

Internal Memory Rehabilitation Strategies in the Context of Post-acute Brain Injury: A Pilot Study

Robert Perna^{1*} and Hana Perkey²

¹The Institute of Rehabilitation Research, Houston, TX, USA

²Families Forward, Augusta, GA, USA

*Corresponding author: Robert Perna, RN, 5930 Kuldell Drive, Houston, Texas, United States, Tel: 706-750-2572; E-mail: dr.perna@juno.com

Rec date: Jan 31, 2016; Acc date: Feb 23, 2016; Pub date: Feb 29, 2016

Copyright: © 2016 Perna R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Memory impairments are one of the most common consequences of acquired brain injury. Poor memory can have a severe impact on a person's daily functioning and his/her quality of life. While research provides some support for using external, compensatory strategies (e.g. diaries, lists, visual or electronic reminders), empirical evidence in favor of internal, restorative strategies (i.e. learning and training strategies that utilize less impaired or healthy cognitive resources to restore function) is much sparser. This study investigates the effects of a rehabilitation treatment comprised of internal strategies on the memory functioning of 11 participants with acquired brain injury associated memory impairments. The interventions utilized in this study included practicing visualization, first letter mnemonics, semantic clustering, elaborative encoding, and completing worksheets from Workbook of Activities for Language and Cognition (WALC 10 Memory). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used for the pre- and post- treatment assessment of memory functioning. Treatment gains as measured by pre-post therapy RBANS differences suggested large memory improvements of a magnitude to suggest clinically meaningful gains. This study was limited by its sample size, absence of a control group, and use of only one outcome measure.

Keywords: Rehabilitation; Brain injury; Memory

Internal Memory Rehabilitation Strategies in the Context of Post-Acute Brain Injury

Memory impairment is a common consequence of acquired brain injury that often causes functional and long-term disability [1]. Memory impairment can be caused by many types of brain injury. By some estimates, in individuals with severe traumatic brain injury (TBI) the prevalence of memory impairment ranges between 40% and 84% [2]. Within the overall TBI population, the percentage of people suffering from some form of memory impairment ranges from 20% to 79%, depending on the severity of the closed-head trauma, the timing of assessment, and the instruments used. Even after one year, 4% to 25% of TBI patients show some form of memory impairment [3]. The prevalence of memory dysfunction post-stroke varies from 23% to 55% in the first 3 months and at one year post-stroke, declines to between 11% and 31% percent [4,5].

Memory impairment can be an obstacle to successful return to work and may even interfere with successful rehabilitation [6]. Individuals with TBI and their family members report post-injury memory deficits as one of the most persistent problems following a TBI [7]. Memory impairments can interfere with independence in activities of daily living, as well as return to work, social participation and the overall quality of life [8]. The long-term persistence of memory impairments and the risk that these impairments will affect functional activities often cause clinicians to target the memory issues as a therapy goal. Cognitive rehabilitation providers report learning and memory as primary post- injury target of rehabilitation [9].

Memory rehabilitation usually involves educating patients about memory functioning and also discussing and practicing a range of interventions. Commonly, treatment involves teaching about and helping the person initiate both external compensatory strategies as well as working on internal or restorative strategies [10-12].

External Versus Internal Strategies

External compensatory strategies involve some form of assistance outside oneself (e.g., diaries, notebooks, to-do lists, electronic organizers, pagers) [8]. Internal memory strategies essentially involve re-teaching the brain to retain information using different mental strategies (e.g., repeating, counting, face-name associations, categorizing, mental visualization, or rhyming mnemonics) [8] and perhaps different parts of the brain. There are strengths and limitations to each approach and each may be more appropriate for certain kinds of individuals. In an updated review of evidence-based rehabilitation, Cicerone et al. [13] recommended training in the use of external compensation strategies (including assistive technology) with direct application to daily activities as a practice guideline for individuals with moderate to severe memory impairment after TBI or stroke. In brief, there has been little research showing that memory can be improved through remediation-oriented therapies and hence external compensation approaches are commonly the treatment of choice. However, the recent advancements in neuroplasticity research have re-invigorated the quest for potentially clinically effective internal strategies.

