**A Systematic Review and Meta-analysis of Randomized Controlled Trials on the Effect of Transcranial Magnetic Stimulation on Tinnitus Management**

**Abstract**

**Introduction:** Tinnitus occurs in 10-15% of the world’s population. It may lead to hearing loss, depression, and suicidal tendencies, as well as reduces quality of life. The aim of this study was to assess whether Transcranial Magnetic Stimulation (TMS) effectively reduces tinnitus handicapping after six months or more follow-up

**Methods**: A systematic review of randomized controlled trials with follow-up of 6 months was undertaken. The review took place through searching Medline, Science Direct, and the Google scholar databases using the keywords:” tinnitus” and “Transcranial Magnetic Stimulation”, and limiting the search results to randomized controlled trials (RCTs) conducted on adults (19 years and older), published between 2005-2015. Meta-analysis was performed on the three similarly designed studies. Different tools were used in studies to measure severity of tinnitus; the tinnitus handicapped inventory (THI) is the most common.

 **Results:** Five RCT's with six-month follow-up were found conforming to the inclusion criteria. In total, there were 119 patients in the trial arm and 115 in the placebo arm. However, the design was different between the studies and was not comparable. Different parameters were used to measure the outcome. Tinnitus handicapped inventory (THI) was the common measured outcome parameter used in all studies. THI score decreased after the TMS in four studies. Meta-analysis was performed on three similarly designed RCTs with the overall effect being insignificant.

**Conclusion:**  In conclusion, rTMS reduces the THI score and decreases the severity of tinnitus in 45% of patients and leads to a complete recovery in some cases. However, the meta-analysis demonstrated lack of significant effect of TMS on tinnitus management.

Keywords: tinnitus; TMS; Transcranial Magnetic Stimulation; Magnetic Field Therapy;

**Introduction**

 Tinnitus is the perception of sound in the ear or in the head without any external acoustic stimulation. Numerous hypotheses have been developed for the pathophysiology of tinnitus. It was suggested, that tinnitus may arise from any abnormality of the neural pathway from the cochlear neural axis to the auditory cortex.1 Thepathophysiological theory implies that the central nervous system is the source or “generator” of tinnitus.2 Tinnitus is often a feature of ear disease and is usually associated with hearing loss, but it may also occur in patients with normal hearing.3

Many cases of tinnitus have no identifiable cause. Environmental exposure to recreational, urban, and occupational noise or ototoxic drugs can develop tinnitus.4 Explosion or firing can cause damage to the peripheral auditory organs which in turn causes the activation of neural plasticity and leads to tinnitus.5 In 39 studies done in European countries, USA, Japan, China, Korea, Australia, Egypt, Nigeria, and Brazil the prevalence of tinnitus ranged from 5.1% to 42.7%. Tinnitus percentage is higher in males than in females.6 The National Health Interview Survey found that 11.2% of the adult US population and 7.5% of adolescents suffer from tinnitus. Tinnitus prevalence increases with age.7, 8 In 1–2% of the population, tinnitus symptoms seriously reduce the quality of life resulting in social isolation, depression, and even suicidal tendencies. 5

 In chronic cases, a variety of treatment approaches are available, including pharmacological treatment, complementary and alternative medicine therapies, sound treatment/associated technologies, psychological/behavioral treatment, and cochlear implants. There is no pharmacological treatment for tinnitus with long-term effect.9 Talk therapy and sound therapy with little support of medication are the primary treatment in developed countries.10, 11 There is little evidence on all tinnitus management forms including Chinese, alternative and complementary medicine therapy such as Ginko Biloba, melatonin, zinc, diet modification, hyperbaric oxygen, temporo-mandibular joint therapy, and acupuncture among others.12 Tinnitus treatment can be reached by interrupting the abnormal activity and neuro-modulation.13 Repetitive magnetic fields generated by repetitive Trans-cranial Magnetic Stimulation (rTMS) can reduce neural over activity in cortical areas and can potentially alleviate tinnitus. 14 It is a non-invasive procedure. 15 Meng et al. review on tinnitus management with TMS suggests addressing its long-term effectiveness.9 Recent and ongoing research studies attempted to assess whether rTMS could be an effective tinnitus treatment for a longer duration. Therefore, the aim of this study was the review of randomized control trials (RCTs) studies addressing the effect of TMS on tinnitus after six months and more.

