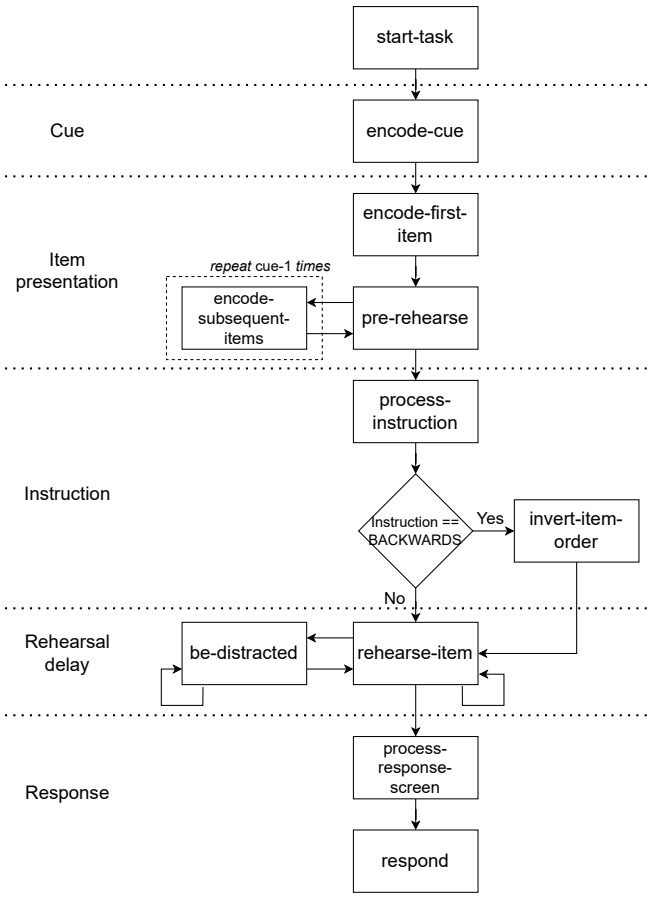

Figure 2.2: Overview of the model production rules. Rectangles with solid borders show cognitive steps that correspond roughly to the actual production rules of the model. Task stages during which the production rules will be active are given on the left of the diagram.

2.8.2 Model design In most ACT-R models, the production rules are the defining features. They form a description of how a task that would normally be executed by humans can be done by the exchange of information between ACT-R modules. An overview of the production rules of the model that executes our VWM task are given in Figure 2.2. The first part of the task follows a rather linear path: The model starts by attending to the location of the fixation cross, commits the cue to working memory (by saving it to the imaginal module buffer), and saves any sequence item it encounters, along with where in the sequence it occurred, to declarative memory. Between item presentations, the model uses the available time to already rehearse all the items it encountered during that trial (which we call 'pre-rehearsal').

Then, based on the instruction presented on the screen, two things can happen: Either the instruction is "FORWARDS" and the model can immediately proceed to the rehearsal stage, or the instruction is "BACKWARDS" and the model first has to invert the order in which the sequence was presented. It does this by retrieving all chunks associated with the previously presented items from declarative memory. Those chunks contain the value of the item (e.g. "harp") and the position in the sequence at which it occurred. The model loads these chunks into the imaginal buffer, modifies the position slot as required, and saves the modified chunk to declarative memory again. Creating or modifying chunks with the imaginal module takes time, and therefore shortens the time window in which the model can effectively rehearse all sequence items. This should lead to lower activation values for the corresponding chunks in the backwards condition, which means that when a response is required, the model will both take longer to retrieve the correct items and be more prone to making retrieval errors.

In the rehearsal stage, the model will continuously retrieve the sequence items in the order specified by the instruction (forwards versus backwards) to consolidate them. However, for the untreated rrMDD patients, we hypothesised that this stage might be disturbed by ruminative processes. In a previous study, rumination has been modelled in ACT-R as a competition between chunks in declarative memory (van Vugt et al., 2018). Our study, on the other hand, focuses on the lack of cognitive control as the source of rumination (Zareian et al., 2021), and the part of ACT-R that has typically been associated with cognitive control is the procedural module, which is in charge of selecting and executing production rules. We have therefore modelled that lack of cognitive control by a competition between the `rehearse-item` and the `be-distracted` production rules. Such a competition happens on the basis of *utility*, a quantity associated with every production rule: When there is a conflict between different production rules, only the one with the highest utility will fire. This contrasts with the competition between chunks, because that relies on activity (rather than utility), which can be subject to decay. In this model, utility has been kept constant for both production rules, but a noise component has been added that can cause a different production rule to be selected on different iterations of the rehearsal stage.

After six seconds of rehearsal, the experiment screen will display the response scene, which asks the model which of two items was presented at a given position in the forwards/backwards sequence. At that point, the rehearsal stage will stop, and a number of different production rules will fire to parse the different elements of the scene. Before we discuss what the model does with the parsed information, however, we should take a moment to reflect upon the different strategies that participants could use at this stage in the task. They could, for instance, use the two presented items on the response screen as cues to retrieve the sequence position associated with them. The association between item and position could be direct, but it could also require traversing the item sequence until one of the cues is encountered. Whatever the

mechanism, the resulting item positions could then be compared to the probed position shown on the response screen. The item of which the sequence position matches the probe position would then be the correct answer. On the other hand, it is also possible that participants will traverse the memorised sequence up to the probed position, and then make a comparison between the retrieved item and the ones shown on screen to determine which one is correct. Human participants could use any of these strategies, or perhaps even a mix of them, and different participants might prefer different strategies. Moreover, these strategies might extend beyond the response stage and also affect how participants execute e.g. the rehearsal stage; for instance, will participants actually perform the sequence inversion as soon as they encounter the "BACKWARDS" instruction, or will they postpone it until they actually need to give a response?

