UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
FACULDADE DE MEDICINA

Gustavo José Luvizutto

Investigação de negligência espacial unilateral após Acidente Vascular Cerebral

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutor em Bases Gerais da Cirurgia.

Orientador: Prof. Dr. Luiz Antônio de Lima Resende

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1. Acidente vascular cerebral - Tratamento. 2. Cérebro - Doenças - Diagnóstico. 3. Cérebro - Ferimentos e lesões.

Dedicatória

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"Deus é um círculo cujo centro está em toda parte e cuja circunferência não está em nenhum lugar"

Empédocles

Resumo da tese

Introdução: A negligência espacial unilateral (NEU) é caracterizada pela incapacidade de reportar ou responder pessoas ou objetos do lado contralateral à lesão cerebral, e ocorre principalmente após Acidente Vascular Cerebral (AVC) do lobo parietal direito, sendo associada à pior desfecho funcional à longo prazo. **Objetivo:** Os objetivos desta tese foram: normatizar os principais testes diagnósticos de NEU e verificar a relação com fatores sócio-demográficos na população brasileira; avaliar as variáveis bioquímicas que interferem na NEU na fase aguda do AVC; e revisar sistematicamente os principais tratamentos farmacológicos na NEU em pacientes após AVC. **Método:** Para o primeiro objetivo foi realizado estudo transversal em 150 indivíduos sem alterações neurológicas, sendo aplicados: teste face-mão (TFM), testes de cancelamento de linhas (TCL), cancelamento de estrelas (TCE) e bisseção de linhas (TBL). Os resultados dos testes foram relacionados com o perfil sócio demográfico da população, sendo estipulado pontos de cortes para a normalidade; para o objetivo 2 foi realizado estudo observacional em 40 indivíduos com diagnostico de NEU após AVC. Foram aplicados os TCL, TCE e TBL, sendo relacionado com o nível de hemoglobina na fase aguda do AVC corrigido para potenciais confundidores; para o objetivo 3 foi realizado revisão sistemática de literatura por meio de ensaios clínicos randomizados e *quasi*-randomizados para determinar o melhor tratamento farmacológico. **Resultados:** os resultados do objetivo 1 estão apresentados nos artigos 1 e 2; o objetivo 2 no artigo 3; e o objetivo 3 no artigo 4. **Conclusão:** Com base nos resultados obtidos dos artigos 1 e 2, o TFM apresenta taxa de normalidade entre 8 a 10 estímulos sensoriais, com prevalência de extinção associada com o grau de escolaridade e aumento da idade; no TCL o ponto de corte para considerar NEU é acima de 0 e no TCE acima de 2, ambos associados à idade. No TBL o ponto médio de corte para considerar NEU foi de 6,6 mm, associado com pior escolaridade. No artigo 3 foi observado que quanto menor o valor de hemoglobina na fase aguda do AVC, pior o desempenho nos testes de NEU; No artigo 4 foi observado que a efetividade e segurança dos tratamentos farmacológicos para NEU após AVC permanecem incertos, necessitando de ensaios clínicos randomizados adicionais para avaliar o efeito deste tratamento.

Palavras-chave: Negligência espacial unilateral; normatização; Acidente vascular cerebral; testes diagnósticos; prognóstico; reabilitação; tratamento farmacológico.

Abstract

Background: Unilateral spatial neglect (USN) is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain and has been associated with poor functional outcomes. **Objective:** The objectives of this thesis were: to standardize the USN tests and verify the relationship with socio-demographic data in the Brazilian population; evaluate the biochemical variables that influence in USN tests after acute stroke; and systematically review the pharmacological interventions to treat USN after stroke. **Method:** For the first aim, we performed a cross-sectional study of 150 individuals without neurological changes by applying: face-hand test (FHT), line cancellation test (LCT), star cancellation test (SCT) and line bisection test (LBT). The test results were related to the sociodemographic data, with cutoff points being stipulated to define USN; the second aim was achieved by conducting an observational study of 40 individuals with USN after acute stroke. The tests applied – LCT, SCT and LBT – were correlated with the hemoglobin level in the acute phase of stroke corrected by confounders; the third aim was analyzed by a systematic review of randomized controlled trials and quasi-randomized clinical trials to determine the efficacy of pharmacological intervention. **Results:** The first aim is presented in Articles 1 and 2, the second aim in Article 3 and the third in Article 4. **Conclusion:** Based on the results of Articles 1 and 2, the FHT shows normal rate between 8-10 sensory stimuli, with an extinction prevalence associated with the education level and increasing age; The LCT cutoff point to define is USN above 0 and SCT above 2, and both were associated with age. The LBT cutoff point to indicate NEU was 6.6 mm, associated with poorer education level. Article 3 reveals the relationship between a lower hemoglobin level in acute phase of stroke with worse performance on USN tests; Article 4 reports that the effectiveness and safety of pharmacological treatments for USN after stroke remain uncertain, requiring additional randomized clinical trials to evaluate the effect of treatment.

