The effect of Repetitive Transcranial Magnetic Stimulation on cognition in depressed patients: Multiple case studies

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is an *in vivo* technique that induces a series of magnetic pulses to cortical areas of the brain. An accumulation of literature reports significant cognitive impairments in patients who suffer from depression, and suggests that these cognitive deficits resolve after rTMS treatment. However, few studies have investigated the efficacy of rTMS, in terms of improving both mood and cognition, as an additional treatment to antidepressants. Using a multiple case-study approach, the present research investigated the effects on cognition of high frequency rTMS, as an adjunctive to antidepressants, in a sample of 4 depressed participants. Treatment involved the application of a handheld coil over the left dorsolateral prefrontal cortex for 20 minutes. Each participant received three rTMS sessions a week for 1 month. Cognitive assessment was conducted at baseline (week 0) and at 2 and 4 weeks (post-baseline). The test battery consisted of a series of computerized neuropsychological tests that assessed memory and emotional decision-making. Results indicated that rTMS concomitant with antidepressants may be a clinically effective combination in the treatment of depression since no significant adverse effects on cognition were observed. In some cases participants showed improvement on neuropsychological test scores. Nevertheless the number of participants in this study is limited and so further investigation into the efficacy of rTMS as a treatment modality for depression could benefit from using an increased number of participants.

Key Words: transcranial magnetic stimulation; neuropsychological effects; major depression; left dorsolateral prefrontal cortex; antidepressants; cognition.

BACKGROUND/RATIONALE

The development of repetitive transcranial magnetic stimulation (rTMS) as a clinical tool in the treatment of depression is largely dependent upon adding to the quantity, and improving on the quality, of studies that investigate the precise cognitive effects of rTMS (Gershon, Dannon, & Grunhaus, 2003). This is because rTMS, as a clinical tool, is marketed as an alternative to electroconvulsive therapy (ECT), which has well-documented adverse effects on cognition (Schulze-Rauschenbach et al., 2005); thus, if it is to be widely used, it must not only be an effective adjunct to psychotherapy and pharmacotherapy or an effective treatment modality on its own, but it must also prove to be less harmful (and perhaps even beneficial), in terms of cognition, than ECT.

The imbalance hypothesis of the pathophysiology of depression postulates that there is relative hyperactivity of the right dorsolateral prefrontal cortex (DLPFC) compared to the left DLPFC (Bermpohl et al., 2006). The implication of this imbalance is that, at the physiological level, regional cerebral blood flow (rCBF) to the cortex is disturbed. Application of high-frequency rTMS treatment has been associated with a significant increase in rCBF in the left DLPFC. These changes in rCBF are associated with a reduction in symptoms of depression, including cognitive impairments in various domains such as, attention, learning, and memory, as well as in executive, motor and perceptual functions (Kito, Fujita, & Koga, 2008; Paus & Barrett, 2004). Thus the majority of studies administer high frequency (fast) rTMS over the left DLPFC and low-frequency (slow) rTMS over the right DLPFC. The following sections review studies that document the effects of these and similar kinds of rTMS administration, on the specific areas of cognition on which the currently proposed case studies focused on: memory, attention, and emotional decision-making. I focus on these specific areas because people who suffer from depression tend to have problems in these areas of cognition (Januel et al., 2006; Speer et al., 2000).

Unilateral rTMS without Concomitant Pharmacotherapy

In most rTMS and cognition studies, researchers measure the effects of the application of rTMS over a single hemisphere (usually the left, and usually in prefrontal regions). Such studies of unilateral rTMS without concomitant pharmacotherapy tend to suggest that rTMS has no negative effects on cognition (e.g., Hausmann et al., 2004; Januel et al., 2006), and in fact some

trials have found improvement on neuropsychological test scores following rTMS (e.g., Bermpohl et al., 2006; Martis et al., 2003).

For instance, Triggs et al. (1999) measured, in a population of depressed patients, the effects of left prefrontal rTMS on motor evoked potential threshold, mood, and cognition. In a 2-week open trial study, the patients remained off antidepressant medication. Neuropsychological tests administered included the Hopkins Verbal Learning Test (HVLT; Shapiro, Benedict, Schretlen & Brandt, 1999), which assesses episodic memory, and the Digit Span (DS) subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), which assesses working memory and auditory attention span. Neuropsychological performance of participants at completion of rTMS and 3 months later was compared to baseline performance. Results indicated no deleterious cognitive effects, and statistically significant improvements on DS performance at completion of rTMS. At 3 months post-rTMS HVLT performance was also statistically significantly better than at baseline.

This pattern of results is paralleled in an analogous design by Fabre et al. (2004). These researchers also observed no significant deterioration of neuropsychological test scores following rTMS. On the contrary, they found improvements in performance on a measure of visuospatial memory at completion of rTMS treatment. Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) results also showed that attenuation of depression was significantly correlated with delayed recall on that measure. However, previous controlled studies of the effects on cognition of rTMS in major depression showed that such improvements in certain aspects of cognition may be independent of the positive mood changes observed after application of rTMS (Moser et al., 2002; Martis et al., 2003).

The studies reviewed above suffer from several limitations. For instance, each of them employed relatively small samples (n = 10 for Triggs et al. (1999) and n = 11 for Fabre et al. (2004)). Small samples introduce bias as uncontrolled variables that may influence the outcomes on neuropsychological measures are not evenly distributed amongst the treatment groups. Additionally, statistical analyses of the neuropsychological measures will be affected by the sample sizes- a larger sample may show differing neuropsychological functioning after application of rTMS. Furthermore, although the investigators used alternative forms of the instruments at follow-up testing, carryover effects (e.g., greater comfort with the instruments, improved mnemonic strategies based on prior experience) may be responsible for some of the

marked improvement in scores. Finally, the data reported by Triggs et al. (1999) may be confounded by the fact that some of their participants resumed their antidepressant regimen prior to the 3-month follow-up test session. The design of that study, and others similar to it, make it difficult to conclude whether or not the cognitive improvements observed were independent of any possible effects of the continued antidepressant medication.

Unilateral rTMS concomitant with pharmacotherapy

Similar studies of unilateral rTMS, this time with concomitant pharmacotherapy, also tend to suggest that rTMS has no negative effects on cognition (e.g., Hoeppner, Schulz, & Irmisch et al, 2003.), and in fact some trials have found improvement on neuropsychological test scores following rTMS (e.g., Avery et al., 2006; Padberg et al., 1999).