**Methods**

*Search strategy*

 Electronic searches on the Medline (PubMed), Scholar Google, and Science Direct data bases were carried out in February 2016. English language articles published between 2005 and 2015 were selected. Cochrane Library was searched for systematic review on the topic. The search keywords used were unilateral or bilateral "tinnitus” and "Trans-cranial Magnetic Stimulation", “TMS”,"TMS treatment", “repetitive TMS” and “rTMS” of randomized controlled clinical trials (RCT) on adults 19 years and above with six months follow-up or more. The authors independently searched the sites, reviewed the titles, abstracts and keywords and agreed on the studies included in the review. The decision for a final inclusion of the studies was done after reviewing the full articles. The authors resolved differences by discussing them together. The libraries of the Faculties of Medicine in some Egyptian Universities were searched on the same topic by another author. No thesis was found on the systematic review of rTMS for tinnitus treatment.

*Study inclusion and exclusion criteria*

Any RCT using rTMS treatment (low/high frequency) with six months of follow-up and more was considered eligible. Excluded were studies withchildren under the age of 19 or adults with total hearing loss.Studies with combined therapy, people suffering from tinnitus treated with pharmacological therapy, diet, psychotherapy, hearing aids, and any metal appliances were also excluded. RCTs with a follow-up period of less than 6 months were excluded.

Different tools are used in RCT studies to measure the severity of tinnitus. The authors tried to find out one common primary or secondary tool for measuring severity (tinnitus handicapped inventory (THI)).

*Data extraction*

General information on publication, authors, article title, journal title, and publication year was extracted. The design of the trial was assessed in regard to trial arms, sample size, randomization process, allocation method, blinding of information, and statistical methods. The total number of intervention and comparison groups of participants was registered with baseline characteristics, age, gender, inclusion and exclusion criteria. The intervention with trans-cranial magnetic stimulus (TMS) pulse, stimulus frequency, and drop-outs were reviewed. Primary and secondary outcomes and other outcomes at baseline and at the end of the treatment and at follow-up were assessed. The number and type of adverse events were also extracted. The conclusion was considered. The review authors assessed the risk of bias in the included studies. The authors collected and extracted data from each RCT study included and authors of the primary studies were contacted to clarify any questions about the data.

*Data synthesis*

A descriptive data synthesis was done according to the reporting of the studies. In addition, meta-analysis of three studies with similar design was carried out in Review Manager 5.

Results of the search

 The electronic search identified 362 articles – 240 from Google scholar, 46 from Medline, 76 from Science Direct from 2005-2015. The authors found 324 studies not related to the criteria of the search, 292 were excluded by reading title and abstract, 24 studies did not mention the follow-up, 7 studies had follow-ups less than 6 months. Only five studies were eligible for inclusion: Andres et al., Hoekstra et al., Khedr et al., Kim et al., and Marcondes et al.16-20 Landgrebe et al. was excluded as the corresponding author did not respond to the authors’ questions regarding his trial results. 21

 [Figure 1]

 Five included studies

 All five studies included in this review were randomized control double blind trials (RCT) from different countries investigating the efficacy of rTMS for at least six months post treatment. Khedr et al.followed up for 10 months.18 Studies were published in 2010 -2014. All studies used low-frequency 1-Hz rTMS in 2-trial arms except Khedr et al. who had 4-trial arms assessing 1-Hz rTMS versus 25-Hz rTMS and ipsilateral rTMS against contralateral.18 Three studies compared rTMS with sham, while Kim et al. and ~~Khedr et al. weighed ipsilateral TMS against contralateral.~~ 19, 18All studies enrolled 42 to 62 chronic tinnitus patients – except Hoekstra et al. with 19 patients – with different conditions. 17 They assigned them randomly to the trial arms. Diverse primary and secondary tools were used to measure the outcomes.The tinnitus handicapped inventory (THI) and the visual analogue rating scores (VAS) were used to measure outcomes in all studies beside diverse other tools at baseline, during follow-up and after six months.

