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Combination treatment in the rehabilitation of visuo-spatial neglect

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Abstract

Background: Visuo-spatial neglect predicts longer hospitalization, poorer recovery of motor skills and greater functional limitation. The aim of the present study was to analyze whether the combined administration of computerized cognitive rehabilitation with right hemifield eye-patching in patients with left spatial neglect following a right hemisphere stroke is more effective than computerized cognitive rehabilitation applied in isolation. **Method:** Randomized clinical trial conducted in 28 patients. These were grouped into two experimental groups: single treatment group (ST) (n= 15) and combined treatment group (CT) (n= 13). All received an average of 15 one-hour sessions of computerized cognitive rehabilitation using the Guttmann, NeuroPersonalTrainer® telerehabilitation platform. Those patients in the TC group performed the sessions wearing a visual device with which the right hemifield of each eye was occluded. **Results:** Following treatment, both the ST and the TC group showed improvements in neuropsychological examination protocol although there were no differences pre- and post-treatment on the functional scale in either group. Likewise, no statistically significant differences were observed in intergroup comparison. **Conclusions:** The results from this study indicate that combination treatment is not more effective than rehabilitation applied in isolation.

Keywords: attention, stroke, spatial neglect, neuropsychology, cognitive rehabilitation, right hemifield eye-patching.

Resumen

Tratamiento combinado en la rehabilitación de la negligencia visuo-espacial. **Antecedentes:** la negligencia visuo-espacial predice mayor tiempo de hospitalización, peor recuperación de las habilidades motoras y limitaciones funcionales. El objetivo fue analizar si la administración combinada de rehabilitación cognitiva informatizada junto con el right hemifield eye patching, en participantes que presentan negligencia espacial izquierda como consecuencia de un ictus hemisférico derecho, es más eficaz que la rehabilitación cognitiva informatizada aplicada de forma aislada. **Método:** ensayo clínico aleatorizado realizado con 28 participantes. Dos grupos experimentales: grupo tratamiento único (TU) (n= 15) y grupo tratamiento combinado (TC) (n= 13). Todos ellos recibieron una media de 15 sesiones de rehabilitación cognitiva informatizada de una hora de duración mediante la plataforma de telerehabilitación Guttmann, NeuroPersonalTrainer®. Los participantes del grupo TC las ejecutaron con un dispositivo visual que llevaba el hemicampo derecho de cada ojo ocluido. **Resultados:** tras el tratamiento, tanto el grupo TU como el TC mostraron mejoras en el protocolo de exploración neuropsicológica aunque no hubo diferencias pre- y post-tratamiento en la escala funcional en ninguno de los dos grupos. Asimismo, no se observaron diferencias estadísticamente significativas en la comparación intergrupal. **Conclusiones:** los resultados derivados de este estudio indican que el tratamiento combinado no es más eficaz que la rehabilitación aplicada de forma aislada.

Palabras clave: atención, ictus, heminegligencia, neuropsicología, rehabilitación cognitiva, right hemifield eye-patching.

Visuo-spatial neglect (VSN) is a defect in the ability to detect, explore, and respond to new or significant stimuli presented on the opposite side of the lesion; this defect is not attributable to a motor or sensory impairment (Heilman & Valenstein, 1979).

VSN is a serious neurological disorder that affects two thirds of participants who have suffered a stroke in the middle cerebral artery or posterior right hemisphere (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). Its etiology is not always of vascular origin: the literature describes cases of VSN following traumatic brain injury (García-Molina, García-Fernández, Aparicio-López, & Roig-Rovira, 2016), multiple sclerosis (Gilad, Sadeh, Boaz, & Lampl, 2006) and neurodegenerative diseases (Silveri, Ciccarelli, & Cappa, 2011).

During the first weeks or even months following a stroke, it is possible to observe a spontaneous recovery of symptoms associated with VSN. However, it is common for them to persist over time (Kerkhoff & Schenk, 2012). One of the first published studies on the rehabilitation of VSN was performed by Lawson in 1962. Since then, numerous strategies have been proposed to rehabilitate VSN (see Lisa, Jughters, & Kerckhofs, 2013; Marshall, 2009; Riestra & Barrett, 2013). Despite this increase, there are currently no evidence-based recommendations to help therapists select a treatment or combination of treatments to rehabilitate the deficits presented by patients with VSN (Kerkhoff & Schenk, 2012).