Keywords: stroke; unilateral spatial neglect; standardization; stroke; diagnostic tests; prognosis; rehabilitation; pharmacological treatment.

Conteúdo

Artigo científico 1

Standardization of the face-hand test in a Brazilian population: prevalence of sensory extinction and implications for neurological diagnosis

Short title: Standardization of the face-hand test in a Brazilian population

M.Sc. Gustavo José Luvizutto[1], Marcelo Ortolani Fogaroli[2], Rodolfo Mazeto Theotonio[2], M.Sc. Hélio Rubens de Carvalho Nunes [3], PhD. Luiz Antônio de Lima Resende[4], PhD. Rodrigo Bazan[4]

[1]Neurorehabilitation. Univ. Estadual Paulista – UNESP – Botucatu Medical School.

[2]Medicine student. Univ. Estadual Paulista – UNESP – Botucatu Medical School.

[3]Department of Public Health. Univ. Estadual Paulista – UNESP – Botucatu Medical School.

[4] Departament of Neurology, Psicology and Psychiatry. Univ. Estadual Paulista – UNESP – Botucatu Medical School.

Corresponding author:

M.Sc. Gustavo José Luvizutto, Neurorehabilitation, Univ. Estadual Paulista – UNESP – Botucatu Medical School. Botucatu, SP, 18618-970, Brasil Fax number: +55 14-38116049E-mail: gluvizutto@fmb.unesp.br

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Abstract

Background: The face-hand test (FHT) is a simple test with high sensitivity to detect psychiatric syndromes and unilateral spatial neglect after stroke**. Objective:** to standardize the FHT in a Brazilian population and relate the results to the sociodemographic data. **Methods:** This is a cross sectional study with 150 individuals. Sociodemographic variables included age, gender, race, body mass index (BMI), and years of education. Standardization of the FHT occurred in 2 rounds of 10 sensory stimuli, and the associations between FHT and sociodemographic variables were analyzed using Mann-Whitney tests and Spearman correlations. Binomial models were adjusted for the number of FHT variations and ROC curves evaluated sensitivity and specificity of sensory extinction. **Results:** There was no significant relationship between the sociodemographic variables and the number of stimuli perceived on the FHT. There was a high relative frequency of detection for 8 of 10 stimuli in this population. Sensory extinction was 25.3%, which increased with increasing age (OR=1.4[1:01–1:07];p=0.006) and decreased significantly with increasing education (OR=0.82[0.71-0.94];p=0.005). **Conclusion:** A normal FHT score range between 8–10 stimuli, and indicate that sensory extinction is associated with increased age and lower levels of education in the Brazilian population.

Keywords: face-hand test; sensitivity; diagnosis; psychiatric syndromes; unilateral spatial neglect.

Introduction

Bender et al. (1950) developed the face-hand test (FHT) in order to investigate specific patterns of neurological disorders through dual concurrent sensory stimulation of the face and back of the hand [1]. They found that the FHT had 2 response patterns: sensory extinction (only one stimulus is recognized by the individual) or displacement (stimuli are recognized elsewhere in the body). Based on these findings, the FHT was proposed as a tool for assessing patients with psychiatric and neurologic diseases [2-3].

The first standardization of the FHT occurred in 1969, based on results from 3 groups of volunteers who were categorized by age (3–6 years old, 7–12 years, and older than 12 years). The results of the FHT in these 3 groups were compared to the FHT scores of patients with schizophrenia, organic psychosis, or aphasia. The authors concluded that the most common errors occurred for sensory extinction of face dominance in patients with organic psychosis and children who were 3–6 years old [4-5].