For instance, Mosimann et al. (2004) measured, in a population of depressed patients, the effects of left prefrontal rTMS on cognitive function. In a 10-day add-on study, patients were randomly assigned to receive either application of active rTMS or sham rTMS. Neuropsychological tests administered included two different measures that specifically assessed executive functions, namely the Stroop test (Stroop, 1935) and the Trail-Making Tests A and B (TMT-A/B; Reitan et al., 1958). Neuropsychological performance at completion of rTMS was compared to baseline performance. Results indicated no adverse effects on cognition. Performance on the Stroop test and on TMT showed no significant changes between the active rTMS group and the sham rTMS group.

In a randomized double-blind study by Shajahan et al. (2002), cognitive performance of depressed patients was assessed using different stimulation frequencies (20Hz, 10Hz, and 5Hz) of rTMS over the left DLPFC. Patients remained on antidepressant medication throughout the duration of the rTMS administration. Neuropsychological tests were administered at baseline, daily after rTMS and 2 weeks after the last session of rTMS. Cognitive measures focusing on memory and attention included (i) the Digit Symbol subtest from the Wechsler Intelligence Scale – Revised (WAIS-R; Wechsler, 1981), (ii) the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway & Nimmo-Smith, 1994), and (iii) the Wechsler Memory Scale (digits backwards and forwards) (WMS; Wechsler, 1987). Results of cognitive performance on these measures after completion of rTMS showed no deleterious effects.

The studies above suffer from several methodological limitations. For instance, Shajahan et al. (2002) failed to employ a control group. Although this study used randomization procedures, failing to use a sham or masked control group makes it difficult for the researcher to conclude the absolute or relative antidepressant efficacy of rTMS on cognitive functioning. Furthermore, Mosimann et al. (2004) tested the cognitive performance of rTMS in an elderly population of patients (mean age 62 years). Published reports with regards to elderly depressed patients receiving rTMS are largely inconclusive. Additionally, no changes in cognitive performance after completion of the rTMS could be attributed to the short duration period of 10 days employed in the study. A delayed antidepressant response to the active rTMS may have influenced the outcomes found on these cognitive performance measures.

Bilateral rTMS concomitant with pharmacotherapy

In most rTMS and cognition studies, researchers measure the effects of the application of rTMS over a single hemisphere (usually the left, and usually in prefrontal regions). However, more recently different stimulation paradigms, such as bilateral rTMS, have been theorized to be more effective than unilateral rTMS. Studies of bilateral rTMS with concomitant pharmacotherapy tend to suggest that it has no statistically significant negative effects on cognition (e.g., Cohen, Amassian, Akande, & Maccabee, 2003), and in fact some trials have found improvements on neuropsychological test scores following bilateral rTMS (e.g., Hoeppner et al., 2003).

For instance, Fitzgerald et al. (2006) studied, in a population of depressed patients, the effect on cognitive performance of sequentially combining high-frequency rTMS to the left DLPFC with low-frequency rTMS to the right DLPFC. In this 6-week double-blind randomized sham-controlled trial patients maintained antidepressant medication regimens throughout the duration of the rTMS treatment course. A neuropsychological battery was administered at baseline and at completion of the 6-week rTMS treatment. Cognitive performance measures predominantly focused on memory and included the following instruments: the HVLT, the DS subtest from the WAIS, and the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, Schretlen, Groninger, Dobraska, & Shpritz, 1996). Overall there were no statistically significant reductions in cognitive performance for either the active rTMS condition or the sham rTMS condition. Only a slight (not statistically significant) decrease was found on HVLT delayed recall for both the active rTMS and sham rTMS conditions. An improvement from baseline to follow-

up was only seen on the DS backward test in the active rTMS condition. This improvement did not correlate with the positive change in mood experienced by patients in the active rTMS condition, suggesting that application of rTMS may affect cognitive performance independent of mood changes.

Likewise, Hausmann et al. (2004), in a sample of depressed patients, measured the cognitive performance of patients who were randomly assigned to 1 of 3 rTMS conditions: (i) unilateral high-frequency rTMS over the left DLPFC, (ii) bilateral rTMS, which consisted of simultaneously administering high-frequency rTMS over the left DLPFC and low-frequency rTMS over the right DLPFC, (iii) and a sham rTMS condition. In this 2-week, double-blind, sham-controlled trial patients remained on antidepressant medication regimes. Neuropsychological performance was assessed at baseline and at 2 weeks following completion of rTMS. Assessment of cognition included measures that focused on attention, executive functions, and memory. Instruments included (i) the Muenchner Verbaler Gedaechtnistest (MVG; Illmberger, 1988), a German equivalent of the California Verbal Learning Test (CVLT; Delis et al., 1987) that assessed short-term and long-term verbal memory, (ii) the TMT-A/B and (iii) the Stroop test. No adverse effects of rTMS on cognition were found for the unilateral rTMS condition or for the bilateral rTMS condition in comparison to the sham rTMS control. For these active rTMS conditions a statistically significant improvement from baseline to follow-up was seen in all three of the neuropsychological measures mentioned above. None of the scores on these cognitive measures after rTMS correlated with positive changes in mood, again suggesting that such improvement occurred independent of the alleviation of depressive symptomology.

The studies reviewed above suffer from several limitations. For instance, administering rTMS as an adjunct to heterogeneous antidepressant medication regimens may be of concern in both these studies. Such a design makes it difficult to exclude the possibility that after the application of rTMS, the antidepressant medications used may have resulted in inconsistent effects on both cognitive performance and depressive symptomology between patients.

Furthermore, Hausmann et al. (2004) employed patients who suffered from unipolar depression and patients who suffered from bipolar depression. Some literature proposes that the profile of cognitive deficits experienced by unipolar depressed patients is different to those experienced by bipolar depressed patients. Thus the scores observed on the neuropsychological

measures may have been confounded by the differing profile of cognitive deficits between unipolar and bipolar patients.

Limitations of extant rTMS studies

As noted in the sections above, numerous methodological limitations hamper the conclusions one can draw from many of the empirical studies in this field. For instance, the problem of employing a small sample size can be corrected by simply increasing the sample size recruited. Increasing the sample size will improve the chances of uncontrollable variables being more evenly distributed among the rTMS treatment groups, making groups similar in composition and more therefore more comparable. Furthermore increasing the sample size will improve the generalizability of the neuropsychological test results after application of rTMS as the statistics will have more power (Triggs et al., 1999).

Another limitation of rTMS studies is with regards to the use of rTMS as an adjunct to pharmacotherapy. Some studies utilize heterogenous medication regimes, a possible factor that may confound the results of neuropsychological tests post rTMS. In the future patients should adhere to homogenous medication regimes, that is, all patients should be administered the same medication. This will help to exclude the possibility that differing antidepressant medications may have had an effect on cognitive measures and will make it easier to conclude that the cognitive improvements observed were independent of any possible effects that the antidepressant medication may have had after application of rTMS (Hausmann et al., 2004).