For the sake of simplicity, we have focused on the cue-based, direct retrieval strategy: Sequence positions are coded explicitly in one of the slots of an item chunk, and once the response screen has been parsed, the model tries to retrieve the position of the item that corresponds to the left item on the screen. Provided that the retrieval is successful, the model compares the retrieved position to the probed position on the screen. If there is a match, the model assumes that the left item is the correct answer and responds by typing 'L'; if not, the model will assume that the correct answer cannot be the left item, which would mean the correct answer must be 'R'. If a retrieval failure occurred, the model will instead attempt to execute the same retrieval and response procedures for the right item. If that also results in a retrieval failure, the model will choose randomly between the two responses. We will call this strategy the 'direct' strategy.

However, to explore the change in behaviour a different strategy could induce, we also implemented the 'sequential' strategy, which involved retrieving every item in the sequence until the one at the probed position was reached. The model would then press 'L' if the retrieved item matched the left one on the screen, and 'R' if the item matched the right one. If there was no match with either item on screen, the model would select a button at random. Because we were merely interested in the effect of using an alternative answering strategy on the model's behavioural measures, we only implemented the sequential strategy for the healthy rather than the depressed model.

In the event that both models would take over 5 seconds to respond (i.e. a time-out), the response screen would disappear and the models would withhold their response.

For all types of models, 50 instances were run to simulate 50 different participants. The ACT-R parameters were kept constant across models and are given in Table 2.1.

Parameter	**Value**
Sub-symbolic level (:esc)	t (nil)
Production utility noise (:egs)	0.2 (0)
Retrieval threshold (:rt)	-0.5 (0)
Activation offset (:blc)	0.25 (0)
Optimised learning (:ol)	nil (t)
Activation noise (:ans)	0.4 (nil)
Number of declarative finsts	5 (4)
Declarative finst span	6 (3)
Utility of `be-distracted`	0.25 (0)

Table 2.1: Parameters of all the ACT-R models. Default values are given in parentheses after the new value. Any parameters not mentioned here were kept at their default values.

3 Results

3.1 Demographic and clinical measures

Demographic measures of the participant sample after exclusion are given in Table 3.1. There were no significant differences between compared groups with respect to gender, age and education. To assess whether treatment affected rumination, a linear mixed-effects (LME) regression model was fitted to the LARSS scores of the rrMDD patients. Backwards-fitting of the fixed effects showed that there were no differences in LARSS scores between the treatment and waiting list groups ($\chi^2(1) = 1.10$, $p = 0.29$), nor that treatment changed the LARSS scores (interaction of treatment and time, $\chi^2(1) = 0.09$, $p = 0.76$).

3.2 Behavioural

Two types of behavioural analyses were done. The first one, the baseline comparison between the healthy controls and the rrMDD patients, was done to get a baseline assessment of how strong the difference in behavioural measures was for our VWM task. The second one was applied only to the rrMDD group and included both measurement time points (baseline and follow-up) to investigate the longitudinal effects of treatment, while also allowing a cross-sectional comparison between the treatment and waiting list groups.

3.2.1 Baseline comparison For the first session, mean reaction times (RTs) of correct trials for both groups are given in Figure 3.1, plotted against the trial load. An LME model was fitted to the log-transformed RTs using forwards-fitting of the random effects and backwards-fitting of the fixed effects. An overview of the final model's coefficients is given in Table 3.2. For the random effects of the models in this section, it can be assumed that only a random intercept per subject was included, unless stated otherwise.

The reaction times of both participant groups appear very similar, which was confirmed by model comparisons, where the group variable was an insignificant addition to the model ($\chi^2(1) = 0.002, p = 0.96$). As Figure 3.1 suggests, whether the sequence was to be remembered forwards or backwards causes an almost constant difference between reaction times ($\chi^2(1) = 251.48, p < 0.001$). When considering the evolution of RT across trial load, we can see a general increase of reaction times as the load increases ($\chi^2(1) = 62.465, p < 0.001$). The one exception to this rule is the RT for forwards trials of load 5: Curiously enough, those RTs seem slightly lower

	Baseline			Follow-up		
	HC	rrMDD	*p*-value	Control	Treatment	*p*-value
Female[a], n (%)						
Default	11 (68.75%)	22 (81.48%)	0.44	14 (77.78%)	9 (60.00%)	0.47
Log-transformed	13 (86.67%)	30 (78.95%)	0.72	12 (80.00%)	15 (62.50%)	0.31
Age[b], mean (SD)						
Default	35.25 (13.44)	34.41 (11.67)	0.83	34.61 (12.80)	37.67 (8.89)	0.44
Log-transformed	35.00 (13.80)	34.97 (12.24)	0.995	35.47 (13.61)	37.92 (10.93)	0.54
Education[b], mean years (SD)						
Default	17.06 (3.58)	17.32 (2.94)	0.24	17.06 (3.11)	17.79 (2.55)	0.49
Log-transformed	16.87 (3.62)	16.78 (3.99)	0.32	16.57 (2.79)	16.96 (2.92)	0.70

Table 3.1: Sample demographics after exclusion. Because the default preprocessing pipeline and the one that included a log-transform resulted in different scans to be excluded, demographics for both situations are shown here. a: Tested with a Monte-Carlo χ^2-test (2000 iterations). b: Tested with an ANOVA.