The FHT has also been used to diagnose perceptual neurological syndromes, such as for clinical differential diagnosis of unilateral spatial neglect (USN). Feinberg et al. (1990) evaluated the FHT scores of patients with unilateral hemispheric lesions 3 months after stroke, finding both contralateral and ipsilateral USN in patients with right hemisphere lesions. However, similar findings did not occur in patients with lesions to the left hemisphere [6]. These findings are important to explaining ipsilateral extinction and indicate a role of the right hemisphere in the mechanisms of spatial attention. The findings also support that the test is precise enough to detect changes in the perceptions of individuals with neurological conditions [7-10].

The FHT is a simple test, as well as being practical and fast, with high sensitivity to detect psychiatric syndromes and USN after stroke. However, the FHT has not previously been assessed in a Brazilian sample; therefore, the objective of the present study was to standardize the FHT for use in the multi-cultural population of Brazil, as well as to identify the main sociodemographic factors affecting the test results. The central hypothesis was that sensory stimuli scores of approximately 10 are typical in the population, and that abnormal patterns on the FHT, such as sensory extinction and displacement, may be associated with lower education levels.

Patients and methods

Participants

This cross-sectional study included graduate students, professionals and patients at the Clinics Hospital of Botucatu (UNESP) between March 2013 to July 2015. The persons were recruited through direct contact with the researcher followed by invitation to participate in the study.

The study was approved by the Ethics in Human Research Committee, under protocol 4223/2012, and all participants gave written informed consent. Participants met the following inclusion criteria (Figure 1): right handed, no history of neurological disease in central and peripheral nervous system, systemic infections, no to be in use psychotropic drugs or antidepressants, conscious during testing with Glasgow Coma Scale of 15, and with a score > 24 on the Mini-Exam Mental State Examination (MMSE). The MMSE cutoff score was selected in order to correspond with the most commonly used value in clinical and epidemiological studies of dementia in Brazil [11-13].

Study variables

The sociodemographic data obtained during interviews with patients were as follows: age (years), gender (men and women), race (Caucasian and non-Caucasian), body mass index (BMI, kg/m^2), and years of education.

Standardization of the FHT was performed with the participant seated to support the trunk, occluded vision, and in a sound-controlled environment. The FHT was conducted by applying 2 rounds of 10 sensory stimuli through cotton in a craniocaudal direction at the 3rd metacarpal, followed by 10 stimuli applied to the cheek region of the face and 10 simultaneous stimuli applied to the face and hand. All stimuli were initially applied on the left side, and then applied on the right. The stimulus intensity could not be measured objectively, but we did have the same researcher apply all stimuli, in order to reduce the potential for confounding effects. Finally, the number of rings and the location of touch perceived by the individual in each testing segment were categorized as normal sensory extinction or displacement. Table 1 shows the sequence of stimuli applied during the FHT.

Table 1. Sequences of stimuli applied during the face-hand test (FHT).

1st round of stimuli:
1. 10 sensory stimuli to the left hand
2. 10 sensory stimuli to the left face
3. 10 sensory stimuli to the left face and the left hand
2nd round of stimuli:
4. 10 sensory stimuli to the right hand
5. 10 sensory stimuli to the right face
6. 10 sensory stimuli to the right hand and the right face

Statistical analyses

Since we are using a sample representative of the target population, our sampling is considered to be intentional and non-probabilistic. We needed a minimum of 150 subjects to obtain a maximum sampling error of 7.5% and a confidence level of 95% based on a pilot study with 20 subjects. The comparison between FHT scores and the sociodemographic variables gender and race were analyzed using nonparametric Mann-Whitney tests. The associations between FHT scores and age, BMI, as well as years of education were assessed using Spearman correlations. The correlations was classified as a poor (0.20), fair (0.20–0.39), moderate (0.40–0.59), good (0.60–0.79), and excellent (>0.8). An adaptation of the binomial distribution assumption was used to model the perceived number of touches, followed by calculating maximum likelihood estimates for the binomial distribution parameters for each variation of the FHT. The relationships between sociodemographic variables and sensory extinction on the FHT were analyzed by multiple logistic regression, adjusted for age and years of education. After adjustments, receiver operating characteristic (ROC) curves were calculated for age and years of education, in order to establish values that maximize the sensitivity and specificity of sensory extinction on the FHT. Associations were considered statistically significant if $p < 0.05$. Analyses were performed using SPSS software (version 21.0, SPSS, Chicago, IL, USA).