Current neuroplasticity research appears to suggest that the brain has the ability to create and modify neural connections and, perhaps, allow the brain to compensate for areas of damage [14]. Based on these findings, the therapeutic goal would then be to facilitate improved

skills through learning strategies and perhaps neural compensation [15]. Internal memory strategies for cognitive rehabilitation do not aim to salvage damaged brain tissue but to promote restoration of function. Retraining of the function is based on the supposition that impaired memory will respond to mental exercise [16].

The rationale behind the use of these strategies is to regain memory through the improvement of encoding and retrieval. Such improvement is likely thought to be secondary to a combination of utilizing a forced-use paradigm and teaching of diverse encoding strategies. The encoding strategies may include employing cognitive strengths and engaging different parts of the brain than those previously used to encode information. Thus, to achieve rehabilitation, imagery may be used to enhance the encoding of verbal information, or numerous elaborative encoding strategies might facilitate retention and retrieval of information. The belief is that the capacity of the function improves if the training is successful and does not depend on context [17].

Until recently, there was little empirical evidence to indicate that these internal memory techniques are of much benefit to patients due to the potentially limited ability to use these strategies automatically and functionally, as well as their narrow generalizability. Evidence supporting the efficacy of restoration of memory functioning in individuals following TBI is still sparse but growing [18]. In 2007, Thick penny- Davis and Barker-Collo [19] found that an 8 session memory treatment intervention involving internal and external memory strategies greatly improved participants standardized memory test performance, and increased their knowledge of memory. Also improved was the use of memory aids and strategies. At a one-month follow-up, the majority of participants reported "sometimes" or "often," using both external and internal strategies.

In their systematic review of internal strategies, Spreij and her colleagues investigated three different interventions: virtual reality-based rehabilitation, Computer-Based Cognitive Retraining (CBCR) and Non-Invasive Brain Stimulation (NBS). Their findings provided support for CBCR as an effective method of improving memory function following an acquired brain injury (ABI). For instance, a randomized controlled trial assessed the effectiveness of computerized working memory (WM) training [20] on WM functioning in ABI patients [17]. A sample of 38 ABI patients were randomly assigned to an experimental group or control group and received 5 weeks of standard rehabilitation in accordance with the usual routine at the clinic. The experimental group was offered an additional training with the Cogmed QM training program. To explore the impact of the training, assessments were done at baseline, after the training program, and at a follow-up 3 months later. The assessment battery consisted of neuropsychological tests and a WM questionnaire measuring WM on functional level (i.e., level of activity in daily life). The experimental group improved much more than the control group. Moreover, Cogmed QM showed a generalized effect on non-trained WM tasks [17]. The use of imagery-based mnemonics has also received some empirical support. Kaschel et al. [21] found that a 30-session program utilizing imagery-based memory rehabilitation was very effective. Participants showed a marked improvement in the delayed recall of materials related to their daily functioning, and their caretakers and/or family members reported reduction in observed memory problems [21].

Nonetheless, to date, the strongest evidence base exists for training that emphasizes external memory strategies primarily in individuals

with mild memory impairment [22]. For example, a study looking at a structured group memory retraining showed significant treatment effects for patients one to seven years post-severe TBI [23]. In this study, treatment occurred four days per week for six weeks [23]. Of the 20 participants in that study, the individuals with mild impairments were far more likely to benefit [23]. Similarly, much of the existing research on treatment involving internal memory strategies suggests that individuals with severe impairments often receive no benefit from this form of rehabilitation [24]. Thus, while there is some support for the efficacy of internal memory interventions, additional work is warranted.

Given the need for more extensive investigation of the effectiveness of internal strategies in cognitive rehabilitation, this study aimed to assess whether measurable gains in memory functioning can be achieved utilizing internal strategies only. The research hypothesis of this study postulated that following a treatment comprised of learning and practicing internal strategies, the participants' memory functioning would show significant improvement on a battery of tests as compared to their initial assessment.