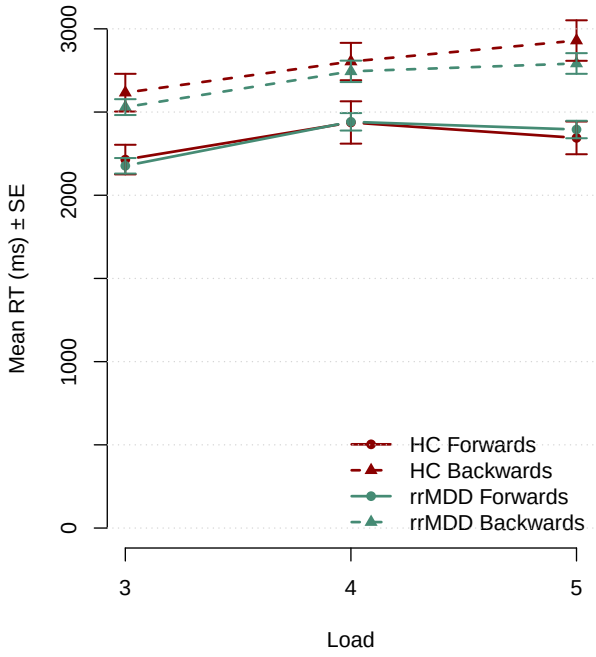

Figure 3.1: Reaction time (RT) over load, for both the HC and the rrMDD groups. Both groups are clearly faster in forwards than in backwards trials. RTs show no clear difference between groups. SE: Standard error of the mean.

than in the load-four forwards trials. This deviation is not present in the backwards trials, where RTs are not only higher overall, but also increase consistently with load. This non-linear pattern was not captured by our linear model. Reaction times therefore only seem to depend on whether a memory sequence should be remembered forwards/backwards and the number of items in the sequence.

Coefficient	**Estimate**	**SE**	***t*-value**
Intercept	7.851	0.016	482.489
Forwards	-0.152	0.009	-16.106
Load	0.037	0.005	7.932

Table 3.2: Coefficients of the model that tries to predict the (log-transformed) RTs for the baseline session. The intercept represents a typical participant (i.e. without any subject-specific random effects), doing a forwards trial with four items in the backwards condition. The other coefficients represent adjustments of that intercept. SE: Standard error.

Coefficient	**Estimate**	**SE**	***z*-value**	***p*-value**
Intercept	0.995	0.134	7.436	< 0.001
Forwards	0.725	0.071	10.145	< 0.001
Load	-0.138	0.070	-1.970	< 0.05
rrMDD	0.113	0.150	0.749	0.454
Load:rrMDD	-0.220	0.081	-2.714	< 0.01

Table 3.3: Coefficients of the model that tries to predict accuracies for the baseline session. A colon between two variables represents the interaction between those variables.

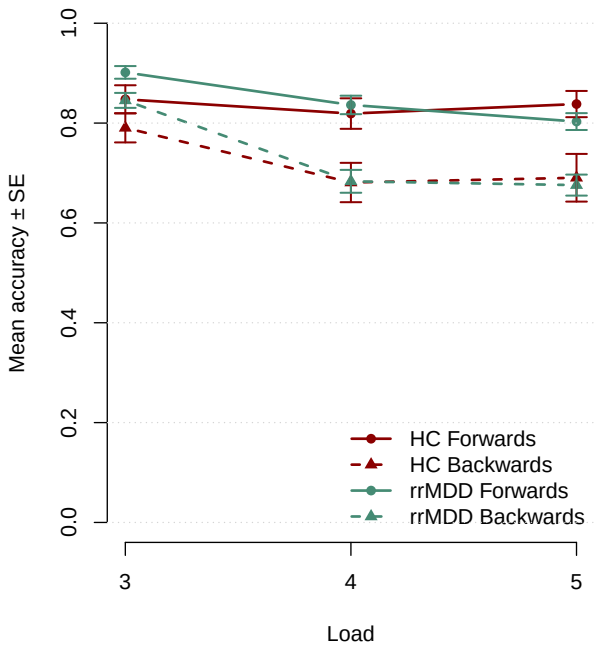

Figure 3.2: Accuracy over load, given for both HCs and rrMDD patients. Both groups are more accurate in the forwards trials. For a load of three, the rrMDD patients seem to be a bit more accurate than the HCs, but this advantage quickly disappears towards higher loads.

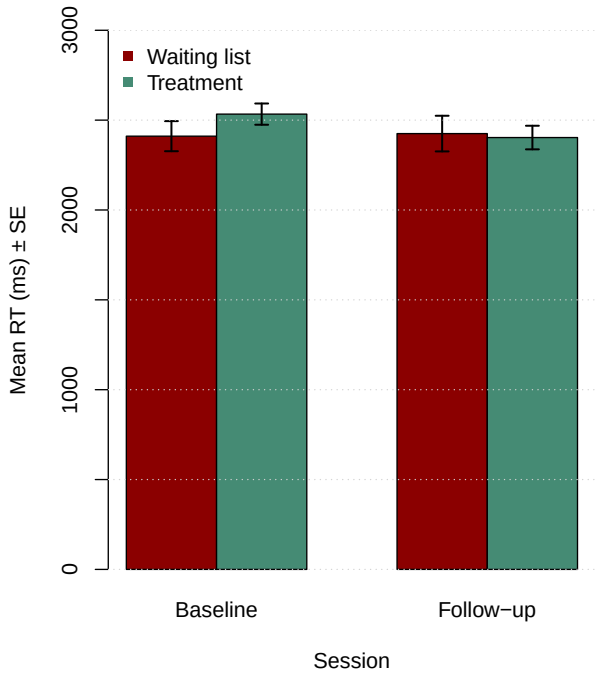

Figure 3.3: Mean reaction time over treatment condition and measurement session. In the baseline session, before treatment, the rrMDD control group seems faster than the treatment group, but this difference is insignificant. The decline of RT due to treatment, however, is significant.

Coefficient	**Estimate**	**SE**	***t*-value**
Intercept	7.804	0.033	237.735
Treatment	0.061	0.042	1.443
Forwards	-0.138	0.014	-9.971
Load	0.033	0.007	4.761
Follow-up	0.004	0.014	0.299
Treatment:Forwards	-0.008	0.018	-0.440
Treatment:Follow-up	-0.063	0.018	-3.542
Load:Follow-up	0.018	0.009	2.065

Table 3.4: Coefficients of the model that predicts the (log-transformed) RTs of the rrMDD group.