Results

We evaluated and screened 250 individuals, but only 150 participants met the inclusion criteria for the study (Figure 1).

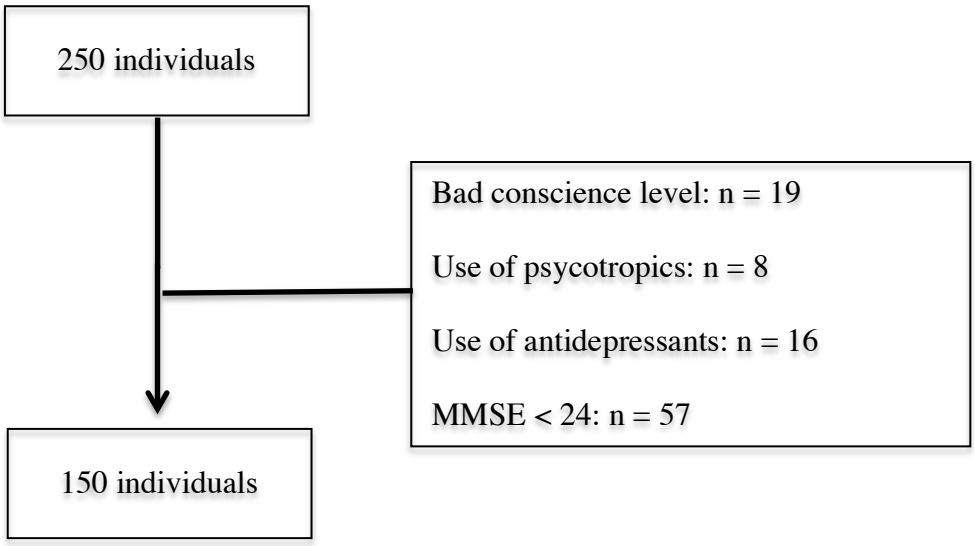

Figure 1 - Screening process indicating patients excluded from the study.

The sociodemographic characteristics and face-hand test examination of the participants are presented in Table 2. Tables 3 and 4 demonstrate that there were no significant associations between FHT scores and sociodemographic variables including gender, race, age, BMI, and years of education.

Table 2. Sociodemographic characteristics and performance of subjects in FHT (n=150).

Variable	**Summary**
Gender (women:men)	76 (50.7%):74 (49.3%)
Race (Caucasian:non-Caucasian)	112 (74.7%):38 (25.3%)
Years of education[1]	11(6–16)
Age[1] (years)	31.5 (18.0–87.0)
BMI[1] (kg/m^2)	22.9 (11.7–35.9)
F-r[1]	10.0 (3.0–12.0)
F-l[1]	10.0 (4.0–13.0)
H-r[1]	10.0 (2.0–12.0)
H-l[1]	10.0 (3.0–13.0)
FH-r[1]	10.0 (2.0–11.0)
FH-l[1]	10.0 (3.0–13.0)
Sensorial extinction	38 (25.3%)

[1]Summary median (min-max); BMI = body mass index; F-r = right face; F-l = left face; H-r = right hand; H-l = left hand; FH-r = right face-hand; FH-l = left face-hand.

Table 3. Face-hand test (FHT) scores by gender and race.

	Gender			Race		
	Women	**Men**		**Caucasian**	**Non-Caucasian**	
FHT	**(n=76)**	**(n=74)**	**p[1]**	**(n=112)**	**(n=38)**	**p[1]**
F-r	10(3–12)	10(6–12)	0.950	10(5–12)	10(3–12)	0.805
F-l	10(4–13)	10(5–12)	0.627	10(5–12)	10(4–13)	0.686
H-r	10(2–11)	10(3–12)	0.529	10(3–11)	10(2–12)	0.132
H-l	10(3–13)	10(3–11)	0.124	10(5–11)	10(3–13)	0.755
FH-r	10(2–11)	10(2–11)	0.887	10(2–11)	10(2–11)	0.466
FH-l	10(3–13)	10(5–12)	0.880	10(5–13)	10(3–12)	0.434

[1]Mann-Whitney. Summary in median (min-max); F-r = right face; F-l = left face; H-r = right hand; H-l = left hand; FH-r = right face-hand; FH-l = left face-hand.

Table 4. Correlation between face-hand test (FHT) scores and age, BMI, or years of education.