Additionally, although some studies may use randomization procedures, many studies have failed to use a sham or a masked control group. The absolute or relative effect that rTMS has on cognitive functioning will be more coherently explained if there is a control group. This is because the cognitive improvement that accompanies a recovery from depression may mask the changes that occur as a result of the rTMS treatment (e.g., Shajahan et al., 2002). Some form of control group will allow the researcher to examine the exact effects of rTMS on cognition in depressed participants. This may explain why a number of studies use healthy participants (e.g., Schulze-Rauschenbach et al., 2005) or electroconvulsive therapy (ECT) or sham groups as control groups (e.g., O' Connor et al., 2003).

Furthermore, the duration period of rTMS treatment needs to be extended. Gershon et al. (2003) reported that studies administering rTMS for more than 10 days showed greater treatment

success than in studies in which less than 10 days of rTMS was administered. Subsequently, post rTMS neuropsychological evaluations need to be carried out. The longevity of the effects of rTMS in depressed patients remains largely unknown (Walsh & Cowey, 1998). Evidence has suggested that rTMS effects clearly last for up to 10 ms at the site stimulated, however little is known about the long-term effects of rTMS on depressed patients' prefrontal metabolism and neurochemistry (Dang et al., 2007).

SPECIFIC AIMS/HYPOTHESIS

The research reported here is the first wave of data collection for a larger study that aims to investigate the effects on memory, attention, and emotional decision-making of high frequency unilateral rTMS over the left DLPFC as an adjunctive to antidepressants in depressed participants. Essentially, this larger research project investigates whether rTMS (administered three times a week over a period of 1 month) accelerates the effect of antidepressants and improves cognition in depressed patients. In participants treated with both rTMS and antidepressants, mood and cognition are measured at 0 weeks (baseline, before the first administration of rTMS), 2 and 4 weeks.

Whereas the larger project compares active and sham rTMS treatment conditions, the first wave of data collection reported here includes only participants in the active condition. (For the purposes of the larger study, participants are randomly assigned to either the active or the sham condition, and it so happened that the first four participants were all assigned to the active condition).

The aims of this study are therefore to (a) provide preliminary data bearing on the question of whether rTMS plus antidepressants are a clinically effective combination in the treatment of depressed individuals, (b) replicate previous literature by demonstrating that rTMS has no adverse effects on memory and emotional decision-making, and (c) investigate whether participants with rTMS as an adjunctive treatment to antidepressants show improved cognitive functioning over the course of the month-long treatment.

METHOD

Participants

Participants were recruited through Valkenberg Hospital. All participants met the criteria for a non-psychotic current depressive episode as outlined in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision; DSM-IV-TR; American Psychiatric Association, 2000) and as determined by the Mini International Neuropsychiatric Inventory (MINI version 5.0.0; Sheehan & Lecrubier, 2002). All participants met the following inclusion criteria for participation:

- Between the ages of 21 and 60 years
- A baseline score of at least 17 points on the Montgomery Asberg Depression Rating Scale (Montgomery & Asberg, 1979; see Appendix C).

Likewise, the following exclusion criteria met by participants included:

- Severe uncontrolled organic disease (as determined by history and physical examination)
- Severe recurrent headache
- Current alcohol abuse
- Use of a pacemaker
- Previous neurosurgery with implants of metal or clips
- Current psychotic symptoms

Table 1.

Demographics of the Four Participants

Demographics	RL	KW	SC	MH
Gender	Male	Female	Female	Male
Age	57	39	57	48
Race	White	White	White	White

The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2008) and all procedures were approved by University of Cape Town Faculty of Health Sciences Research Ethics Committee and by the Valkenberg Hospital Research Committee. Participation was voluntary, and participants were provided with a consent form (see Appendix A) that informed them about the nature, the possible risks and benefits, and the

purpose of the treatment, as well as the instruments to be utilized (see Appendix B). Furthermore, because of concern for the participants' well-being and interests information disclosed remained confidential.

Benefits

There is no current local experience of rTMS use in South Africa. The investigators were trained by Professor Jack van Honk from the University of Utrecht. rTMS is approved for clinical use for the treatment of depression in Canada and Israel and currently being considered by the FDA for this indication in the United States (N. Horn, personal communication, April 17 2008). rTMS has a remarkably low side-effect profile, and the two occasions when seizures were reported as side-effects took place when safety limits were exceeded (Wassermann et al., 1996; 1998). rTMS has a good safety record in both clinical and healthy populations. The lack of impedance by the skull to the magnetic field generated using this technique means that it can be administered at a relatively low intensity, and usually painless fashion to participants while they are awake (Stewart, Ellison, Walsh & Cowey, 2001).

Risks

The possibility of tissue damage caused by overheating of neurons through the electric current is not considered a significant hazard of rTMS (Wassermann, 1998). The intense clicking sound produced by the TMS devices has been demonstrated to raise auditory threshold of participants, and may theoretically result in earache. Therefore, in the current study earplugs were offered to participants. rTMS procedures were carried out in accordance with the guideline suggested from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation (Wasserman, 1998).

Procedure

Drug Treatment

In accordance with their psychiatrist(s), the four participants in this study were on differing dosages and types of antidepressants. Any other psychotropic medications that participants relied on were recorded and maintained at the same dosage throughout the study. Low doses of

diazepam (2-10mg/24 hours) for sedative purposes were administered if required, and similarly this was recorded but was also considered as a possible confounder in the study.

rTMS Procedure

Testing took place in a private room at Valkenberg Hospital. The rTMS procedure was carried out by research clinicians using the Magstim Super Rapid Stimulator (Magstim Co, Whitland, U.K.) with a figure-eight coil. Participants were offered earplugs to minimize any adverse effects on hearing. In the first session, the motor threshold of the abductor pollicis brevis site in the left motor cortex was determined by visual inspection using a method of limits (Pridmore et al., 1998). Stimulations were given at 120% of the motor threshold to the left DLPFC, located 5cm anterior to the point of optimal stimulation for the abductor pollicis brevis in the parasagittal plane. Each participant received 3 sessions of rTMS treatment over a 4-week period. Each session consisted of 25 trains of 5Hz stimulations for 10 seconds, with 20-second intervals. No anaesthetic was required during the rTMS procedure, and the subject was fully conscious throughout the treatment.

Neuropsychological Evaluation

Cognitive assessment were conducted at week 0 (baseline), week 2, and week 4. These assessments consisted of computerized tests of memory and emotional decision-making. The battery examined functions that are generally associated with the fronto-cortical brain regions that are usually implicated in depression. Based on current literature a subset of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition, 2006) was selected. An additional series of computerized cognitive tasks was also used.