 [Table 1]

 Analysis of studies

Random allocation was described in all studies except for Marcondes et al. study. 20 The blinding process was explained in all trials except for in Kim et al.19 All studies had 3.8% (low risk) to 19.6% (high risk) drop outs except for Khedr et al.18 Reasons given by Kim et al. were 4 patients received additional treatment during follow up and one patient had severe headaches.19 During the rTMS treatment no serious side-effects were reported. Nine patients from all studies experienced headache as adverse effects and only sporadic dizziness, pain at the site of stimulation, and sleep pattern changes.

Diverse scales were applied to measure the primary and secondary outcomes, however, tinnitus handicapped inventory (THI) was used in all studies. Only two studies had scales for secondary outcome.18, 17 The measurements were taken at baseline, after rTMS treatment or placebo, 2-10 times during follow-up and 6 months after the intervention. Only one study measured them after 10 months. Andres et al.found significant reduction of the total score of basic scales that measure tinnitus severity. 16 Hoekstra et al.pointed out that tinnitus was unchanged. 17 Khedr et al. revealed that 32.25% of all patients recovered completely from tinnitus, 27.4% improved in having tinnitus only at night before sleeping.18 Kim et al reported improvement in 46.7% of the ipsilateral group and 51.6% of the contralateral group. 19 For Marcondes et al., 40% had a significant reduction of tinnitus severity after 5 days and for 1 to 6 months after treatment of active rTMS. 20 Overall, more than 45% of patients experienced improvement. Three of the studies assessing depression and anxiety with different scales did not find any differences between the groups during follow-up.16, 17, 18  Khedr et al.used VAS for loudness, awareness, and annoyance level of symptoms. After 10 months follow-up, the contralateral group showed more improvement regarding the annoyance level than the ipsilateral group. 18 In the study of Kim et al., the annoyance level did not show a significant difference. 19

Although the comparison between high and low rTMS and ipsilateral and contralateral is of importance, the aim of our study implies the comparison of rTMS versus ‘sham’ which was applied in three studies. 16, 17, 20 THI was the common scale used for the comparison of outcomes at baseline, during follow-up, and 6 months after the intervention. There is improvement in the THI scores in the rTMS group in the RCTs of Andres et al. and Marcondes et al., but not in Hoesksta et al. 16, 17, 20 No significant differences were found between rTMS and the sham group in all three studies at baseline, during follow-up or 6 months after the intervention except in the study of Marcondes et al. directly after rTMS.20

Meta-analysis of the three studies with similar design was performed. Two separate comparisons between the outcomes of the tinnitus handicapped inventory (THI) scores in rTMS and sham group were set using data derived from the three studies. The first comparison at the 1-4 weeks post-intervention, favored the rTMS intervention over the sham, but not to a statistically significant level (Test of overall effect: Z = 0.29, P = 0.77; Fig. 2). The second comparison at the 6-months post-intervention, favored also the rTMS intervention over the sham, but not to a statistically significant level (Test of overall effect: Z = 0.93, P = 0.35; Fig. 3).

 [Table 2]

[Figure 2, 3]

 **Discussion**

 There is little evidence on the effectiveness of different treatments on chronic tinnitus~~,~~ ~~including rTMS~~. According to this systematic review, rTMS reduced the severity of tinnitus in four RCTs in over 45% of the patients for duration of six months following the intervention. Around one third of patients in one study were completely recovered from tinnitus.18 Only one study did not find any changes.17 The outcome differences of the THI scores of the trials is due to diverse inclusion criteria of patients or technical application of rTMS. Two studies measuring depression and anxiety ~~didn’t~~ did not find any changes after rTMS application despite reduction of tinnitus. It is likely that depression and anxiety take longer to improve, which explains the accompanying use of talk therapy in some regimens.10,11

As the primary aim of our review was to compare rTMS with ‘sham’, only three studies matched.16, 17, 20 Andres et al. reported significant reduction of the total score of basic scales that measure tinnitus severity even for patients with a mean duration of nine years not responding to pharmacological treatment.16 For 40% of patients exposed to rTMS in the Marcondes et al. trial the tinnitus severity decreased as measured with the tinnitus handicapped inventory (THI).20 In contrast, the study of Hoekstra et al. indicated no changes,17 probably as the latter included non-fluctuating tinnitus patients while the other two trials mentioned just unilateral and bilateral tinnitus patients.