Coefficient	**Estimate**	**SE**	***z*-value**	***p*-value**
Intercept	1.158	0.103	11.279	< 0.001
Forwards	0.617	0.068	9.025	< 0.001
Load	-0.375	0.044	-8.422	< 0.001
Follow-up	0.179	0.068	2.680	< 0.01
Forwards:Load	0.152	0.068	2.221	< 0.05

Table 3.5: Coefficients of the model predicting the accuracies of the rrMDD group.

As for accuracy, Figure 3.2 indicates higher accuracies for the rrMDD group at low loads, which then decrease rapidly towards accuracies similar to those of the HC group. This was confirmed by a binomial generalised LME model (see Table 3.3), which indicated that being part of the rrMDD group does not significantly change the accuracy by itself, but does have an influence on the slope with which accuracy decreases over load. More concretely, the model predicts a steeper slope for rrMDD patients, as indicated by the significant interaction between 'Load' and 'rrMDD' ($\chi^2(1) = 7.28$, $p < 0.01$). In fact, Figure 3.2 seems to suggest that for the Forwards condition, the accuracy of the healthy controls is independent of the trial load, but this interaction was not a significant addition to the model ($\chi^2(1) = 0.622$, $p = 0.43$).

3.2.2 Treatment comparison In the second session, only rrMDD patients participated, which were split into a group that received preventive cognitive therapy and a group that was placed on a waiting list. Figure 3.3 shows the mean reaction times of these conditions for both the baseline and follow-up session. Coefficients of a model fitted on the log-transformed RTs of these data are given in Table 3.4. This model also contained a random slope for load per subject, in

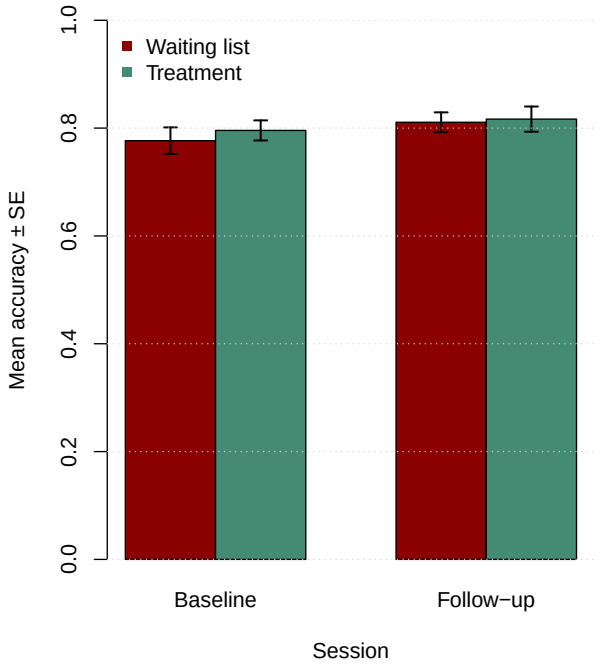

Figure 3.4: Accuracy over treatment condition and measurement session. From the baseline to the follow-up session, the accuracy increases slightly for both groups. There are no significant differences between groups.

addition to the random intercept per subject.

Curiously, the largest difference in mean RT seems to already occur in the baseline session, where neither group had received treatment yet: The treatment group already started with higher RTs ($M = 2533.44$, $SE = 59.11$) than the waiting list group ($M = 2410.75$, $SE = 83.71$). The coefficient for the treatment group in the baseline session suggests that the treatment group might indeed be about $\exp(0.061) \approx 1.063$ times slower than the waiting list group before receiving treatment, but the t-value of this estimate is relatively small and might not reflect an actual effect. However, after treatment, the treatment group enjoyed a slight decrease in mean RT, while the waiting list group seemed to suffer from a slight increase in RT. Especially this decrease in RTs is a significant addition to the model ($\chi^2(1) = 12.54$, $p < 0.001$), suggesting that the treatment has had an effect on reaction times.

Somewhat contrary to the pattern depicted in Figure 3.3, where the treatment group appeared to perform worse on the VWM task during baseline (i.e. reaction times were higher), Figure 3.4 suggests higher accuracies for the treatment group in both sessions. However, this was not confirmed by a generalised LME model (see Table 3.5): After backwards-fitting of the fixed effects, the effect of treatment turned out to be a non-significant addition to the model ($\chi^2(1) = 0.44$, $p = 0.51$). On the other hand, Figure 3.4 also suggests an overall increase in accuracy for both groups from baseline to follow-up, which does seem to be confirmed by the model ($\chi^2(1) = 7.14$, $p < 0.01$).

3.3 fMRI

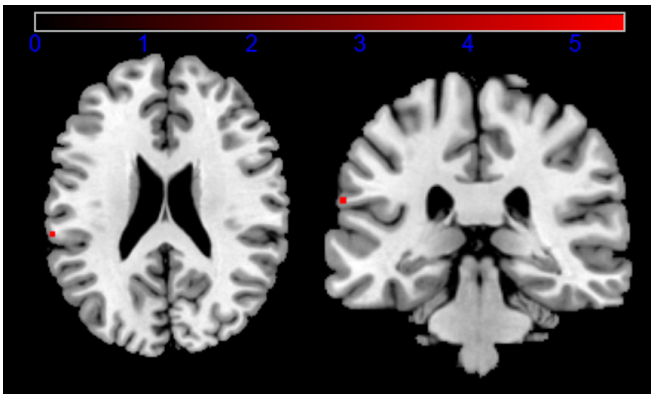

Figure 3.5: Significantly greater HC activation during backwards trials with a load of 3. Colour bar gives pseudo-t-statistics.

We ran second-level parametric analyses to assess the baseline activation differences between healthy controls and rrMDD patients. These parametric analyses did not include the data from the Siemens scanner, as those might not adhere to the analysis assumptions due to coil issues. The baseline comparison consisted of two sample t-tests of all contrasts. No contrasts contained any clusters that survived the family-wise error correction at $\alpha = 0.05$, neither for the whole brain nor with small volume correction. Similar analyses were run for the comparison between the follow-up data of the treatment and waiting list rrMDD patients. Again, for the whole brain and small volume correction, there were no contrasts with significant clusters.