Instruments

Clinical assessments were conducted at week 0 (pre- rTMS) and at week 4 after completion of rTMS treatment. The primary measure used was the MADRS score. Remission was defined as a MADRS score of 8 or less, and response as a reduction in baseline MADRS score by 50%. The secondary outcome was the Sheehan Disability Scale scores and the neuropsychological tests as described below.

Memory

The CANTAB *Delayed Matching to Sample* test (CANTAB, 2006) is a measure of immediate and delayed visual memory. In this test, participants were shown a complex visual pattern (the sample) at the top of the computer screen and then, after a brief delay, four patterns in the middle of the computer screen. In some trials the sample and the four choice patterns were shown simultaneously, whereas in others a delay (of 0, 4 or 12 seconds) was introduced between the presentation of the sample pattern and the four choice patterns. The subject had to indicate on the computer touch-screen which of the four choice patterns is identical to the sample that appeared at the top of the computer screen. The dependent variable of interest here was the accuracy of the participant's responses; given that there were a total of 11 trials for each delay interval, the maximum obtainable score was 11.

The *Object Relocation* test (Van Honk & Schutter, 2006) is a measure of delayed memory and visual memory. In this task participants were presented with images (small black and white photographs of people's faces with differing emotional expressions) serially for 2 seconds in a number of places on the screen. Participants had to try and memorize where on the screen the images appeared. After a short time the images appeared at the top of the screen in a line, and the participant had to use the left mouse button to place the images as close as possible to where they had previously appeared on the screen. This test was made up of 12 trials, with 8 faces in each trial. Out of the 8 faces, 4 were neutral and 4 had an emotional expression (either sad, happy, or fearful). The dependent variable of interest here was an average deviation score derived from the difference between the location in which the emotion had original appeared and the location where the participant placed it.

Emotional Decision-Making

The *Emotion Recognition* test (Van Honk et al., 2006) is a measure of emotional decision-making. In this task a series of black and white images were displayed sequentially on a computer screen. Participants were initially shown an emotionally neutral face. When the participant pressed the 'enter' button on the keyboard, the face developed an emotional expression. In this test, faces morphed in increasing intensities. There were nine levels of intensity, and within each level of intensity, each of the emotions were presented 4 times in a random order. The participant had to choose as quickly as possible the emotion that was being

expressed. This was done by means of the numerical keyboard (1 = angry, 2 = happy, 3 = sad, and 4 = fearful). The answer options were shown on the screen so participants did not have to memorize them. Participants only had one chance to identify the emotion on each face. The dependent variable of interest here was accuracy of the participant's responses; given that, altogether, in each session, each emotion appeared a total of 36 times, the maximum obtainable score was 36.

The order of administration of these tests is shown in Table 2.

Table 2.
Order of Administration of the Neuropsychological Instruments Used in the Case Studies

Test Name	Domain Tested	Time (mins)	Previous Study in Which Used
1. Object Relocation	Memory	20	Van Honk & Schutter (2006)
2. Emotion Recognition	Emotional Decision-Making	15	Van Honk et al. (2006)
3. Delayed Matching to Sample	Memory	25	Porter et al. (2003)

RESULTS

These multiple case studies provide the basis for a progress report. This approach is often used in neuropsychological studies, especially where only a small number of participants are available (Shallice, 1988; Walsh, 1985). With such a small number of participants, and with all of them being in the active rTMS treatment condition, adopting such an approach is most sensible.

All four participants successfully completed the neuropsychological tests at week 0 (pre-rTMS), 2, and 4 (post r-TMS), as well as the clinical assessments at week 0 and week 4 (refer to Table 3). The observed scores discussed below provide useful preliminary data with regards to (a) the clinical effectiveness of combining rTMS with the use of antidepressants in treating depressed populations (b) the question of whether or not rTMS as a treatment modality in depression has adverse effects on memory and emotional decision-making and (c) whether the application of rTMS in conjunction with antidepressants demonstrates an improvement in cognitive functioning.

It is important to note that the results obtained from week 0, week 2 and week 4 do fluctuate. This may be attributable to the participants delivering sub-optimal effort on these tests. Their performance was not motivated in any way since the tests are being given solely for the purposes of research. There was no financial gain or incentives for participants to perform at their optimal level.

Table 3.

Clinical Assessment Results

	Case 1 – RL		Case 2 – KW		Case 3 –SC		Case 4 – MH	
	Pre-rTMS	Post-rTMS	Pre-rTMS	Post-rTMS	Pre-rTMS	Post-rTMS	Pre-rTMS	Post-rTMS
MADRS	30	12	39	36	27	31	27	25
Sheehan Disability Scale								
Work	7	8	7	9	7	8	10	10
Social Life	3	1	9	8	9	10	8	9
Family Life	3	4	9	9	7	7	9	8
Perceived Stress	9	7	5	7	8	7	9	7

Case study 1- Name: RL

The *neuropsychological test data* for RL are presented in Table 4.

Table 4.
Case 1- RL: Neuropsychological Test Performance

		Week 0	Week 2	Week 4
DMS				
	No Delay	10	9	8
	Delay	7	7	7
Object Relocation				
	Sad	2.70	6.34	2.11
	Fear	4.55	9.05	11.90
	Happy	0.38	8.33	0.45
Emotion Recognition				
	Angry	23	28	25
	Happy	33	35	35
	Sad	27	27	30
	Fearful	28	32	34

Note. Raw scores are presented.

With regards to the *DMS* test, RL's performance did not change much. Accuracy for the 'no delay' trials dropped overall by only 2 points, which cannot be regarded a significant change. With the DMS test, participants are performing to ceiling from week 0 as illustrated in Table 4. Thus, there is not much room to show that rTMS may be improving memory capacities in depressed people. More of an attentional component is needed on this measure to really entertain the ability of depressed individuals, and yield results that could be more meaningful. However when looking at the DMS test performance, of great relevance are the scores obtained in the 'delay' trials. In the literature, the cognitive side effects of depression include memory impairment (Schulze-Rauschenbach et al., 2005). If rTMS is to be concluded as efficacious or safe (i.e., does not result in deleterious cognitive functioning), then scores on the 'delay' component of trials must either improve, or stay relatively stable. The fact that the accuracy of

these scores did not deteriorate for RL may illustrate that rTMS can be administered without adverse effects on memory.

With regards to the *Object Relocation* test, the most important condition to look at is 'sad', particularly with regard to how it compares to the 'happy' condition. This is because evidence suggests that individuals who suffer from major depressive disorders show a tendency to remember negative material better than they can remember positive material (Levin et al., 2007). In judging performance in this test, a lower average standard deviation illustrates an improvement. It indicates that the individual can more accurately memorize and therefore place the emotional face closer to where it had originally appeared. Overall, between week 0 and week 4 RL showed an improvement in placing sad faces; relative to happy faces, however, he continued to perform poorly. One possible explanation for this finding is that there are two negative emotion conditions in this task ('sad' and 'fearful'), whereas there is only one positive emotion condition ('happy'). Therefore, remembering the location of happy faces is an easier task and one that is much less prone to interference.