Some other inclusion criteria such as hearing loss or tinnitus duration can have an effect on the outcome. Marcondes et al.20 reported a positive effect of rTMS on subjects with normal hearing*.* Hearing loss might influence the effect of rTMS.The trial of Khedret al.18 reported that hearing impairment might exacerbate the plastic changes in neural function causing tinnitus and that decreases the effect of rTMS. This is in agreement with the study of Kleinjung et al. and Smith et al. reporting on the negative influence of hearing loss on the efficacy of rTMS. 13, 22 In contrast, Lehner et al. did not find a relationship between hearing loss and rTMS efficacy.23 Andres et al. included only normal hearing patients.16 The studies of Hoekstra et al and Kim et al. did not report on this issue in their results although they both included patients with impaired hearing.17, 19 In addition, all studies included chronic tinnitus patients. Tinnitus duration should be considered when explaining the different outcomes between the five included studies. Khedr et al.’s 18 trial showed that there was a significant correlation between the duration of symptoms and change in THI (at baseline and 10 months after). This is substantiated through other studies that found patients who had the shortest history of tinnitus tended to respond the best to rTMS therapy; 13, 24-26 although yet other studies did not find this effect.22, 23 Andres et al. stated that their trial lowered the severity of tinnitus even in chronic patients who had it for 9 years.16 The other three studies did not mention the effect of tinnitus duration on the outcome. 20, 17, 19

 Another clinical implication of our review suggests that low-frequency rTMS, ipsi- or contralateral positioning of the coil on the temporo-parital cortex or auditory cortex reduces the severity of tinnitus. The auditory cortex is thought to play an important role in tinnitus, but there is strong evidence that the auditory cortex with the limbic system, prefrontal and parietal cortex determines tinnitus distress.27- 30 The parietal cortex and its connections to the auditory-cortex could be involved in tinnitus through the mediating effect that the parietal cortex has on auditory attention.31, 32  Repetitive TMS of these areas could therefore decrease a patient’s reaction to tinnitus, leading to a reduction in the perception of tinnitus. Another study reported that a combination of temporal and prefrontal stimulation showed a significant effect on tinnitus.13 Repetitive TMS works by interfering with baseline activity in the cortex and decreases tinnitus. This opinion is confirmed by Smith et al.who found greater response of the contralateral stimulation using low-frequency rTMS.22 In contrast Kim et al.’s trial found no significant difference between ipsilateral and contralateral stimulation, and tinnitus was reduced in half of the patients regardless of the side of stimulation**.** 19 Hoekstra et al. found no effect of bilateral stimulation of the auditory cortex*.* 17 Marcondes et al. did not mention this point.20 The use of low-frequency rTMS was applied by the five trials, which is contrary to Meng et al.who found “very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus” after four months of follow-up. 9

The duration of rTMS is another factor that might influence its effect. In Andres et al.trial and Khedr et al. the patients were treated for 2 weeks.16, 18In Marcondes et al., Hoekstra et al., and Kim et al.the patients were treated for one week.20, 17, 19 It is reported that results may be better after a longer duration of treatment over 2 weeks. 33

 Meta-analysis was not applied to all the RCT studies as they differed in their design (Table 1). Kim et al. used ipsilateral versus contralateral.19 Khedr et al had four trial arms comparing between high- and low-frequency and ipsilateral versus contralateral.18 Three RCTs abided to the primary aim of our study – Andres et al., Hoekstra et al., and Marcondes et al.- using rTMS versus sham in their trial arms.16, 17, 20 The tinnitus handicapped inventory (THI) was used as measurement for tinnitus severity by all studies. The meta-analysis was performed on those RCTs with comparable design16, 17, 20, favoring the rTMS intervention however without significant effect. More than three identified RCTs for the meta- analysis would have given stronger evidence. ~~One of~~ The limitations of this review was lack of funding, its performance on limited database and only on those articles published in English language.