As for the log-transformed fMRI data, HCs were found to have significantly higher activation in the left inferior parietal lobule (see Figure 3.5) than rrMDD patients during backwards trials with a load of 3 (cluster size = 1 voxel, MNI coordinates: $x = -63$, $y = -31$, $z = 23$, FWE-corrected $p = 0.0421$). No significant differences were found between treatment and waiting list patients at follow-up.

Spatial independent component analyses (SICAs) were run to explore what brain networks were active during the task. The analyses were run for both the baseline and follow-up (Philips) data. For the baseline data, 33 components were discovered, while 36 were found for the follow-up data. Not all of these components contained relevant regions, and some represented artefacts, so in total 23 baseline and 28 follow-up components were excluded from further analysis. The means of the back-reconstructed maps of the remaining components are displayed in Figures 3.6 (baseline) and 3.7 (follow-up);

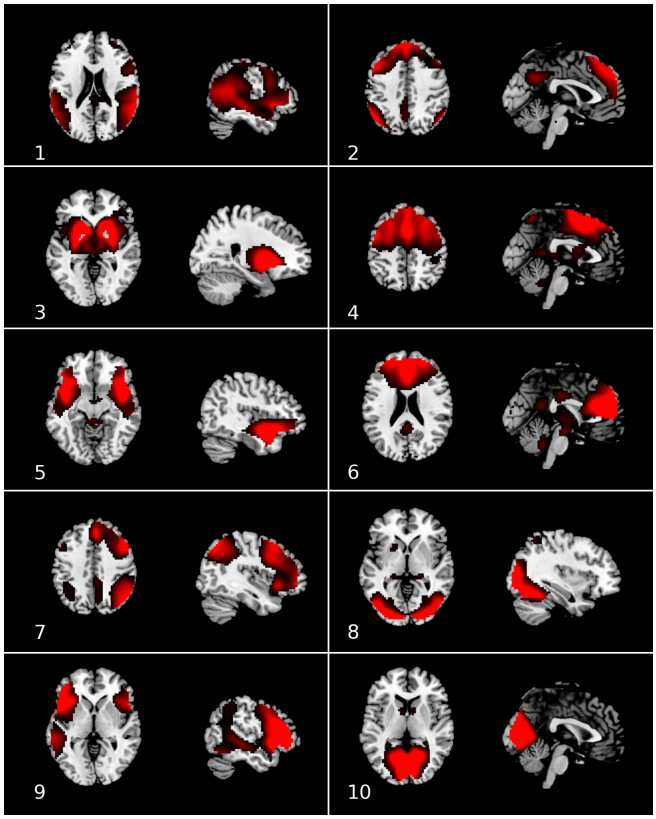

Figure 3.6: Back-reconstructed maps of selected mean spatial components for the baseline (healthy control and all Philips patient) data. The red regions represent z-scores, with the colour scale ranging from 2 to 10.

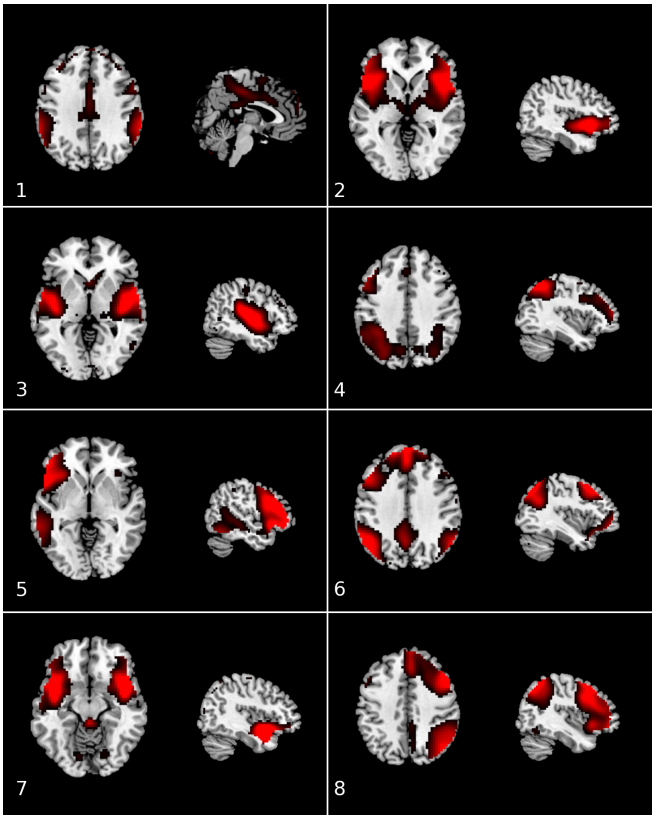

Figure 3.7: Back-reconstructed maps of selected mean spatial components for the follow-up (treated and untreated patient) data. Red regions represent z-scores, colour scale ranges from 2 to 10.

these maps indicate the amount of connectivity between an independent component and all voxels. Among the back-reconstructed maps, some show lateral frontoparietal networks, while others also contain medial FPNs, temporal cortex or even limbic systems. Yet other maps show strong activations in the visual cortices. We compared the maps of the HCs and rrMDD patients using two sample t-tests, but found no significant differences. A comparison between treatment and waiting list patients at follow-up also yielded no significant results.