Likewise, with regards to the *Emotion Recognition* test, of great relevance is the performance of individuals in accurately identifying the emotion 'sad'. From week 0 through to week 4 RL shows a slight improvement in correctly identifying this emotion. In comparison to the accuracy in correctly identifying the 'happy' faces RL shows a slight improvement, but as illustrated by the results he is performing at ceiling level.

In *summary*, the observed positive changes on the Object Relocation test and the Emotion Recognition test, and the relatively stable (i.e., non-deteriorating) performance of RL on the DMS test, suggests, first, that rTMS did not adversely affect memory or emotional decision-making capacities, and may in fact have led to some improvements in these cognitive domains over the course of the month-long treatment. Furthermore, the clinical response illustrated in RL's MADRS scores (see Table 3) suggests that rTMS in conjunction with antidepressants may be a clinically effective combination in the treatment of depression.

Case study 2- Name: KW

The *neuropsychological test data* for KW are presented in Table 5.

Table 5
Case 2- KW: Neuropsychological Test Performance

		Week 0	Week 2	Week 4
DMS				
	No Delay	8	10	10
	Delay	10	9	9
Object Relocation				
	Sad	14.20	1.37	12.88
	Fear	10.32	12.32	4.28
	Happy	5.49	9.52	16.95
Emotion Recognition				
	Angry	29	30	33
	Happy	31	36	36
	Sad	23	25	22
	Fearful	32	32	35

Note. Raw scores are presented.

In looking at the neuropsychological performance of KW, the same components of the tests examined in the case of RL will be looked at here. With regards to the *DMS* test, KW showed stable performance and no significant cognitive deterioration over the month-long rTMS treatment period. KW's performance on the 'delay' trials is more than satisfactory in light of her MADRS score (refer to Table 3).

Likewise, with regards to KW's performance on the *Object Relocation* test, her placement of the 'sad' faces improved from week 0 to week 4. This does not indicate that KW's depression is disappearing; it may however suggest that she is feeling considerably less sad than she did at week 0. It is important to note here that there is a considerable fluctuation of results when comparing week 0 to week 2. This may be attributable to the previously mentioned lack of motivation by participants in completing these tests.

Additionally, KW's accuracy in identifying the correct emotion in the *Emotion Recognition* test over the 4 weeks was stable. Although she improved in accuracy in correctly identifying angry, happy and fearful expressions, her performance in accurately identifying 'sad'

at week 4 is only one point off her accuracy score at week 0. This drop in one point is not significant enough to conclude rTMS was having an adverse effect on her emotional decision-making capacities.

In *summary*, the evidence provided by this case is consistent with that provided by the first case study. Although in this case there was a lack of clinical response to the adjunctive treatment (as highlighted by the minor change in MADRS scores; see Table 3), rTMS still appears to be a safe treatment modality that does not display deleterious affects on cognition, more specifically in memory and emotional decision-making capacities. If anything, the slight improvements shown in Table 5 contribute to the evidence which proposes that rTMS in combination with antidepressants can improve cognitive functions in people suffering from depression.

Case study 3- Name: SC

The *neuropsychological test data* for SC are presented in Table 6.

With regards to SC's performance on the *DMS* test, like RL and KW her accuracy scores remained relatively stable. Accuracy of correctly identifying the matching pattern despite the introduction of a delay is, at week 2 and week 4, one point off scoring 100% for the test. Once again this highlights that performance on the DMS test is at ceiling level. The minor change is once again is not significant enough to conclude that rTMS was having adverse effects on memory.

SC's performance on the *Object Relocation* test was somewhat poor, however. The standard deviations for accurately placing the sad faces worsen from week 0 to week 4. This deterioration in performance is consistent across all conditions in this test, suggesting that it may be accounted for by her apparently worsening affective state (see Table 3).

With regards to the *Emotion Recognition* test, SC's performance improves considerably across time, suggesting that she becomes more sensitive to accurately identifying the sad faces. This result might be accounted for by the fact that her depression appears to worsen from Week 0 to Week 4 (see Table 3); as noted earlier, depressed mood states are associated with increased processing of negative affective material. (She also improves at recognizing other negative emotions.) On the other hand, from Week 0 through Week 4 she performs at ceiling in terms of recognizing happy faces, a result that is at odds with cognitive theories of depression.

Table 6
Case 3- SC: Neuropsychological Test Performance

		Week 0	Week 2	Week 4
DMS				
	No Delay	9	11	11
	Delay	11	10	10
Object Relocation				
	Sad	3.86	2.21	6.04
	Fear	9.19	8.91	12.23
	Happy	2.71	13.32	14.20
Emotion Recognition				
	Angry	29	32	35
	Happy	36	36	36
	Sad	27	33	34
	Fearful	31	36	35

Note. Raw scores are presented.

In *summary*, SC's neuropsychological test results are consistent with those presented before in suggesting that rTMS demonstrated no adverse effects on SC's emotional decision-making capacities. However, it is difficult to conclude the same about the effects that rTMS had on memory functioning in this case because the measures used (DMS and Object Relocation) to test this capacity displayed contradictory findings. These results may have been hampered by methodological limitations in this study which will be discussed in full in a later section. With regard to mood, it appears that rTMS concomitant with antidepressants may not be effective in treating SC's depression; her lack of a clinical response to the combined treatment is reflected in her worsening MADRS and Sheehan Disability Scale scores (Table 3).

Case study 4- Name: MH

The *neuropsychological test data* for MH are presented in Table 7.

Table 7.
Case 4- MH: Neuropsychological Test Performance

		Week 0	Week 2	Week 4
DMS				
	No Delay	9	10	11
	Delay	9	6	7
Object Relocation				
	Sad	3.28	13.04	2.60
	Fear	2.75	5.24	10.05
	Happy	7.74	6.31	16.1
Emotion Recognition				
	Angry	28	24	25
	Happy	36	36	36
	Sad	33	34	30
	Fearful	36	34	34

Note. Raw scores are presented.

With regards to the *DMS* test, MH's performance on the 'delay' trials did not change much. Accuracy within these trials dropped overall by 2 points, which cannot be regarded as a significant change. Therefore, it cannot be deduced that rTMS is having a deleterious effect on MH's memory.

With regards to the *Object Relocation* test, MH's performance from week 0 to week 4 illustrates that he showed an improvement in placing sad faces; relative to happy faces. This data contributes to the ability of rTMS to be administered without causing significant adverse effects on memory capacities in depressed individuals, and in this case shows that it may be responsible for improving his memory.