F-r = right face; F-l = left face; H-r = right hand; H-l = left hand; FH-r = right face-hand; FH-l = left face-hand. ρ = Spearman correlation.

Factor	**F-r** ρ (p value)	**F-l** ρ (p value)	**H-r** ρ (p value)	**H-l** ρ (p value)	**FH-r** ρ (p value)	**FH-l** ρ (p value)
Age (years)	-0.29(<0.001)	0.03(0.674)	-0.35(<0.001)	-0.10(0.218)	-0.27(<0.001)	-0.21(0.009)
BMI (kg/m^2)	0.04(0.588)	0.10(0.221)	-0.05(0.517)	-0.006(0.941)	0.03(0.628)	0.10(0.186)
Years of education	0.29(<0.001)	0.17(0.03)	0.32(<0.001)	0.34(<0.001)	0.23(0.004)	0.24(0.002)

Table 5 presents data for the number of touches perceived, according to FHT variations. We observed a relatively high percentage of participants who perceived at least 8 touches during all variations of the FHT, particularly during the Fd, Fe, FH-d, and FH variations, in which more than 90% of participants noticed at least 8 touches. The percentage of participants perceiving 8 or more touches was lower for the Hd and H variations, but was still >80%.

Table 5. Number of touches by face-hand test (FHT) variation.

Number of	**FHT variation**											
touches on	**F-r**		**F-l**		**H-r**		**H-l**		**FH-r**		**FH-l**	
FHT	**n**	**fr**	**n**	**fr**	**n**	**fr**	**n**	**fr**	**n**	**fr**	**n**	**fr**
0	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000
1	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000
2	0	0.000	0	0.000	1	0.007	0	0.000	2	0.013	0	0.000
3	1	0.007	0	0.000	2	0.013	2	0.013	1	0.007	1	0.007
4	1	0.007	2	0.013	2	0.013	2	0.013	0	0.000	0	0.000
5	2	0.013	1	0.007	6	0.040	4	0.027	3	0.020	3	0.020
6	6	0.040	3	0.020	3	0.020	3	0.020	3	0.020	3	0.020
7	2	0.013	4	0.027	9	0.060	6	0.040	1	0.007	3	0.020
8	7	0.047	10	0.067	8	0.053	5	0.033	7	0.047	5	0.033
9	9	0.060	13	0.087	11	0.073	19	0.127	12	0.080	13	0.087
10	122	0.813	117	0.780	108	0.720	109	0.727	121	0.807	122	0.813
≥ 8 touches	138	0.920	140	0.934	127	0.846	133	0.887	140	0.933	140	0.933

Legend: n = number of touches; f = relative frequency of perceived touches; F-r = right face; F-l = left face; H-r = right hand; H-l = left hand; FH-r = right face-hand; FH-l = left face-hand. n = absolute frequency; fr = relative frequency.

Table 6 shows the binomial models adjusted for the number of rings perceived in each variation of the FHT.

Table 6. Probabilistic models adjusted for the number of rings with each perceived change on the face-hand test (FHT), for a total of 10 stimuli.

FHT variation	**Distribution**	**Pr [t ≥ 8]**
F-d	Bin (10;0.949)	0.987
F-e	Bin (10;0.950)	0.988
H-d	Bin (10;0.913)	0.950
H-e	Bin (10;0.930)	0.971
FH-d	Bin (10;0.947)	0.986
FH-e	Bin (10;0.956)	0.991

Bin = binomial distribution; Pr = estimated probability of perceiving at least 8 of 10 stimuli received under the fitted distribution; F-r = right face; F-l = left face; H-r = right hand; H-l = left hand; FH-r = right face-hand; FH-l = left face-hand.

Table 7 shows the association between sociodemographic variables and the probability of sensory extinction during the FHT. We observed a statistically significant increase in the probability of sensory extinction with increasing age (OR = 1.04, range 1.01–1.07; p = 0.006 and a significantly reduction in probability of extinction with increasing years of education (OR = 0.82, range 0.71–0.94; p = 0.005).

Table 7. Regression adjusted logistics for the probability of extinction on the face-hand test (FHT).