After analyzing the techniques used in the treatment of VSN, Saevarsson, Halsband, and Kristjansson (2011) suggest that the combined therapeutic approach is better than the isolated

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application of such techniques or procedures. According to these authors, combined interventions may affect more than one clinical sign of all those that can be seen in participants with VSN.

Among the approaches used in the treatment of VSN, we find right hemifield eye patching (RHEP). RHEP involves placing a patch over the right eye hemifield of each eye (the patch is located in an external device, usually glasses in which the right hemifield is occluded in both lenses). This procedure induces the patient to concentrate their attention on the contralesional space and consequently, to decrease the tendency to move towards the ipsilesional visual space. Several theories have been postulated to explain the fundamentals of RHEP (for an exhaustive review, see Smania et al., 2013).

The aim of this study is to assess whether combined use of computer-based cognitive rehabilitation and RHEP in VSN patients as a result of a right-hemisphere stroke is more effective than computer-based cognitive rehabilitation alone. The assumption is that patients who receive combined treatment will improve more than patients who only receive computer-based cognitive treatment.

This study is a replication of the article by Aparicio-López et al. (2015); the methodology used herein is identical to the one used in that study. It was considered appropriate to extend the sample in order to check whether the improvements obtained after the intervention were maintained, increased or disappeared (Ioannidis, Munafo, Fusar-Poli, Nosek, & David, 2014; Nosek et al., 2015).

Method

Participants

Participants were recruited among patients at the Institute Guttmann Neurorehabilitation Hospital, Brain Injury Unit between May 2013 and June 2014. Inclusion criteria included: (1) suffering a right-hemisphere stroke diagnosed by Computed Axial Tomography or Magnetic Resonance Imaging; (2) being 18 or older at the time of lesion; (3) right-handedness; (4) Spanish as mother tongue; and (5) obtaining scores suggestive of VSN in the neuropsychological exploration protocol used to assess visuo-spatial attention. Patients with the following conditions were excluded from the study: (1) severe language alteration limiting the patient's communicative ability; (2) significant visual acuity impairment caused by cataracts, diabetes, retinopathy and/or glaucoma; and (3) pre-morbid history of other neurological diseases, psychiatric disorders, and/or drug abuse.

During the sample recruitment period, 59 right-hemisphere stroke patients were assessed; 31 did not meet the study's inclusion criteria (see Figure 1). The final sample consisted of 28 participants (17 male and 11 female); 14 of them had suffered an ischemic stroke, and the rest a hemorrhagic stroke. The mean age at the time of the stroke was 47.9 years (SD = 9.07; range= 34-67 years); 50% had been educated to primary level, 25% had received higher education, and 25% had been educated to degree level.

The time to admission to treatment after injury was 82.96 days (SD = 55.28; range= 16-236 days). These 28 patients were randomized into two treatment groups: one group received a single treatment (ST; n = 15), and the other a combination treatment (CT; n = 13). The treatment included a mean number of fifteen 1-hour sessions. Patients performed a mean of 2.71 sessions per week (SD = .65; range = 2-5 days). No statistically significant baseline differences were observed between the two groups (see Table 1).

The study was approved by the Institute Guttmann's Teaching and Research Committee and Ethic Committee.

Instruments

All patients included in the study were submitted to a specific neuropsychological exploration protocol for assessing visuospatial attention: Bell Cancellation Test (Gauthier, Dehaut, & Joanette, 1989), Figure Copying of Ogden (Ogden, 1985), Line Bisection (Schenkenberg, Bradford, & Ajax, 1980), Baking Tray Task (Tham, 1996) and a Reading test. The latter test was specifically designed for this study and consisted of reading three sentences