Methods

Participants

The participant sample consisted of 13 individuals who suffered ABIs in the past 12 months and who had various cognitive impairments. Nine participants were men and four were women. Mean age was 44.5 years (SD=15.7), mean educational level was 13.7 years (SD=2.9), and mean time since injury was 6.3 months. All participants were unemployed and only one retained driving privileges while participating in treatment. At the time of admission, the elapsed period of time since the participants' injury ranged from 2 to 12 months with the mean being 6.3 months post-acute. The participants' impairments resulted from varied causes such as traumatic injuries, stroke, anoxia, and brain tumor resection. All participants had memory impairments at the time of admission and received twice weekly cognitive rehabilitation from a neuropsychologist throughout their outpatient post-acute care with a specific goal to work on short-term memory skills. Data for this study was retrospectively collected from the participant's clinical records. Some data suggested that a few patients had weeks with fewer than two individual therapy sessions.

It was determined early in treatment that two of the 13 participants were not sufficiently motivated to work on internal strategies. Accordingly, their treatment was largely focused on use of their compensatory external strategies, which included smartphones and day planner use. In addition, both of these participants' initial assessment scores were significantly below the rest of the sample (i.e. placing them in the 1st percentile of the norming sample versus the 13th and 5th scores of the remaining participants), which corresponded with a moderate to severe impairment as supposed to the borderline and low average functioning of the rest of the group. Finally, these participants evidenced no improvement in their memory functioning. Thus, their scores constituted outliers in the data set, which would likely skew the overall assessment the group's performance. Given these issues, the data of these two participants were not included in the group analyses (Table 1).

Demographic	1	2	3	4	5	6	7	8	9	10	11
Age	50	63	73	56	28	66	24	36	22	48	23
Gender	Female	Male	Male	Male	Female	Male	Male	Male	Female	Male	Female
Time since Injury (months)	12	10	3	2	2	7	2	12	2	4	3
Injury Type	Tumor resection (FL)	Tumor resection (TL)	Stroke (MCA)	Stroke (MCA)	TBI (TL)	Cancer	TBI	Brain tumor	TBI	Stroke (MCA)	TBI
Education (years)	16	12	20	12	18	12	12	13	12	12	12
Time b/t Testings (weeks)	6	6	5	6	6	5	5	4	4	4	4
Work status	No	No	No	No	No	No	No	No	No	No	No
driving	No	No	No	Yes	No	No	No	No	No	No	No

Table 1: Participant (Internal memory strategy group) demographic data

While each participant received nearly identical cognitive rehabilitation for their short- term memory, they each may have had a different level of involvement in physical therapy, occupational therapy, and speech therapy. None of the participants were involved in personal injury litigation, a disability claim, or other apparent secondary gain situation.

Measures

The Repeatable Battery for the Assessment of Neuropsychological Status [25,26]: RBANS was initially introduced in 1998 and consists of twelve subtests which produce five Index scores as well as a Total Scale score. The five scores indicate level of functioning in the following five domains: immediate memory, visuospatial/constructional, language, attention, and immediate and delayed memory. Index scores have a mean of 100 and standard deviation of 15. The battery was normed on a sample of 540 healthy adults and has shown to have good clinical validity [26], adequate test- retest reliability [27] and excellent diagnostic accuracy [28].

Materials

WALC 10 Memory: Workbook of Activities for Language and Cognition [29]: This workbook was developed to assess patients' coding strategies, assist them to apply those strategies to new context, as well as facilitate learning and practicing of new encoding strategies. WALC 10 Memory incorporates lessons focused on 14 different memory strategies (e.g. Word/Mental Picture Associations, Chaining Word Lists, Following Written and Oral Directions, or Associated Visual Pairs). The interventions utilized in this study incorporated several worksheets from some of the following lessons: Sorting and Remembering Categories, using first letter mnemonics, and Paired Words: Associated. Each participant was given multiple practice trials to use these strategies on different word lists and other information. Participants were also asked to think about and talk about other strategies they may use or would like to practice. Strategies were chosen that were consistent with the published empirically supported interventions for internal memory strategies.

Procedures

All participants completed the RBANS at the time of admission. Additionally, participants were retested at approximately five weeks post admission. The interventions for these participants included twice weekly individual cognitive rehabilitation and for some individuals there was also a once weekly participation in a memory group.