However performance on the *Emotion Recognition* test demonstrates that emotional decision-making for MH worsens from week 0 to week 4 in terms of accuracy in identifying the 'sad' faces. However, MH is performing at ceiling level with regards to accurately identifying the 'happy' faces. Whether or not MH's lack of sensitivity to the 'sad' faces is attributable to the effects of rTMS is difficult to conclude.

In *summary,* MH's neuropsychological test results suggest that rTMS applied as an adjunct to antidepressants may not be the most clinically effective combination in treating his depression since MADRS scores did not improve significantly (see Table 3). The literature on depression does propose that the severity of ones depression correlates with ones performance on tests of pattern recognition and delayed matching (with increased severity leading to poorer performance) (Stewart et al., 2001). However rTMS did not result in any significant adverse effects on cognition as accuracy scores on both the DMS test and the Emotion Recognition test are near ceiling level. To the contrary rTMS may be responsible for the improved performance observed on the Object Relocation test.

Overall Summary of Cases

Summary data for the participants' performance in neuropsychological tests is provided in Table 8.

Table 8
Summary of the Neuropsychological Test Performance Scores for the Four Participants

		Week 0	Week 2	Week 4
DMS				
	No Delay	9.00 (0.82)	10.00 (0.82)	10.00 (1.41)
	Delay	9.25 (1.71)	8.00 (1.83)	8.25 (1.50)
Object Relocation				
	Sad	6.01 (5.48)	5.74 (5.33)	5.91 (4.97)
	Fear	6.70 (3.63)	8.88 (2.89)	9.62 (3.68)
	Happy	4.08 (3.21)	9.37 (2.95)	11.93 (7.74)
Emotion Recognition				
	Angry	27.25 (2.87)	28.50 (3.42)	29.50 (5.26)
	Happy	34.00 (2.45)	35.75 (0.50)	35.75 (0.50)
	Sad	27.50 (4.12)	29.75 (4.43)	29.00 (5.03)
	Fearful	31.75 (3.30)	33.50 (1.91)	34.50 (0.58)

Note. Means of raw scores, with their standard deviations in parentheses, are presented.

Averages for the neuropsychological test performance scores of the four participants were computed. With regards to the *DMS* test, in particular the delay trials, performance was at ceiling level and the differences observed in scores pre-rTMS and post-rTMS indicate a decrease by one point. This minor change is by no means significant. The overall performance on the DMS test by the four participants suggests that rTMS in conjunction with antidepressants in the treatment of depression, does not have an adverse effect on memory.

With regards to the *object relocation* test, the average performance between the four participants advocate the proposition that rTMS may in fact alleviate symptoms of depression i.e. improve cognitive performance. The average deviation scores of the sad faces decrease from week 0 to week 4, indicating that participants over the month-long rTMS treatment period began to more accurately place the sad face closer to where it had originally appeared. This once again may be interpreted as evidence that rTMS could possibly be responsible for the improvement of memory functions in depressed people.

With regards to the *emotion recognition* test, as Table 8 illustrates, emotional decision-making by participants improves over the duration of the study. In this test, the averages calculated suggest that the participants became more sensitive to correctly identifying the sad faces. Once again this data contributes to the advocacy of rTMS in the treatment of depression.

In *summary*, the crudely calculated averages in Table 8 highlight that rTMS concomitant with an antidepressant regime may be a clinically effective combination in the treatment of depression. More specifically the results yielded demonstrate that rTMS does not have any significant deleterious effects on memory and emotional-decision making capacities in depressed individuals. To the contrary, in some cases it has shown evidence of improved cognitive functioning over the month-long treatment process.

DISCUSSION

The cognitive biases and impairments implicated in the pathophysiology of psychiatric disorders such as depression have been hypothesized to play a role in the maintenance of depression (Levin et al., 2007). However as the present case studies indicate, the administration of rTMS to a specific region of the brain (i.e. the left DLPFC) may alleviate such dysfunctions (Stewart et al., 2001).

The mild cognitive improvements seen in some of the participants could be a result of associated changes that rTMS is reported to have on the neuroanatomical functions of the left DLPFC. Kito, Fujita, and Koga (2008) report that the mechanisms underlying the supposed antidepressant efficacy of rTMS treatment still remain unclear. However, single photon emission computed tomography (SPECT) has suggested that rTMS modulates or normalizes the abnormal rCBF and metabolism that is associated with depression. Additionally, the frequency of rTMS is believed to alter the neuronal activity of the cerebral cortex. Stewart et al. (2001) propose that in general, 'greater activity in a brain region is associated with better performance on the cognitive functions localized to that region, and reduced activity is associated with poorer performance' (p. 212). rTMS induces neuronal firing and therefore evokes greater neuronal activity, thus possibly explaining the improvements observed in the neuropsychological test scores However this neuronal activity that is evoked cannot predetermine a precise pattern of neuronal activity, and so might explain the differing neuropsychological test performance scores observed among the participants (Stewart et al., 2001).

The multiple case studies in this investigation provides evidence that application of rTMS as an adjunct to antidepressants, in the treatment of depression, has no significant adverse effects on neither memory nor emotional decision-making capacities. Although MH admitted to experiencing visual auras, and KW and SC reported that they had experienced transient headaches during and after the rTMS procedure, no seizures were induced. There are many studies that have investigated the antidepressant efficacy of rTMS as a treatment modality in depression and reported similar discomfort of their patients (Cohen et al., 2004).

It is however difficult to compare current findings to those of other studies as stimulation parameters and designs differ considerably.

Limitations and Future Directions

The design of the present study has resulted in several methodological limitations that may potentially confound the results yielded in this study (Fitzgerald et al., 2007). Firstly, due to the random allocation of all these participants into the active treatment condition, there was no control group i.e. a sham (inactive rTMS) treatment condition with which to compare the current findings. The implication of this for the present study is that no conclusions can be drawn in relation to the absolute or relative effects of rTMS on depressed participants (Schulze-

Rauschenbach et al., 2005). Additionally, the capacity to demonstrate a difference between alternative conditions in this case is unfeasible and the use of more meaningful and complicated analyses cannot be conducted (Fitzgerald et al., 2007). However, because this is just a progress report, the lack of a comparison group should not be considered as a methodological limitation per se since the larger study intends on adopting the use of a sham rTMS treatment condition.

Grunhaus et al. (2003) also propose that the observed effects of the rTMS treatment may be secondary to the effects of the interaction between the psychiatrist and the participant. The presumed psychological effect of the interaction may be regarded as masking any effects that the rTMS may have on the participant. The use of a comparison group i.e. participants on antidepressants who are not receiving rTMS, could help to resolve whether or not the interaction is a confounding variable.

