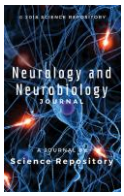

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Research Article

Anhedonia in Major Depressive Disorder (MDD) is Reduced by Transcranial Magnetic Stimulation (TMS)

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ABSTRACT

Background: TMS is effective in the treatment of MDD. It is time and resource intensive and there is not means of predicting the eventual outcome of a course.

Objective: To determine whether the change in subjective anhedonia from pre- to mid-treatment is an indicator of the eventual outcome.

Methods: Naturalistic study – before and on completion of the course, the six-item Hamilton Depression Rating Scale (HAMD6) and a complementary six-item visual analogue scale (VAS6), with a further VAS6 administered after 10 treatments. Change in subjective anhedonia (pre- minus mid-treatment VAS6 Item 2 scores) assessed as predictor of outcome.

Results: Change in subjective anhedonia predicted the ultimate outcome (post-treatment HAMD6 total score).

Conclusions: A replication study is justified. Change in subjective outcome may predict the outcome of treatment – potentially alerting to the need to modify the treatment strategy for optimal effect.

Introduction

Anhedonia (inability to experience pleasure) is a feature of many brain conditions including depression, schizophrenia, substance use disorder, post-traumatic stress disorder, anxiety and obsessive-compulsive disorder. It has no established therapy and is a central feature of major depressive disorder (MDD) [1]. According to the DSM-5, for this diagnosis to be supported, either depressed mood or anhedonia must be present. Recent work confirms that in MDD anhedonia and sadness are highly correlated [2]. Early work suggested that selective serotonin reuptake inhibitors could worsen the anhedonia of MDD, but a more recent opinion is that most antidepressants provide some reduction [3, 4]. A study of MDD patients treated with agomelatine found a reduction in anhedonia was a strong predictor of improved social functioning [5].

Spano et al. suggested anhedonia as a "transdiagnostic psychopathological dimension", which may respond to non-invasive brain stimulation (NIBS) [6]. They also suggested that when anhedonia is a core feature of a mental disorder, this may indicate the parent disorder will respond to NIBS. Their review of the literature located insufficient reports for conclusions, and further exploration of the topic is indicated. Downar et al. treated MDD patients with TMS using a non-standard coil placement (dorsomedial prefrontal cortex) [7]. Two groups emerged: responders and non-responders – the non-responders demonstrated markedly higher baseline anhedonia. Our group has shown that in MDD, stimulation of the standard left dorsolateral prefrontal cortex (DLPFC) using a routine protocol, reduces objective anhedonia scores [8]. Acute courses of TMS are a minimum of 20 daily treatments, which may take up to 26 days, if treatment is unavailable at weekends. There is no established means of predicting the response of MDD to any form of treatment. Some evidence suggests that $\geq$ 20% symptom reduction after 2 weeks of medication and other somatic treatments is an indicator of a better prognosis [9, 10]. A valid method of prediction at the mid-point of TMS treatment might signal when an adjustment of the treatment strategy is needed to prevent the waste of patient and clinician time and resources.

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We have studied the response of private patients with MDD treated with TMS since 2004. In a naturalistic setting, using standardized instruments, we have gathered objective and subjective anhedonia data. Our objective was to determine: 1) any effect on anhedonia when acute MDD is treated with TMS, and 2) when acute MDD is treated with TMS, whether change in anhedonia scores from pre- to mid-course predicts the eventual outcome.

Methods

Selection criteria include a diagnosis of MDD using DSM-5 criteria, with exclusion criteria including the routine contraindications of metal in the head, a history or epilepsy or neurological disease and current drug withdrawal.

TMS treatment is applied to the left DLPFC, stimulation is at 120% of motor threshold, 10 Hz, in 4 second trains, 75 trains separated by 15 second rest periods, providing 3000 pulses per daily treatment. Before and on completion of the course of treatment, the six-item Hamilton Depression Rating Scale (HAMD6) and a six-item visual analogue scale (VAS6) are completed (see below) [11, 12]. Also, after 10 treatments, a mid-course VAS6 is administered.

Using the HAMD6 total score, relapse is operationalized as $\geq$7 and remission as $\leq$4 [13, 14]. The HAMD6 items are, 1) depressed mood, 2) work and activities, 3) somatic symptoms, 4) feelings of guilt, 5) anxiety (psychic), and 6) retardation. Item 2, 'work and activities', accesses anhedonia – the scripted version of the HAMD6 asks, "How would you describe your level of interest and motivation to complete daily activities" and "How many hours a day do you spend doing things that interest you?" [15]. The subjective VAS6 was designed to complement the objective HAMD6 [16]. To complement the 'work and activities' Item 2, subjective experience is assessed using a 10 cm line with the anchor points of "Activities give normal pleasure" and "Activities give no pleasure" at either end.