To assess how strongly the discovered spatial components contribute to the different stages of our task (cue, item encoding, instruction, rehearsal delay, and response), we ran a linear regression for every subject between the component strength over time and the subject's design matrix. We compared the resulting beta weights between participant groups. To account for the multiple comparisons problem, we applied Bonferroni correction for the number of compared components within each experiment stage ($n = 10$ for baseline and $n = 8$ for follow-up); p-values displayed here are Bonferroni-corrected. When compared to rrMDD patients, HCs were found to have significantly larger component 5 (see Figure 3.6) beta weights for the instruction stage ($t(44) = 2.851$, $p = 0.033$), as well as for response stages in forwards load 4 trials ($t(44) = 2.946$, $p = 0.026$), backwards load 3 trials ($t(44) = 2.917$, $p = 0.028$), and backwards load 4 trials ($t(44) = 2.695$, $p = 0.050$). In contrast, the HCs had significantly smaller component 6 ($t(44) = -3.339$, $p = 0.009$) and component 10 ($t(44) = -3.070$, $p = 0.018$) beta weights for the cue stage.

For the follow-up components, no significant differences were found between the beta weights of treatment and waiting list patients.

3.4 ACT-R

To explore the way in which rumination could influence our verbal working memory (VWM) task and determine whether the application of PCT would be accompanied by changes in rumination, we created an ACT-R model capable of executing the VWM task. Two different versions of the model were made: A 'healthy' model that performed the task normally, and a 'depressed' model, of which cognitive control was disturbed during the rehearsal phase. As discussed in Section 2.8.2, there are multiple strategies that a model could use when completing our VWM task. Here, we present the results

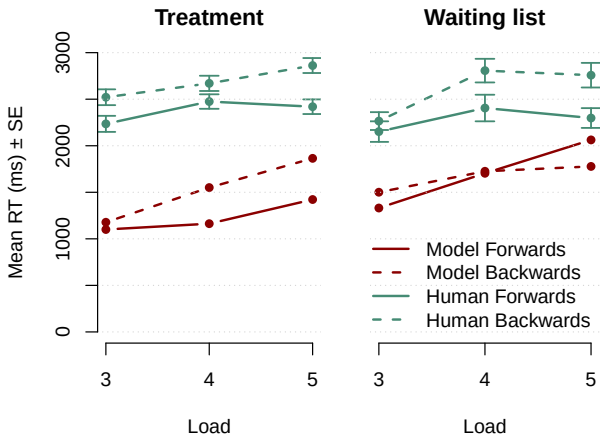

Figure 3.8: Comparison of model and human reaction time. The left graph shows data for the treatment patient group at follow-up, along with the healthy model data. The right graph shows data for the waiting list group and the depressed model. Overall, the models are about a full second faster than the humans. SE: Standard error of the mean.

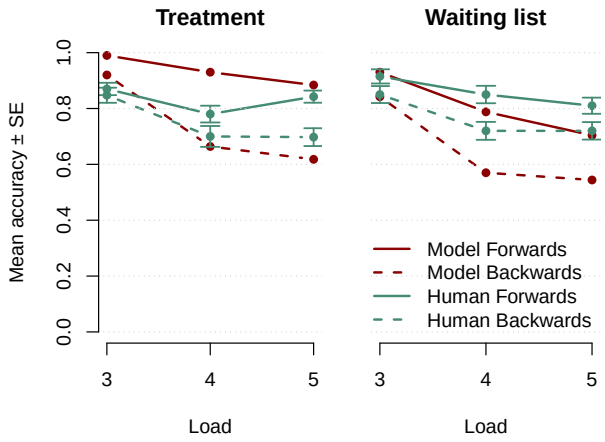

Figure 3.9: Comparison of model and human task accuracy. The left graph shows follow-up treatment and healthy model data. The right graph gives follow-up waiting list and depressed model accuracy. Whereas the healthy model tends to be more accurate than the treated patients, the depressed model performs quite similarly to the waiting list group.

of models that use the direct strategy. The reaction times of the healthy and depressed direct-strategy models, along with the follow-up RTs of the (human) treatment and waiting list groups, are shown in Figure 3.8. One of the most prominent differences between models and humans is that the models are about a second faster. In addition, whereas there is a clear gap between forwards and backwards RTs for the humans, the model RTs do not show such a consistent gap. For the healthy model (treatment graph), the gap is present for trials with a load of four and five, but almost absent for load three trials. For the depressed model (waiting list graph), the lines for forwards and backwards even cross over, which does not match the pattern of the waiting list human data. This also means that, between the treatment and waiting list groups, the models show more difference than the human participants do.

Figure 3.9 shows the accuracies for the two models and their human counterparts. Here the correspondence between humans and models is, although not perfect, better than for the reaction times. This is especially true for the depressed models (waiting list graph), although the accuracies for higher loads are a bit too low. For the treatment group, the model is still too accurate at lower loads. In addition, while the healthy model (treatment graph) seems slightly more accurate than the depressed one, this effect seems to be reversed for the human data, with waiting list patients performing slightly better than the treated ones. Please note, however, that the backwards-fitting procedure for the generalised binomial LME model from Section 3.2.2 did not deem this difference between treatment and waiting list group significant.

To illustrate the impact that different cognitive strategies can have on the task performance, we have also created a model that traversed the sequence of its memorised items until it reached the probed sequence position, rather than using the presented items as cues for a memory retrieval. We refer to this strategy as the sequential strategy. The RTs of healthy models using those strategies are shown in Figure 3.10, plotted alongside the human HC data. Although both model types show a discrepancy with respect to the human data, the sequential model has higher reaction times overall, which brings it closer to the human RTs than the direct model. Additionally, for the sequential model, the differences between the forwards and backwards conditions are more pronounced, although that difference might have grown too big for trials with a load of four.

As for task accuracy, both model strategies perform similarly (see Figure 3.11). The only noticeable difference becomes apparent in the backwards trials with a load of five, where the sequential model is slightly less accurate than the direct one, resulting in a poorer fit.