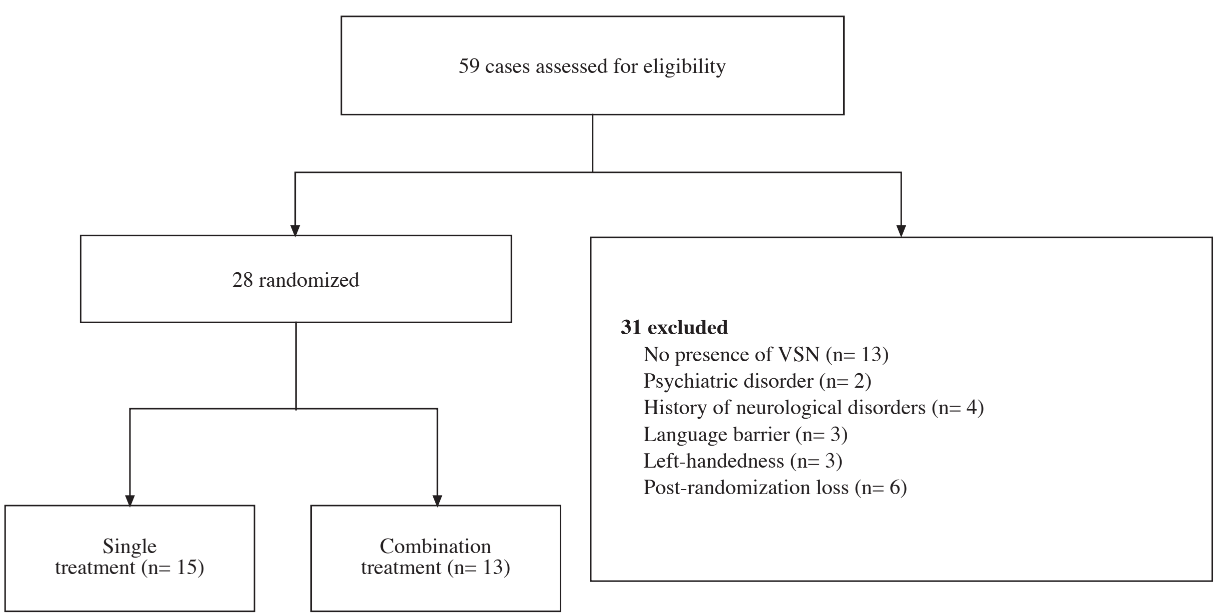

Figure 1. *Flow chart for patients recruited*

Table 1
Summary of characteristics of the patients included in the study

	Single treatment (n= 15)	Combination treatment (n= 13)	p
Age at injury (years)[1]	45.67 (8.05)	50.54 (7.61)	.173
Gender[2]	9/3	8/5	.934
Stroke (type)			
Ischemic	7	7	
Hemorrhagic	8	6	.705
Education level (%)			
Primary	53.3%	46.2%	
Secondary	20.0%	30.8%	.806
Degree	26.7%	23.1%	
Time between stroke and admission to the treatment (days)[1]	85.26 (67.31)	80.30 (39.69)	.596
Sessions per week[1]	2.73 (.45)	2.69 (.85)	.467

[1] Mean (Standard deviation)
[2] Male/Female

on a horizontal A4 sheet. The total number of words read by the patient was counted, with the highest score being 43. Scores ≤ 41 were considered suggestive of VSN. The Catherine Bergego scale (Bergego et al., 1995) was also used for assessing VSN in daily life activities. The test was given either to the patient (self-administered version) or to a relative (rater version).

Procedure

Participants who satisfied the inclusion criteria of the study were given the information sheet about the study (both the patient and primary caregiver). One of the researchers explained to them the experimental procedure in order to obtain their cooperation and to confirm their understanding of it. Once the informed consent of the participants had been obtained they were allotted a study number. These numbers corresponded to the order in which the patients entered the study. A simple randomization procedure was performed according to a computer-generated random number table based on a uniform distribution (0, 1). The application of such a simple randomization procedure yielded 15 patients in the ST group and 13 in the CT group. The research assistant who generated the allocation scheme was not clinically involved in the study (neither in the assessment nor in the administration of treatment to the patients).

The ST group followed a cognitive rehabilitation program using the computer-based platform Guttmann, NeuroPersonalTrainer® (García-Molina et al., 2010). Exercises included attention, memory, and executive function tasks. In all cases, adequate performance of the assigned tasks required visual processing of stimuli homogeneously distributed across the screen. The CT group carried out the same cognitive treatment as the ST group, combined with the RHEP. RHEP was implemented by using non-prescription glasses specially made for the study. These glasses had a completely opaque right half-field for each eye. This group wore these glasses during all cognitive treatment sessions.

Before starting treatment and also afterwards, the neuropsychological exploration protocol described in the Instruments section was administered. The researcher in charge of the exploration was the same person responsible for the planning and monitoring of treatment.