Tinnitus handicapped inventory (THI) scores indicate that rTMS has a role in decreasing the severity of tinnitus. It sustains the improvement and reduces handicapping for the duration of six months in three RCTs or, as the case in one trial, even 10 months. Four studies reported reduction in tinnitus severity after rTMS in over 45% of patients even after six months’ follow-up.16, 18, 20, 19 One of the four studies had one third of patients completely recovered from tinnitus. 18 Only one study found rTMS not effective on any outcome parameter. 17

 Although the meta-analysis of the three studies with similar design of rTMS and sham favored rTMS intervention, however, the overall statistical effect showed no significant difference between both groups as regards the tinnitus handicapped inventory (THI) scores. Given the scarce number of RCTs (2005-2015) more studies in multi-centers with the same protocol: design, inclusion / exclusion criteria, technological procedure and outcome measurements will provide stronger evidence. Follow-up in future studies should preferably be longer than 6 months to accrue stronger evidence.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

**Acknowledgement**

The authors would like to thank Prof. Aly MN Makhzangy – Dept. Department of Otorhinolaryngology, Faculty of Medicine - Ain Shams University, Cairo - Egypt for this Meta-analysis contribution and Sarah Keller for editing the English of this article.

**References**

1. Crummer R, Hassan G. Diagnostic approach to tinnitus. American Family Physician. 2004; 69(1),120-6.

2. Atik A, Pathophysiology and Treatment of Tinnitus: An Elusive Disease.[Indian J Otolaryngol Head Neck Surg](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3918281/). 2014 Jan; 66(Suppl 1): 1–5.

3. Kehrle H, Granjeiro R, Sampaio A, Bezerra R, Almeida V, Oliveira C. Comparison of auditory brainstem response results in normal-hearing patients with and without tinnitus. Arch Otolaryngol Head Neck Surg, 2008;134 (6), 647–651.

4. Mazurek B, Stöver T, Haupt H, Gross J, Szczepek A. The role of cochlear neurotransmitters in tinnitus. *HNO* 2007; **55**(12):964–71.

5. Moller A. Pathophysiology of tinnitus. Otolaryngol Clin North Am. 2003; 36, 249–266, v–vi.

6. McCormack A, Edmondson-Jones M , Somerset S , Hall D. A systematic review of the reporting of tinnitus prevalence and Severity. Hearing Research 337 (2016) 70e79

7. Zelaya CE, Lucas JW, Hoffman HJ, MMWR QuickStats: Percentage of adults with selected hearing problems, by type of problem and age group—National Health Interview Survey, United States, 2014. MMWR. 2015;64(37):1058. Available from  <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6437a8.htm>.

8. Mahboubi H, Oliaei S, Kiumehr S, Dwabe S, Djalilian HR. The prevalence and characteristics of tinnitus in the youth population of the United States. Laryngoscope. 2013;123(8):2001–8.

9. Meng Z, Liu S, Zheng Y, Phillips JS.Repetitive transcranial magnetic stimulation for tinnitus (Review). The Cochrane Collaboration. 2011. JohnWiley & Sons, Ltd.

10.Langguth B, Kreuzer PM, Kleinjung T, De Ridder D.Tinnitus: causes and clinical management.Lancet Neurol. 2013 Sep;12(9):920-930. doi: 10.1016/S1474-4422(13)70160-1

11. Baguley D, McFerran D, Hall D. Tinnitus. The Lancet. 2013; 382, (9904),1600–1607.

12. Li Y, Zeng RF, Zheng D. Acupuncture for tinnitus.Cochrane Database of Systematic Reviews2009, Issue 4. Art. No.:CD008149. DOI: 10.1002/14651858.CD008149

13. Kleinjung T, Eichhammer P, Landgrebe M, Sand P, Hajak G, Steffens T. Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study. Otolaryngology - Head and Neck Surgery. 2008; 138(4), 497–501.