To determine the effect of TMS on the anhedonia, the difference between the pre- and post-treatment HAMD6 Item 2 and VAS6 Item 2 scores were calculated. To determine whether change in anhedonia scores from pre- to mid-treatment, predict the eventual outcome, we subtracted the mid-treatment VAS6 Item 2 scores from the pre-treatment VAS6 Item 2 scores and examined whether these answers predicted the post-treatment HAMD6 total score. For comparison, we examined whether the pre-treatment HAMD6 total score predicted the post-treatment HAMD6 total score.

Results

There were 208 courses of treatment delivered to 160 participants, mean age 43.5 years (SD=15.0 years), 124 (78%) female. There was no association between age or sex and the outcome variables of interest. There was a significant reduction (p=.001) in the objective depression scores, moving the group HAMD6 total from the relapse range in the pre-treatment period, into the remission range, post-treatment (Table 1). Over the full course of treatment there was a significant reduction in anhedonia scores based on self (VAS6 Item 2) and clinician (HAMD6 Item 2) ratings (Table 1). Subjective anhedonia (VAS6 Item 2) reduced by 35% from pre-treatment to mid-treatment, and a further 33% from mid-treatment to post-treatment. Both the change in subjective anhedonia (pre- minus mid-treatment VAS6 Item 2 scores) and the pre-treatment HAMD6 total score predicted the final outcome (post-treatment HAMD6 total score) (Table 2).

Table 1: Pre- and post-treatment HAMD6 Total and Item 2 scores, and pre-, mid- and post-treatment VAS6 Item 2 (anhedonia) scores.

N=208	Pre	Mid	Post	Difference
HAMD6 Total	10.8 (2.2)	NA	3.9 (2.8)	p=.001
HAMD6 Item 2 – Work and activities	2.6 (0.8)	NA	0.7 (0.8)	p=.017
VAS6 Item 2 – Work and activities	7.1 (2.2)	4.6 (2.2)	3.1 (2.2)	p=.030

Table 2: Regression table for post treatment Total depression score on the HAMD6.

	B	SE B	β
Total HAMD6 score pre-treatment	.30	.09	.23
Change in Anhedonia pre to mid treatment (VAS6)	-.26	.07	-.23
Constant	1.36	.94	

Notes. R^2=0.10, p<.001.

Discussion

It may be considered a limitation of this study that anhedonia was measured using only two items/questions. Larger batteries exist, but none of these have achieved wide acceptance. The items we have used have face validity and a long history of usage. The HAMD was first described in 1960 and remains the most widely used clinician rated depression instrument in existence. Its 'work and activities' item expressly address 'loss of interest', 'feelings of incapacity' and 'fatigue', which are central to anhedonia. The VAS has been used for almost a century and the anchor points we employed are appropriate. The VAS has the advantage of assessing the immediate emotions of the individual, which is important when examining change over a brief period. One item/question plumbs the subjective experience and the other is an objective tool, together they provide a two-perspective assessment. Another limitation may be that this material is not derived from blind placebo-controlled trials. On the other hand, these results carry the advantages of having been drawn from real-life clinical settings.

Spano et al. suggest that anhedonia may be a "transdiagnostic psychological dimension" and speculates that the presence of anhedonia may indicate a predisposition to respond to TMS treatment [6]. We cannot comment on these broader points but provide important information on anhedonia in MDD. In this naturalistic study we have shown that for acute MDD, a course of TMS may induce remission and significantly reduce both subjective and objective anhedonia. We have also shown that for TMS treatment, both the pre-treatment HAMD6 total score, and the change in subjective anhedonia from pre- to mid-treatment, are indicators of the eventual outcome.

We have previously shown that in acute MDD, treatment with TMS significantly reduces the objective anhedonia [8]. We have now shown a similar impact on subjective anhedonia. That the pre-treatment HAMD6 total score is predictive of response to TMS is not surprising – more severe depressive illness at outset is associated with a less favorable outcome for all forms of MDD treatment. A potentially important finding of this study is that the change in subjective anhedonia – from pre-treatment to mid-treatment – may predict the eventual outcome. A course of TMS takes four weeks and is resource and labor intensive – the ability to predict the probable outcome at the mid-point of treatment might allow the modification of the management of those with an unfavorable predictions, thereby maximizing their prospects and minimizing wastage of time and resources. We examined change in subjective anhedonia during the pre- to mid-treatment period. However, the HAMD6 offers six items which may (perhaps should) be examined from both the objective and subjective perspectives. A replication of this study, preferably expanded to examine other items, may provide a means of improving the management of MDD patients.

Ethics Committee Approval

The collection and use of this data were approved by the institution ethics committee.

Consent

Before treatment, patients were informed that their data may be collected and used in anonymous research, and all signed agreement.

Conflicts of Interest

None.

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