Data analysis

Data was described using absolute and relative rates, along with means and standard deviations, according to the type of variables. Two types of comparison were made. The first one was a between-group comparison using a signed rank test to assess cognitive and functional alterations among pre- and post-treatment settings. A Mann-Whitney test was used to study the between-group effect. The size of the effect was estimated using Cohen's *d*. The relative size of Cohen's *d* was: negligible effect (≥ - .15 and < .15); small effect (≥ .15 and < .40); medium effect (≥ .40 and < .75); large effect (≥ .75 and < 1.10); very large effect (≥ 1.10 and < 1.45); huge effect (> 1.45). Analyses were carried out via the SPSS v.16.0 statistical software for Windows and the set level of significance was p<.05.

Table 2
Group comparison of primary outcomes

	Single treatment (n= 15)			Combination treatment (n= 13)		
	Pre	**Post**	**p**	**Pre**	**Post**	**p**
Bell Cancelation Test	20.07 (9.16)	29.67 (3.83)	.001*	14.08 (9.35)	23.15 (9.20)	.003*
FCO	2.13 (1.72)	.60 (.98)	.016*	2.46 (1.89)	1.62 (1.75)	.131
Line Bisection (percent positively for rightward deviations)	20.58 (10.39)	11.28 (6.13)	.002*	27.51 (16.70)	21.13 (16.39)	.019*
Line Bisection (percent negatively for leftward deviations)	-9.44 (7.65)	-9.64 (6.85)	.955	-7.23 (7.42)	-13.82 (11.30)	.248
Line Bisection (lines omitted)	3.53 (4.10)	.93 (1.38)	.017*	5.23 (4.64)	2.85 (3.55)	.066
BTT - left	2.73 (3.34)	4.07 (3.41)	.026*	2.42 (2.98)	4.50 (4.63)	.042*
BTT - right	13.27 (3.34)	11.93 (3.41)	.026*	13.58 (2.98)	11.50 (4.63)	.042*
Reading Task	37.47 (12.02)	40.93 (6.43)	.321	31.15 (15.43)	35.46 (13.23)	.108
CBS - self	7.13 (6.48)	6.14 (6.13)	.925	6.82 (6.87)	4.40 (3.37)	.064
CBS - rater	10.58 (8.46)	8.83 (6.70)	.308	11.86 (7.73)	10.33 (6.60)	.552

Mean (Standard Deviation)
FCO: Figure Copying of Ogden; BTT: Baking Tray Task; CBS: Catherine Bergego Scale.
* Significant difference p<.05

Results

Table 2 shows the means and SD for the administered test before and after treatment in both groups. No statistically significant between-group comparison at baseline was observed: Bell Cancellation Test (p = .108), Figure Copying of Ogden (p = .525), Line Bisection (right deviation) (p = .316), Line Bisection (left deviation) (p = .467), Line Bisection (lines omitted) (p = .217), Baking Tray Task (left) (p = .717), Baking Tray Task (right) (p = .717), Reading Task (p = .201), Catherine Bergego Scale self-version (p = .821) and Catherine Bergego Scale rater version (p = .555).

After the intervention, the ST group showed statistical significance in Bell Cancellation Test (p = .001), Figure Copying of Ogden (p = .016), Line Bisection (right deviation) (p = .002), Line Bisection (lines omitted) (p = .017), Baking Tray Task (left) (p = .026), and Baking Tray Task (right) (p = .026), whereas the CT group showed statistical significance in Bell Cancellation Test (p = .003), Line Bisection (right deviation) (p = .019), Baking Tray Task (left) (p = .042), and Baking Tray Task (right) (p = .042) (see Table 2).

No differences in either group were observed in the Catherine Bergego Scale administered pre- and post-intervention.

In the between-group comparison with the differences in the neuropsychological explorations post- and pretreatment, no statistically significant differences were obtained (see Table 3).

In the estimation of the effect size (Cohen's *d*) we obtained a medium effect on the Line Bisection test, both in the percent positively for rightward deviations (*d* = .43) and in the percent negatively for leftward deviations (*d* = .57).