Variable	**β**	**SE**	**Wald**	**p**	**OR**	**CI 95%**
Men	-0.63	0.46	1.83	0.176	0.53	(0.22–1.32)
Age (years)	0.04	0.01	7.48	0.006	1.04	(1.01–1.07)
BMI (kg/m^2)	-0.01	0.05	0.01	0.904	0.99	(0.90–1.10)
Race (non-Caucasian)	-0.47	0.53	0.76	0.382	0.63	(0.22–1.79)
Years of education	-0.20	0.07	7.98	0.005	0.82	(0.71–0.94)
Constant	-0.24	1.56	0.02	0.876	0.78	

BMI = body mass index; β = estimates of the model parameters; SE = standard error; Wald = Wald test; p = p value; OR = odds ratio; CI = confidence interval.

Figure 2 shows the ROC curves for effects of age and years of education, which were used to establish values that maximize the sensitivity and specificity for sensory extinction detected by the FHT. For age, sensitivity and specificity of 68.4% and 72.3%, respectively, at 41.5 years of age produced an area under the curve of 0.78 (95% CI = 0.70–0.85; $p < 0.001$; Figure 2a). For years of education, sensitivity and specificity of 68.4% and 69.6%, respectively, were associated with 10.5 years and generated an area under the curve of 0.77 (95% CI; 0.68–0.85; $p < 0.001$; Figure 2b).

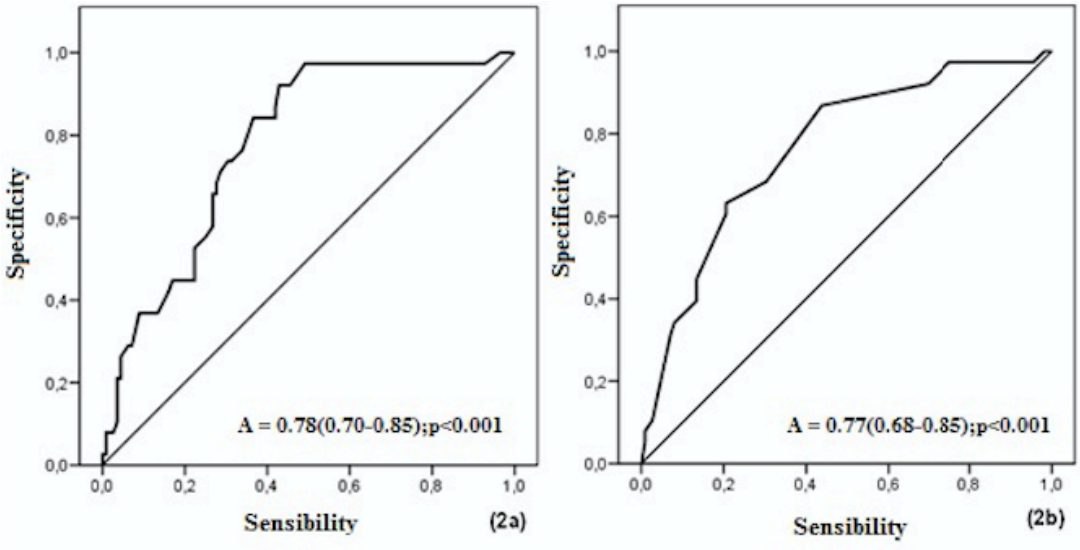

Figure 2 - Receiver operating characteristics (ROC) curves for age (2a) and years of education (2b), in order to determine the values that maximize the sensitivity and specificity of sensory extinction in the face-hand test (FHT).

Discussion

The present study accomplished standardization of the FHT in a typical population without neurological disorders and demonstrated low variability for <8 touch stimuli, with the highest frequency of stimulation between 8 and 10. The initial normative study suggests that no stimuli should be neglected, that the most common error resulted from sensory extinction by the stimulus, and that responses are less accurate in patients with organic psychological syndromes and in children 3–6 years of age with face dominance [1].

We found associations between sensory extinction and increasing age, as well as lower education. The number of years of education is associated with neuropsychological performance on tasks that assess various brain functions such as memory, attention, language, and executive functions. In studies on regulation or in

comparative analyses between groups, education is often the most relevant variable, followed or accompanied by age [14].

There is also a relationship between brain atrophy and age in individuals with low education, and education levels are associated with various environmental experiences that affect cognition and attention. Additional education may be associated with increased synaptic connections or cerebral vasculature, thereby increasing higher cortical functioning [15-16].