Intervention

During the initial therapy session participants were educated regarding the benefits and utility of using both internal and external compensatory strategies for memory. Psychoeducation on the memory process and the potential value of various elaborative information encoding strategies was also provided. Moreover participants were taught and began practicing multiple internal memory strategies. Specifically, they were introduced to practicing visualization, first letter mnemonics, putting words into sentences or stories, and semantic clusters. Throughout the rehabilitation treatment, participants were given exercises to encourage processing information in multiple modalities: by listening, reading, writing, drawing, and making the to-be remembered meaningful so that the information is processed more diffusely and in a more in-depth manner.

Each participant practiced strategies during the weekly therapy sessions and also received semantic clustering homework sheets. Each participant also had homework assignments involving semantic clustering, elaborative encoding, and taking notes and making to-do lists each day. At the time of memory retesting, participants had on average 8 individual therapy sessions and 4 group therapy sessions.

Results

Two of 13 participants decided early in treatment to just work on external memory strategies. The data from those individuals was not included in either Table 1 or Table 2. The individuals who did not have internal strategies memory training showed absolutely no changes on memory re-testing though only six months post injury. In the 11 internal memory strategies training individuals, paired sample t-testing was completed comparing the immediate RBANS scores to the

re-testing results approximately five weeks after the initial assessment 3. The initial mean Word List score was in the borderline range [M = 76, SD = 13.1], which was significantly increased to the high end of the average range [M = 105, SD = 8.0, t (9) = 7.4, p <.001]. Delayed recall for the word list also significantly improved [t (8) = 4.5, p <.01] (Table 2).

Tests Administered	Initial Assessment	Memory Retesting	Actual Change SS Points	RCI Values
Wide Range Achievement Test 4 (WRAT-4) Word Reading	90.8 (11.2)	-----		
RBANS- Word List	71 (12.1)	97 (14.1)	29	16.4
Story	72 (22)	107 (10.6)	24	12.9
Figure	101 (19.3)	-----		
Digit Span	89.4 (18.6)	-----		
List Recall	66.1 (13.4)	99 (12.7)	29	12.8
List Recognition	65 (20)	105 (11.1)	40	17.6
Story Recall	76 (22)	106 (2.8)	23	10.1

Table 2: Initial assessment and test-retest scores. Note: All scores are standard scores. Scores represent group means (standard deviations).

Despite significant improvement in the immediate free recall and delayed free recall for the word lists, delayed recognition did not improve significantly, however there was significant missing data for this variable. Story memory (immediate recall) scores improved from low average (M = 83, SD = 22) to the high end of the average range [M = 107, SD = 10.6, t (8) = 4.6, P <0.01]. In order to determine whether changes in scores carried clinical significance, Reliable Change Index (RCI) values were computed for the memory tests that were re-administered. RCI statistic has been used in behavioral research to establish the number of scale points on a given psychometric measure that represents statistical reliable change [30,31]. Thus, RCI indicates whether the change in scores from pre-intervention to post-intervention occurred due to a meaningful change rather than chance score variability [30,31]. For each test re-administered in the participant group, the score improvement was greater than the corresponding RCI. This suggests that the memory improvement in the treatment group was likely meaningful.

Qualitative data (in the form of interviews) were also collected in the form of participant feedback regarding their memory. Each participant stated that they felt their memory had improved and no longer reported any functional memory impairments. Though objective memory testing was administered, no measures were administered to assess for memory carry over.

Discussion

Memory rehabilitation interventions should always be designed based on the specific needs and characteristic of the individual patient. As with the two participants in this study whose scores were excluded from the final analysis, some individuals with brain injury-related memory impairments may have a limited capacity to carry out the

work necessary to fully benefit from internal, remediation-oriented memory strategies. Thus, external compensatory strategies would likely be the most effective course of treatment for some individuals to achieve functional improvement. Conversely, as this research suggests, many memory-impaired patients undergoing treatment might benefit from inclusion of internal interventions. As hypothesized, this study found that participants who were in the internal memory strategy training showed improved memory scores after treatment, as their scores post-treatment suggested a clinically meaningful improvement of function. Specifically, the individual differences between the pre- and post-treatment assessment were higher than the calculated scale-determined RCIs.