Discussion

The aim of this study was to analyze whether the combined administration of computerized cognitive rehabilitation and RHEP in participants with VSN as a result of a right hemispheric stroke was more effective than computerized cognitive rehabilitation applied in isolation. Based on the findings of the review carried out by Saevarsson et al. (2011) and Aparicio-López et al. (2015), as well as those studies that have made substantial changes by combining techniques in the rehabilitation of patients with VSN (Arai, Ohi, Sasaki, Nobuto, & Tanaka, 1997; Tsang et al., 2009; Zeloni, Farnè, & Baccini, 2002), our hypothesis was that combination treatment would be more effective than a cognitive rehabilitation program. Therefore, we expected to observe group differences in neuropsychological assessment and functional post-treatment in favor of the group that received the combination treatment. The results show neither psychometric nor functional between-group differences after treatment.

It should be noted that Saevarsson et al. (2011) place special emphasis on the fact that the design of the intervention plays a prominent role, downplaying other variables such as the number of sessions and their intensity. Perhaps the design of the intervention implemented in our study was not the most appropriate. On considering this study, we thought that the intervention by means of the Guttmann, NeuroPersonalTrainer® cognitive rehabilitation program would impact on cognitive functions, and that the application of RHEP would force structural changes at the level of the central nervous system; these changes would be reflected in an improvement of the symptoms of VSN. When comparing our methodology with others that have obtained statistical differences after applying a combined approach similar to the one used by us, we consider that our methodology is not very different. Tsang et al. (2009) applied 1 hour of RHEP on a daily basis together with occupational therapy for 4 weeks. Zeloni et al. (2002) applied the RHEP from the time the patient got up until they went to bed, coupled with training compensation strategies; the control group did not apply the RHEP. However, in other studies, the results are similar to ours. Fong et al. (2007) obtained similar results after applying RHEP 1 hour daily 5 days a week for 4 weeks; similarly, Ianes et al. (2012) did not observe differences between the application of RHEP 8 hours a day over 15 consecutive days, and training in visual scanning for 40 minutes a day during the same period. Machner et al. (2014) also obtained significant improvements after applying the RHEP intensively for 7 days. We think that, in our case, the application time may have influenced the final result.

One limitation of the study is that, despite having applied a treatment aimed at rehabilitating functions such as attention, memory, and executive functioning, no changes were produced at this level after treatment. It is noteworthy that when the patient is in an acute state, VSN itself makes it difficult to administer some of the tests used to assess these functions. For this reason, we did not have sufficient data to compare changes of pre-treatment with respect to exploration results upon completion. In the literature, we found a recent study which obtained significant changes following application in the subacute phase, an intervention by means of computer exercises, for a sample of patients who had suffered a stroke (Zucchella et al., 2014). The experimental group received 16 1-hour sessions of computerized cognitive rehabilitation and the control group spent the same period of time with a psychologist discussing general current issues and their daily activities. The results show significant differences compared to the control group in functions like verbal memory and visual attention; the latter also used to be impaired in patients with VSN (Husain, Shapiro, Martin, & Kennard, 1997). These authors attribute the improvements to the approach of "retraining" which is based on the assumption that the repetition of the exercises can lead to the restoration of brain function and synaptic connectivity (Kim et al., 2009; Sturm et al., 2004). It would be of particular interest to

Table 3
Pre-post comparison group differences and effect size

	p	d
Bell Cancelation Test	.856	.07
FCO	.496	.35
Line Bisection (percent positively for rightward deviations)	.387	.43
Line Bisection (percent negatively for leftward deviations)	.467	.57
Line Bisection (lines omitted)	.892	.05
BTT - left	.751	.28
BTT - right	.751	.28
Reading Task	.118	.06
CBS - self	.254	.27
CBS - rater	.751	.03

FCO: Figure Copying of Ogden; BTT: Baking Tray Task; CBS: Catherine Bergego Scale.
p<.05
d = Cohen's d effect size

see in future studies whether there is a direct relationship between improving some of the cognitive functions and improving VSN; in this way, we could implement different forms of intervention.