4 Discussion

In this study, we set out to investigate the relation between cognitive control (which was found to be negatively correlated with rumination (Joormann & Tanovic, 2015)) on the one hand and the connection between lateral and medial frontoparietal networks (FPNs) on the other in (remitted) depression. To do so, we used data of a verbal working memory (VWM) task from the NEWPRIDE study (van Kleef et al., 2019), which investigated the effect of preventive cognitive therapy (PCT) on remitted depressed patients. Since not much is known about the mechanisms of PCT, we cre-

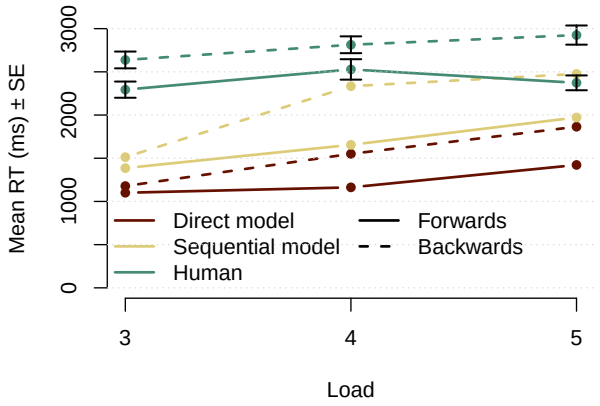

Figure 3.10: Comparison of the reaction times of different model strategies to the healthy human data. The sequential strategy yields higher RTs than the direct one, bringing the model closer to the human data.

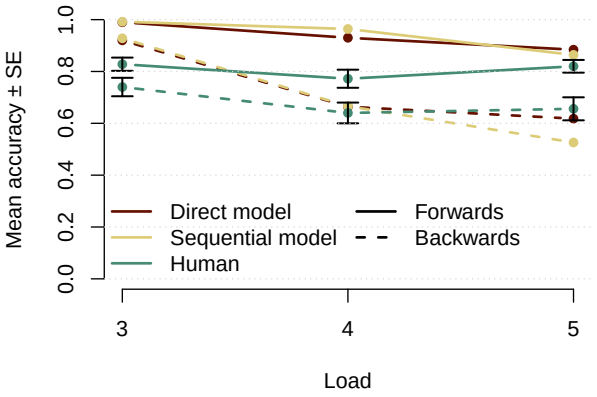

Figure 3.11: Comparison of the accuracy of different model strategies to the healthy human data. There is little difference in model performance for these strategies.

ated an ACT-R (Anderson, 2007) model and compared its behavioural data to that of the human participants to assess how well PCT was able to reduce rumination in treated patients. We additionally compared the fMRI data from treated patients to the data from the untreated patients, using both t-tests of the first-level contrasts and spatial independent component analyses (SICAs).

4.1 Behavioural

The behavioural results show effects of trial load and instruction on the reaction times (RTs), but whether the participants were healthy or remitted depressed did not seem to matter significantly. This finding can be contrasted with that of Joormann, Levens, and Gotlib (2011), who found significantly larger response latencies for (acutely) depressed patients in a similar working memory task. This could mean that our (unmedicated) remitted depressed participants had recovered well enough to no longer show any signs of their past episodes in their reaction speed. It should be noted, however, that Joormann and colleagues also included items of positive and negative valence in their experiment, while our experiment only featured emotionally neutral stimuli. Especially for negative items, their depressed patients showed comparatively high RTs in the backwards condition; perhaps our remitted participants might have done the same, had we included negatively valenced stimuli. For accuracy, they found no main effect of participant group (healthy control versus depressed), which corresponds to our findings (even though there was a significant interaction between participant group and trial load in our case). Our results are also in line with other working memory (n-back) experiments on remitted depressed patients, where no effect of remitted depression was found on either RT or accuracy (Bartova et al., 2015; Kerestes et al., 2012).

In contrast, if we focus our attention on comparing the treated remitted patients to those placed on the waiting list, we see an effect of the interaction between treatment group and session (baseline or follow-up) on reaction times: The reaction times of the treated participants have decreased. Curiously, Figure 3.3 seems to suggest that the treatment group already was slower than the waiting list group before treatment started, and that this reduction after treatment was merely removing that difference. On the other hand, our linear mixed-effects model suggests otherwise: The t-value for the main effect of treatment is rather small, while the value for the interaction between treatment and session is not. However, given that, in the baseline comparison, no main effect of group (healthy versus remitted depressed) was found, this result is hard to interpret: The advantage of the treatment group seems unlikely to have been brought about purely through an alleviation of depressive characteristics. A possible explanation could be that the treatment made the remitted depressed patients more susceptible to the effects of practice and consolidation, but more research is required to confirm this suggestion.

4.2 ACT-R models

The results of the ACT-R models show moderate differences between the model and human accuracies, and quite large discrepancies for the reaction times. Clearly, the models are missing something: Some cognitive processes that take place in human participants are probably left unaccounted for, which might explain the fact that the models are much quicker than their human counterparts. Unfortunately, this means that the models are not suited to judge the influence of rumination on how participants execute the VWM task, since some of the

processes that might be affected in human participants could simply not be present in the models.

Of course, the question that remains is what kind of cognitive processes could be missing from the models. When considering the impact of alternative strategies on the behavioural results, it becomes apparent that they can have a large influence on at least the reaction times of the model. Although the strategies studied here were only limited to the response stage of the experiment, it is quite possible that different strategies are also available during earlier stages (e.g. postponing the sequence inversion to the response stage instead of doing it at the start of the rehearsal stage). Not only can the availability of different strategies explain some of the discrepancies between model and human data, it can also mean a source of inhomogeneity within the participant groups, which might be reflected in the fMRI data.

In addition, some other limitations specific to ACT-R should be considered. One issue is the absence of any mechanism that resembles intentional forgetting: Once a chunk has been entered into ACT-R's declarative memory, the only way in which its activation value can be reduced is by the passage of time. This can cause a large amount of interference from chunks acquired in previous task trials - more than seems plausible. We had to combat this phenomenon by explicitly assigning a trial number to every chunk, which allowed us to specify our retrieval requests in such a way that no chunks of previous trials would be retrieved in the current trial. However, it is doubtful that human participants did not experience any interference from previous trials whatsoever. This exemplifies how the default mechanisms of the ACT-R architecture prevented a more accurate modelling of our VWM task.