14. Eichhammer P, Hajak G, Kleinjung T, Landgrebe M, Langguth B. Functional imaging of chronic tinnitus: the use of positron emission tomography. Prog Brain Res. 2007; 166, 83–88.

15. Miller, M. [Magnetic stimulation: a new approach to treating depression?](http://www.health.harvard.edu/blog/magnetic-stimulation-a-new-approach-to-treating-depression-201207265064) Harvard Health Publications. 2012.

16. Andres M, Dvorakova J, Rathova L, Havrankova P, Pelcova P, Vaneckova M. Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: a randomized, placebo controlled study. Neuro Endocrinol Lett. 2010; 31,238–249.

17. Hoekstra C, Versnel H, Neggers S, Niesten M, Van Zanten G. Bilateral Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Auditory Cortex in Tinnitus Patients Is Not Effective: A Randomised Controlled Trial. Audiol Neurotol. 2013; 18,362–373.

18. Khedr E, AboElfetoh N, Rothwell J, El-Atar A, Sayed E, Khalifa H. Contralateral versus ipsilateral TMS of temporoparietal cortex for the treatment of chronic unilateral tinnitus: a comparative study. European Journal of Neurology. 2010; 17, 976–983.

19. Kim HJ, Kim DY, Kim HI, Hee S, Sim NS, Moon IS. Long-Term Effects of Repetitive Transcranial Magnetic Stimulation in Unilateral Tinnitus. The Laryngoscope. 2014; 124, 2155-2160.

20. Marcondes R, Sanchez T, Ono C, Buchpiguel C, Langguth B. (). Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study. European Journal of Neurology. 2010; 17, 38–44.

21. Landgrebe M, Binder H, Koller M, Eberl Y, Kleinjung T, Eichhammer P. Design of a placebo-controlled, randomized study of the efficacy of repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus. BMC Psychiatry. 2008; 8, 23–31.

22. Smith J, Mennemeier M, Bartel T, Chelette K, Kimbrell T, Triggs W, et al.Repetitive transcranial magnetic stimulation for tinnitus: a pilot study. Laryngoscope. 2007; 117(3), 529– 534.

23. Lehner A, Schecklmann M, Landgrebe M, Kreuzer P, Poeppl T, Frank E, et al. Predictors for rTMS response in chronic tinnitus. Front Syst Neurosci. 2012; 6, 11.

24. De Ridder D, Vertraeten E, Der Kelen V. Transcranial magnetic stimulation for tinnitus: influences of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol Neurol, 2005; (26), 616–619.

25. Plewnia C, Reimold M, Najib A, Reischl G, Plontke S, Gerloff C. Moderate therapeutic efficacy of positron emission tomographynavigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. J NeurolNeurosurg Psychiatry. 2007; 78, 152–156.

26. Khedr E, Rothwell J, Ahmed M, El-Atar A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. J Neurol Neurosurg Psychiatry. 2008; 79, 212–215.

27. Schlee W, Hartmann T, Langguth B, Weisz N. Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neurosci. 2009; Feb 19,10,11. doi: 10.1186/1471-2202-10-11.

28. Roberts L, Eggermont J, Caspary D, Shore S, Melcher J, Kaltenbach J. Ringing ears: the neuroscience of tinnitus. J Neurosci. 2010; 30, 14972–14979.

29. De Ridder D, Elgoyhen A, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci USA. 2011; 108, 8075–8080.

30. Leaver A, Renier L, Chevillet M, Morgan S, Kim H, Rauschecker J. Dysregulation of limbic and auditory networks in tinnitus. Neuron. 2011; 69, 33–43.

31. Cuny C, Norena A, El Massioui F, Chéry-Croze S. Reduced attention shift in response to auditory changes in subjects with tinnitus. Audiol Neurotol. 2004; 9, 294–302.

32. Searchfield G, Morrison-Low J, Wise K. Object identification and attention training for treating tinnitus. Prog Brain Res. 2007; 166, 441–460.

33. Loo C, Mitchell P. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. J Affect Disord, 2005; 88, 255–267.