The absence of changes at functional level in both groups (ST and CT) corroborate the conclusions of the review *"Cognitive rehabilitation for spatial neglect following stroke"* by The Cochrane Collaboration. The authors of this study indicate that the rehabilitation of VSN improves performance in psychometric tests but does not improve the disability itself (Bowen & Lincoln, 2007). The literature contains studies using scales such as the Barthel Index (Mahoney & Barthel, 1965) and the Functional Independence Measure (Granger, Hamilton, Keith, Zielezny, & Sherwin, 1986) to evaluate the functionality of participants with VSN. Both scales correlate significantly with the Catherine Bergego Scale but do not directly assess the impact of the VSN deficit in daily life (Chen, Hreha, Fortis, Goedert, & Barrett, 2012). The Catherine Bergego Scale is a useful and effective tool for evaluating the effectiveness of rehabilitation. It also provides good reliability and validity and is sensitive to change after applying a rehabilitation program (Bergego et al., 1995; Samuel et al., 2000). Several studies have obtained a significant improvement on the Catherine Bergego Scale after applying specific rehabilitation programs in participants with VSN (Cazzoli et al., 2012; Ertekin, Gelecek, Yildirim, & Akdal, 2009; Fortis et al., 2010; Kim, Chun Yun, Song, & Young, 2011; Staubli, Nef, Klamroth-Marganska, & Riener, 2009; Wu et al., 2013). However, as in our case, the authors also found that no statistically significant differences were obtained pre- and post-treatment for this scale (Mizuno et al., 2011; Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010). In the present study, the lack of change in the scores on the Catherine Bergego Scale after treatment could be attributed to the fact that all participants received treatment during hospitalization. We believe that this situation significantly limits the patient's ability to adequately perceive their deficit. In addition, there may be biases in the responses provided by the family, either underestimating or overestimating the deficit in the patient. In the case of overestimation, this could be based on a comparison between the current situation and that experienced shortly after the injury, causing the family to overvalue the positive evolution experienced by the patient and minimizing existing effects. In other cases, perhaps the family is not aware of the magnitude of the deficit in the patient, assigning little relevance to it (Tirapu, García-Molina, Rios, & Ardila, 2012).

Another aspect to consider is the time at which the rehabilitation program is started. As stated in the literature, the benefits of rehabilitation tend to be higher the shorter the time between injury and the start of treatment (Kolb, Teskey, & Gibb, 2010). Tsang et al. (2009) obtained psychometric improvements after initiating treatment an average of 22.18 days (SD = 15.87) following a stroke. However, the greater the time between the start of treatment and the time of the lesion, the less significant is the role of spontaneous recovery and, by extension, the more "pure" the impact of the applied technique. Nijboer, Kollen, and Kwakkel (2013) report that spontaneous recovery in VSN can take up to 12-14 weeks post-stroke; after this time the symptoms associated with VSN begin to stabilize. In the present study, we obtained psychometric intragroup differences pre- and post-treatment in both groups, starting the rehabilitation program a median of 10 weeks after stroke. In future studies it would be advisable to assess the role of this variable (time of evolution at the beginning of the rehabilitation program) in treatment outcome. However, it should be noted that there is a wide sampling variability with regard to the time of evolution at the start of treatment (between 16 and 236 days post-stroke). In future research, it would be necessary to control this variable in order to homogenize its distribution and reduce the time dispersion suffered by the current study.

It is known that the size and location of the lesion influences the manifestation and magnitude of symptoms associated with VSN; we therefore believe that the inclusion of neuroanatomical information would have enriched our research (Ogourtsova, Korner-Bitensky, & Ptito, 2010). We also believe that anosognosia is an aspect that needs to be assessed and treated as part of the rehabilitation of VSN. The presence of anosognosia has been associated with recovery from stroke (Gialanella & Mattioli, 1992; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1997), as well as with the severity of VSN (Dauriac-Le Masson et al., 2002). Vossel, Weiss, Eschenbeck, and Fink (2013) note that the patient's awareness of their own visuospatial deficit is more important for the performance of activities of daily life than the severity of the visuospatial deficits per se. Another variable to include in future studies is the active participation of the family in the rehabilitation process. Osawa and Maeshima (2010) have shown a direct link between inclusion of the family in the treatment and improvement of symptoms associated with VSN. In future research, it would also be appropriate to recruit more participants.

Given the magnitude, persistence, heterogeneity, and disabling effects of VSN, further research is necessary to help us improve the diagnosis and rehabilitation of this deficit. The results from this study indicate that combination treatment (RHEP along with a cognitive rehabilitation program using the Guttmann, NeuroPersonalTrainer® computerized platform) does not enhance the effects of cognitive treatment applied in isolation.

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