Similarly, the group mean scores evidenced significant differences: the RBANS Word List mean improved 29 scale points and the Story recall improved 24 points.

Past empirical research on the topic has emphasized some potential parameters associated with successful outcomes of memory rehabilitation. For example, researchers have indicated that individuals with more mild injuries [23,24], higher level of functioning, and those that are more recently injured and younger [32] are more likely to benefit from memory interventions.

Conversely, some research findings are beginning to challenge these limitations. Johansson and Tornmalm [33] found that even participants with severe impairments of WM benefitted from learning internal strategies. In addition, their study further found that the patients who started rehabilitation at the lowest levels of training realized the largest improvements [33]. In accord with these new positive findings, this study tentatively supports the utility of internal strategies for patients of diverse ages, as the significant improvements were experienced by all participants whose ages ranged from 22 to 73. In addition, the participants entered into the rehabilitation process as early as two months after their injury to as late as a year post-acute.

Although the results indicate successful outcomes, it is necessary to interpret these findings with caution. There was essentially no control group other than the few individuals who had just external strategy training. Also, the small sample size in txas encouragement for further, more rigorous empirical investigation rather than research evidence that can establish standard of care. The small sample size and acuity of injury of the individuals in this study both limit the generalizability of these findings to the general brain injury population. Additionally, the use of only one outcome measure restricts the breadth of assessing the realized improvements in terms of the context and number of areas of functioning. Thus, it is difficult to establish the degree of carry over benefits and the generalizability of the gains across environmental settings.

Given the limitations of this investigation, studies with larger sample sizes, including a control group, and using diverse outcome measure which would allow better appreciation of the extent of the treatment benefits. As numerous investigators have pointed out, the paucity of research in this area makes it difficult to conduct formal reviews [4] that might lead to changes in how clinicians approach an treat memory deficits associated with brain injury. Equally, more pilot studies or preliminary investigations, are needed to assess which memory strategies may be effective.

References

1. Hall RC, Hall RC, Chapman MJ (2005) Definition, diagnosis, and forensic implications of postconcussional syndrome. *Psychosomatics* 46: 195-202.