Additionally, the positive results observed in the neuropsychological test scores may be a result of the improvement in mood over the duration of the study (this may be the case for RL). Therapeutic interventions often improve the state-dependent cognitive dysfunction in depressed individuals (Martis et al., 2003). In some studies, healthy control participants have shown improvements in cognitive performance after receiving active rTMS. However a study by Moser et al. (2002) found improvement in executive functioning scores for only the depressed participants receiving rTMS, and not for the sham condition participants. The statistically significant finding did not correlate with HDRS scores. It can therefore be deduced that in studies using depressed participants, improvements seen may be a result of the rTMS treatment independent of mood status (Martis et al., 2003).

Thus far, the conclusions that we can draw in this progress report is limited due to the lack of a control group. Information reported herein is only on the first wave of data collection. This will obviously be remedied by time as data collection will continue and participants will be randomly allocated into either active or shame rTMS treatment conditions.

Another confounding variable in these case studies which may hamper the interpretation of the observed results is the use of a heterogeneous antidepressant medication regime. The poor performance, albeit not significant, may be attributable to the participants' differing antidepressant medication regimes. Firstly, the differing dosages and types of antidepressants used by the participants make it difficult to draw conclusions about the absolute efficacy of rTMS. Also, the use of antidepressants may have interfered with the specificity of the brain

effects of stimulation and partial remission or delayed drug effect may be responsible for the observed changes in the neuropsychological tests (Fitzgerald et al., 2007; Höflich et al., 1993). Questions have been raised as to which antidepressant is the most efficacious in conjunction with rTMS treatment. In the present study, the use of rTMS as an adjunctive to antidepressants may be regarded as potentially useful in treating depressed people since no significant adverse side effects were found (Rumi et al., 2005).

Martin et al. (2003) has highlighted that the method utilized to target the stimulation site is itself unreliable. In some cases the positioning effects may adversely impact on the outcome of studies (Grunhaus et al., 2003). This might explain the results observed in the neuropsychological tests for MH and SC. The technique of coil positioning to identify the left DLPFC was based on a 'probabilistic surface anatomy approach' (p. 1215) targeting 5cm anterior to the motor threshold location. The use of a neuronavigational method such as magnetic resonance imaging for assistance in identifying the target area would have been a more precise method since it would account for individual differences in the brain anatomy of the participants (O'Reardon et al., 2007).

Furthermore, Martis et al. (2003) suggest that the observed improvements in the neuropsychological tests may be attributable to practice effects, and thus may have masked any adverse effects of rTMS. In future data collection, the use of alternative versions of the tests could be used to resolve this possibility.

Current Limitations of rTMS Studies in General

In a systematic review and meta-analysis of rTMS for the treatment of depression, Martin et al. (2003) concluded that overall results remain largely inconclusive. Not only is there is simply insufficient evidence that supports rTMS as an effective adjunct to antidepressants in the treatment of depression, but the quality of studies are poor. This may be for several reasons.

The exact mechanisms by which rTMS applied over the left dorsolateral prefrontal cortex might improve depression still remain unclear (George et al., 2000; Martin et al., 2003). Research remains indefinite as to whether the effects observed are a direct result of a treatment response to the rTMS, or if the effects are instead nonspecific changes in brain activation produced by rTMS and thus independent of the treatment response (Fitzgerald et al., 2007).

However, there is a lack of evidence which supports the notion that the left dorsolateral prefrontal cortex is the optimal point of stimulation. More studies need to investigate the localization, frequency and treatment duration of rTMS more thoroughly. Additionally the type of coil used and the number of trains per session administered need further investigation (George et al., 2000). Garcia-Toro et al. (2006) propose that the individualization of rTMS parameters may ameliorate the antidepressant effect of rTMS because the brain activity that underlies depression differs from one participant to another.

Evidence from blood flow and electrical activity in cortical areas suggest that the physiological effects following rTMS are not restricted to the target area; anatomically linked areas may also be affected. It has been recommended that in order to improve localization, stimulation sites should be found using magnetic resonance imaging (MRI's) of the participants' brain. It must also be noted that administration of rTMS results in a tapping sensation as well as stimulation of facial muscles. These effects are 'time-locked' with the magnetic pulse and this may result in sensory and cognitive performance being influenced (Walsh & Cowey, 1998, p. 107). To resolve this, it has been recommended that one stimulates a control site close to the target site as this reproduces the unwanted effects of rTMS, therefore acting as a control (Walsh & Cowey, 1998).

Conclusion

One of the main strengths of the current study is the use of rTMS treatment for a period of a month. Grunhaus et al. (2003) reported that the majority of extant studies use between only 1 and 2 weeks of treatment. It has been suggested that the shorter the period of stimulation, the weaker the antidepressant efficacy (Grunhaus et al., 2003). Likewise the use of a 120% motor threshold intensity in this study is one of the highest intensities used in existing rTMS studies. It appeared to be a relatively safe and well-tolerated treatment modality as evidenced by the lack of seizures (Rumi et al., 2005).

In summary, as a progress report, these multiple case studies contribute to the data pertaining to the clinical effectiveness of combining rTMS and antidepressants in the treatment of depression. It has successfully replicated previous literature by demonstrating that overall rTMS has no significant adverse effects on memory and emotional decision-making, and in some cases has shown that participants administered rTMS as an adjunctive treatment to

antidepressants show improved cognitive functioning over the course of the month-long treatment. Overall, the findings in these multiple case studies approach contribute to the information of rTMS as a treatment modality for depression and can help guide further investigations.

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APPENDIX A

Participant Consent Form

Does Repetitive Transcranial Magnetic Stimulation accelerate the effect of antidepressants and improve cognition in depression? A double blind placebo-controlled study.

University of Cape Town Human Ethics Committee Reference Number: 075/2007

1. I _____ agree to the recording of my mood, brain activity and my bodily responses to the computer tasks.

2. I understand that the results of the analysis carried out on the recorded material will not be made known to me, due to the fact that the analysis is for research purposes only. I understand therefore that I will gain no immediate benefit from the research in the event of any scientific breakthrough.

3. I understand that some people who have treatment with rTMS may experience headache as a side effect.

4. I understand that the recordings will only be utilised for research purposes, subject to approval of the University of Cape Town Research Ethics Committee, and that any information from such research will remain confidential.

5. I understand that I may withdraw my consent for any aspect of the above at any time.

6. All of the above has been explained to me in a language that I understand and my questions answered by:

Signature of researcher: _____ Date: _____

Signature of participant: _____ Date: _____

APPENDIX B

Participant Information Sheet

Does Repetitive Transcranial Magnetic Stimulation accelerate the effect of antidepressants and improve cognition in depression? A double blind placebo-controlled study.