4.3 fMRI

The meaning of the fMRI results is difficult to pinpoint. The fact that we observed little to no significant activation in just the rehearsal stage is at odds with the results of Jolles et al. (2010), who found strong lateral FPN activation in that stage. To figure out why this is the case, it might be helpful to consider where our task and that of Jolles and colleagues differs the most: The response stage. Whereas Jolles et al. provided a single picture and then required participants to answer with its position in the sequence, we presented two pictures and then asked which of those two was presented at position p. Our approach reduced the number of possible answers from five to two and provided the participants with an additional visual cue. This changes the availability of different response strategies considerably: For instance, in our task it was possible to select the correct picture by eliminating the one that is known to be incorrect, even if the correct picture itself could no longer be remembered. The ACT-R models have shown that a change of strategy can have a large effect on the reaction times, probably because different cognitive processes are involved in each strategy. Therefore, if our task invited participants to use a different strategy than what was efficient in the task of Jolles and colleagues, then our participants most likely use different cognitive processes than those of Jolles et al., which would explain the discrepancies in fMRI observations between our studies.

Also when comparing the baseline activations of healthy and remitted depressed participants, or the follow-up activations of the treatment and waiting list patients, we see almost no difference for the default preprocessing pipeline. This contrasts with Bartova et al. (2015), who found evidence for stronger medial FPN activation for the remitted depressed in an n-back task, a finding which is mirrored in patients with acute depression (Rose, Simonotto, & Ebmeier, 2006). A potential reason for the absence of these group differences is the possible strategy inhomogeneity that was highlighted by the ACT-R results: If different cognitive processes are being employed within groups, then a test that looks for group differences within one specific cognitive process might suffer a reduction in sensitivity.

On the other hand, for the preprocessing pipeline that included the log-transform, we did find a significant difference between healthy controls and remitted patients in backwards load 3 trials: Healthy controls had a significantly higher activation in the anterior part of the inferior parietal lobule (IPL). This region is part of the lateral FPN (Uddin et al., 2019), and therefore this result might implicate increased involvement of that network in solving the VWM task. Given that the lateral FPN is antagonistic to the medial FPN (Sridharan, Levitin, & Menon, 2008), this result could indirectly be in accordance with the increased medial FPN dampening in healthy controls as found by Bartova et al. (2015). This interpretation should be treated with care, however, as no more than a single voxel in a single contrast was found to display a significant difference. In fact, the lack of results that conform to previous fMRI studies on WM in (remitted) depression leads us to suspect that the data quality issues mentioned in Section 2.6 have had a jeopardising effect on the power and validity of our study.

4.3.1 Spatial independent component analyses The spatial independent component analyses (SICAs) demonstrated that functionally relevant brain networks can in fact be extracted from the data. When comparing the connectivity maps directly between groups (baseline and follow-up comparisons), no significant differences were found. However, comparing the beta coefficients of these networks after a regression between design matrices and independent component strength does show significant differences between healthy controls and remitted depressed patients. Especially component 5 (see Figure 3.6), the maximum activation of which is located in the superior temporal gyrus (STG), is stronger for healthy controls in the instruction and several response stages. The STG has been shown to be suppressed in first-episode MDD patients who had to make effortful decisions, possibly to compensate for caudate nucleus insensitivity to cost-benefit decision making (Yang et al., 2016). The increased STG component in the instruction stage (where participants can already make an estimate of how effortful the trial is going to be) and the response stages of our ex-

periment suggests that this deficiency lasts beyond remission from depression. However, without more research to confirm this suggestion, it remains highly speculative.

In contrast, remitted depressed patients showed stronger component 6 and 10 activation in the cue stage. Component 6 has its locus of activation mainly in the medial prefrontal cortex, which is part of the medial FPN (Uddin et al., 2019), while the core of component 10 is situated in the cuneus. Decreased suppression of the medial FPN is associated with increased levels of rumination (Zhou et al., 2020), which might mean that the rrMDD patients start to ruminate more often after seeing how many items will be presented on the current trial. Perhaps trials with high loads are deemed too effortful to pay full attention to, which would tie in well with the theory that decision making is disturbed in individuals with MDD. Meanwhile, it is unclear why the cuneus should be more pronounced for the remitted depressed patients, especially since it has been found to display hypo- rather than hyperactivation in (young) depressed patients, where it is associated with anhedonia (C. H. Miller, Hamilton, Sacchet, & Gotlib, 2015).

4.4 Future directions

In our study, we tried to answer the question how the connection between the lateral and medial FPNs relates to cognitive control and rumination in remitted depression, as well as how the aforementioned is influenced by PCT. Unfortunately, the ACT-R models and LARSS scores provided no evidence that PCT affected rumination, which casts doubt on whether our experimental manipulation of rumination was successful. This meant that our research question could no longer be answered. In addition, explorative SICAs yielded no proof for any difference in the lateral-medial FPN connectivity due to treatment. Future research, however, should investigate this issue with a more targeted connectivity analysis. Especially dynamic causal modelling (Friston, Harrison, & Penny, 2003) and the parametric empirical Bayes framework (Friston et al., 2016), where specific hypotheses about directed connections between regions of interest are compared, come to mind. Additionally, other connectivity measures between the lateral and medial FPN could be fed to a mixed-effects regression analysis to assess the effect of the interaction between treatment and measurement session. Future studies might, for instance, conduct an analysis of Granger causality (Granger, 1969) to provide such connectivity measures.

Finally, to determine how cognitive control ties in with the lateral-medial FPN connection in depression, future studies should investigate the effect of treatments that have already been proved to improve cognitive control. These studies could also be done with the acutely rather than the remitted depressed, as that might make the relationship more pronounced.

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