2. Goldstein FC, Levin HS (2001) Cognitive outcome after mild and moderate traumatic brain injury in older adults. *J Clin Exp Neuropsychol* 23: 739-753.
3. Cappa SF, Benke T, Clarke S, Rossi B, Stemmer B, et al. (2003) EFNS guidelines on cognitive rehabilitation: report of an EFNS task force. *Eur J Neurol* 10: 11-23.
4. Nair RD, Lincoln NB (2007) Cognitive rehabilitation for memory deficits following stroke. *Cochrane Database Syst Rev* : CD002293
5. Snaphaan L, de Leeuw FE (2007) Poststroke memory function in nondemented patients: a systematic review on frequency and neuroimaging correlates. *Stroke* 38: 198-203.
6. Ryan TV, Sautter SW, Capps CF, Meneese W, Barth JT (1992) Utilizing neuropsychological measures to predict vocational outcome in a head trauma population. *Brain injury* 6: 175-182.
7. Oddy M, Coughlan T, Tyerman A, Jenkins D (1985) Social adjustment after closed head injury: a further follow-up seven years after injury. *J Neurol Neurosurg Psychiatry* 48: 564-568.
8. Fish J, Manly T, Emslie H, Evans JJ, Wilson BA (2008) Compensatory strategies for acquired disorders of memory and planning: differential effects of a paging system for patients with brain injury of traumatic versus cerebrovascular aetiology. *J Neurol Neurosurg Psychiatry* 79: 930-935.
9. Holmqvist K, Kamwendo K, Ivarsson AB (2009) Occupational therapists' descriptions of their work with persons suffering from cognitive impairment following acquired brain injury. *Scand J Occup Ther* 16: 13-24.
10. (1999) National Institute of Health Consensus Development Panel on Rehabilitation of Persons with Traumatic Brain Injury. Rehabilitation of persons with traumatic brain injury. *The journal of American Medical Association* 282: 974-983.
11. Sohlberg MM (2005) External aids for management of memory impairment. In: High W, Sander AM, Struchen MA, Hart KA (eds.) *Rehabilitation for Traumatic Brain Injury* Oxford University Press, NY, New York.
12. Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, et al. (2005) Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch Phys Med Rehabil* 86: 1681-1692.
13. Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, et al. (2011) Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Arch Phys Med Rehabil* 92: 519-530.
14. Kimberley TJ, Samargia S, Moore LG, Shakakya JK, Lang CE (2010) Comparison of amounts and types of practice during rehabilitation for traumatic brain injury and stroke. *J Rehabil Res Dev* 47: 851-862.
15. Li K, Robertson J, Ramos J, Gella S (2013) Computer-based cognitive retraining for adults with chronic acquired brain injury: a pilot study. *Occup Ther Health Care* 27: 333-344.
16. Brooks BM, Rose FD (2003) The use of virtual reality in memory rehabilitation: current findings and future directions. *NeuroRehabilitation* 18: 147-157.
17. Björkdahl A, Akerlund E, Svensson S, Esbjörnsson E (2013) A randomized study of computerized working memory training and effects on functioning in everyday life for patients with brain injury. *Brain Inj* 27: 1658-1665.
18. Spreij LA, Visser-Meily JM, van Heugten CM, Nijboer TC (2014) Novel insights into the rehabilitation of memory post acquired brain injury: a systematic review. *Front Hum Neurosci* 8: 993.
19. Thickpenny-Davi, KL, Barker-Collo SL (2007) Evaluation of a structured group format memory rehabilitation program for adults following brain injury. *Journal of head trauma rehabilitation* 22: 303-313.
20. <http://www.cogmed.com/qm>.
21. Kaschel R, Sala SD, Cantagallo A, Fahlblöck A, Laaksonen R, Kazen M (2002) Imagery mnemonics for the rehabilitation of memory: A randomized group controlled trial. *Neuropsychological rehabilitation* 12: 127-153.
22. Wilson BA, Emslie HC, Quirk K, Evans JJ (2001) Reducing everyday memory and planning problems by means of a paging system: a randomized control crossover study. *Journal of neurology, neurosurgery and psychiatry* 70: 477-482.
23. Ryan TV, Ruff RM (1988) The efficacy of structured memory retraining in a group comparison of head trauma patients. *Arch Clin Neuropsychol* 3: 165-179.
24. O'Neil-Pirozzi T, Strangman G, Goldstein R, Katz D, Savage C, et al. (2010) A controlled treatment study of internal memory strategies (I-MEMS) following traumatic brain injury. *J Head Trauma Rehabil* 25: 43-51.
25. Randolph C. (1998) *Repeatable Battery for the Assessment of Neuropsychological Status*. San Antonio, TX: The Psychological Corporation.
26. Randolph C, Tierney MC, Mohr E, Chase TN (1998) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *Journal of clinical and experimental neuropsychology* 20: 310-319.
27. Silva JD, Humphreys JD, Dempsey JP, O'Bryant SE, Sutker PB (2006) Test-retest reliability of the Repeatable Battery for the Assessment of Neuropsychological Status in a memory disorder clinic sample. *Archives of clinical neuropsychology* 21: 560-561.
28. Duff K, Humphreys Clark JD, O'Bryant SE, Mold JW, et al. (2008) Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. *Archives of clinical neuropsychology* 23: 603-612.
29. Tomlin KJ (2007) *WALC 10 Memory: Workbook of activities for language and cognition*. East Moline, IL: Linguistics, Inc.
30. Jacobson NS, Follette WC, Revenstorf D (1984) Psychotherapy outcome research: Methods for reporting variability and evaluating clinical significance. *Behavior therapy* 15: 336-352.
31. Jacobson NS, Roberts LJ, Berns SB, McGlinchey JB (1999) Methods for defining and determining the clinical significance of treatment effects: Description, application, and alternatives. *Journal of consulting and clinical psychology* 67: 300-307.
32. Evans JJ, Wilson BA, Needham P, Brentnall S (2003) Who makes good use of memory aids? Results of a survey of people with acquired brain injury. *J Int Neuropsychol Soc* 9: 925-935.
33. Johansson B, Tornmalm M (2012) Working memory training for patients with acquired brain injury: effects in daily life. *Scand J Occup Ther* 19: 176-183.