University of Cape Town Human Ethics Committee Reference Number: 075/2007

You are being invited to take part in a research study that involves the use of transcranial magnetic stimulation (TMS). TMS is a promising therapeutic tool that has recently been investigated for use in conditions such as depression. We are carrying out this study because we are trying to learn more about the response of depressed people to TMS. In this study we aim to assess a total of 50 participants 50% of who will receive active TMS and 50% will receive "sham" TMS, in order to investigate the value of TMS in depression. After the 1st course of treatment you will be offered active TMS if your symptoms have not improved and you have received "sham" TMS.

TMS is much safer than other physical treatments for depression like ECT, and requires no anaesthetic. It works by placing a powerful magnet next to the brain which causes changes in electrical activity and most studies show that this helps with depression.

Participants will be excluded from the study if they have

- Severe uncontrolled organic disease excluded by history and physical examination
- Severe recurrent headache
- Current alcohol or drug abuse
- A pacemaker
- Previous Neurosurgery with implants of metal or clips
- Current psychotic symptoms

If you want to withdraw from this study you may do so at any time. This study is for research purposes only and is not funded by a pharmaceutical company.

The most common side effect of repetitive TMS applied to the non-motor cortex is head-ache and is higher in low frequency than high frequency repetitive TMS. This study will use high frequency TMS. If headaches occur it is usually relieved by simple analgesic medication such as Paracetamol. A very low rate of temporary mania has also been reported. Earplugs will be offered to you to reduce any discomfort from the noise the machine makes.

You will be expected to visit us four times during the study in addition to receiving the treatment. If you are willing to participate, this is what is expected of you at each visit:

Visit 1

You will be given a participant information sheet, which you should read and understand before signing the informed consent. You will be given a few self-report questionnaires to fill in and have a clinical interview with a research clinician. This visit should take no more than 2 hours.

After this, if you are accepted into the study, you will receive rTMS 3 times a week for 4 weeks.

Additional visits

You will be asked to participate in a number of computerised tasks and questionnaires (every 2 weeks). Each of these visits last about 2 hours.

If you have any questions, please feel free to speak to any one of the researchers or contact Dr Horn, the Principal Investigator at neil.horn@uct.ac.za or 021 4403176

APPENDIX C

Montgomery Asberg Depression Rating Scale

1) **Apparent Sadness**

Observed

Representing despondency and gloom and despair (more than just ordinary transient low spirits) reflected in speech, facial expression and posture. Rate by depth and inability to brighten up.

0) No sadness
1)
2) Looks dispirited but does brighten up without difficulty
3)
4) Appears sad and unhappy most of the time
5)
6) Looks miserable all the time. Extremely despondent

2) **Reported sadness**

Are you feeling sad or depressed or low today?
If yes – is it all the time, or do some things cheer you up?
More questions to clarify if necessary

Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity and duration and the extent to which the mood is reported to be influenced by events

0) Occasional sadness in keeping with circumstances
1)
2) Sad or low but brightens up with difficulty
3)

4) Pervasive feelings of sadness or gloominess. The mood is influenced by external circumstances

5)

6) Continuing unvarying sadness or despondency

3) **Inner Tension**

Do you feel anxious or panicky? More questions to clarify if necessary

Representing feelings of ill-defined discomfort edginess, inner turmoil, mental tension mounting to either panic dread or anguish. Rate according to intensity frequency duration and extent of reassurance called for.

0) Placid only fleeting inner tension

1)

2) Occasional feelings of edginess and ill defined discomfort

3)

4) Continuous feeling of inner tension or intermittent panic which patient can only master with some difficulty

5)

6) Unrelenting dread or anguish. Overwhelming panic

4) **Reduced sleep**

How are you sleeping in the last few days? More questions to clarify if necessary

Representing the experience of reduced duration or depth of sleep compared to subject's own pattern when well

0) Sleeps as usual

1)

2) Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep

3)

4) Sleep reduced or broken by at least 2 hours

5)

6) Less than 2-3 hours sleep

5) **Reduced Appetite**

How is your appetite? More questions to clarify if necessary

Representing feeling of loss of appetite compared when well. Rated by loss of desire for food or need to force oneself to eat

0) Normal or increased appetite

1)

2) Slightly reduced appetite

3)

4) No appetite food is tasteless

5)

6) Needs persuasion to eat at all

6) **Concentration difficulties**

Do you have any difficulties with concentrating? More questions to clarify if necessary

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration

0) No difficulties in concentration
1)
2) Occasional difficulties in collecting ones thoughts
3)
4) Difficulty in concentrating and sustaining thought which reduces ability to read or maintain a conversation
5)
6) Unable to read or converse without great difficulty

7) **Lassitude**

Do you have any difficulty getting started with things in the morning or during the day? More questions to clarify if necessary

Representing difficulty getting started or slowness initiating and performing everyday activities

0) Hardly any difficulty in getting started – no sluggishness
1)
2) Difficulties in starting activities
3)
4) Difficulties in starting simple routine activities which are carried out with effort
5)
6) Complete lassitude unable to do anything without help

8) **Inability to feel**

You have reduced interest in things that you usually like? Or are you not enjoying things as much as usual? More questions to clarify if necessary

Representing the subjective experience of reduced interest in surroundings or activities, which usually give pleasure. The ability to react with normal emotion to people or circumstances is reduced

0) Normal interest in surroundings or people
1)
2) Reduced ability to enjoy usual interests
3)
4) Loss of interest in surroundings Loss of feelings for friends and acquaintances
5)
6) The experience of being emotionally paralysed

9) **Pessimistic thoughts**

Do you have any bad thoughts about the future or yourself? Or Guilty thoughts? More questions to clarify if necessary

Representing thoughts of guilt, inferiority, self reproach sinfulness remorse and ruin

0) No pessimistic thoughts
1)
2) Fluctuating ideas of failure self reproach or self depreciation
3)
4) Persistent self accusation or definite but still rational ideas of guilt sin Increasingly pessimistic about the future
5)
6) Delusions of ruin remorse or unredeemable sin. Self accusations are absurd and unshakeable

10) **Suicidal thoughts**

Do you have any suicidal thoughts? Do you feel tired of living? More questions to clarify if necessary

Representing the feeling that like is not worth living that a natural death would be welcome suicidal thoughts and preparation for suicide. Suicidal attempts should not in themselves influence the rating

0) Enjoys life or takes it as it comes
1)
2) Weary of life. 0nly fleeting suicidal thought
3)
4) Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution but without specific plans or intention
5)
6) Explicit plans for suicide when there is an opportunity. Active preparations for suicide