We observed that 25.3% of participants had sensory extinction during double stimulation of the face and hand. Under the original classification system, the FHT is divided into 4 distinct groups: (A) individuals who detect all applied stimuli, (B) individuals who detect sensory stimuli only in the face, (C) individuals who detect 2 simultaneous sensory stimuli in the face, (D) individuals who detect sensory stimuli only in the hands. The previous results have demonstrated that most errors were in relation to extinction in the face [5]. In a study that found an association between EEG activity and sensory stimulation of the median or tibial nerves, EEG recordings were as predicted in the median nerve in 75% of patients, demonstrating cortical dominance of the upper limb functions for sensory stimulation; therefore, the observed results on the FHT have a neurophysiological basis [8].

Another potential application of the FHT is for evaluation of the attention network, comprising the right perisylvian region (posterior parietal lobe, superior temporal cortex, as well as middle and prefrontal cortex). The FHT may be used to test errors that influence this network, with potential application to diagnosis of syndromes such as unilateral spatial neglect [17-20].

The FHT may also demonstrate that patients with right hemisphere USN present with both ipsilateral and contralateral sensory deficits, whereas patients with left hemisphere damage would have deficits elicited by the FHT only the right side, indicating right hemisphere dominance for attention and somatosensory integration [21-23].

Limitations of the present study include that we recruited participants through a single research center, and we also did not compare the findings with findings from participants with psychological or organic diseases. However, we demonstrated normal score ranges and outlined benchmarks for their application to clinical practice. Another limitation relates to the intensity of the stimulus applied, as stimulus intensity can directly interfere with sensation. Additionally, given that factors such as nociceptive processes, respiratory discomfort, or other sensations may interfere with stimulus perception, we conducted the tests in a controlled stimulation room with minimal external environmental stimuli.

In conclusion, normal responses on the FHT present patterns of simultaneous stimulation with scores between 8 and 10 in a Brazilian population. Additionally, sensory extinction is associated with increased age, with a cutoff point of 41 years. Sensory extinction is also associated with fewer than 5 years of education, with a cutoff point of 10.5 years.

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Artigo científico 2

Standardization of unilateral spatial neglect tests in a Brazilian multicultural population

Short title: Standardization of USN tests in Brazil

Gustavo José Luvizutto[1]; Marcelo Ortolani Fogaroli[2]; Rodolfo Theotonio[2]; Tamiris Aparecida Monteiro[1], Hélio Rubens de Carvalho Nunes[3]; Luiz Antônio de Lima Resende[4]; Rodrigo Bazan[4].

1 – Doutorando em Bases Gerais da Cirurgia; 2 – Aluno de graduação do curso de Medicina; 3 – Estatístico da Faculdade de Medicina de Botucatu; 4 – Docente do Departamento de Neurologia, Psicologia e Psiquiatria. Universidade Estadual Paulista – UNESP – Faculdade de Medicina de Botucatu

Corresponding author:
M.Sc. Gustavo José Luvizutto
Departamento of Neurology, Psychology and Psychiatry
Univ. Estadual Paulista – UNESP – Botucatu Medical School
CEP: 18618-970 Botucatu-SP-Brasil
E-mail: gluvizutto@fmb.unesp.br

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Abstract

Objective: the aim was to standardize USN tests in a Brazilian population and relate the results with sociodemographic variables. **Method**: This is a cross-sectional study of 150 individuals with no neurological history. The sociodemographic variables were: age, sex, race, body mass index, and education. We used the line cancellation test (LCT), star cancellation test (SCT), and line bisection test (LBT) to standardize USN testing. The odds ratios (OR) for omissions in LCT and SCT were considered in relation to sociodemographic variables. The ROC curve was used to find the relationship between LCT and SCT with age. The association between LBT and sociodemographic variables was performed by Mann-Whitney and Spearman correlation considering significant if $p < 0.05$. **Results**: In LCT, 143 (95.3%) subjects had default level 0 and the occurrence of failure above 0 was significantly associated with ageing (OR=1.1[1.02-1.2];p=0.012) with a cutoff age of 49.5 years. In SCT, 145 (96.6%) patients had failure below 2 and the occurrence of failure above 2 was significantly associated with ageing (OR=1.07[1.03-1.11];p<0.001) with a cutoff age of 45.5 years. In LBT, deviations were lower with the highest education levels (r=0.20;p=0.015) and the observed median deviation from the center was 6.2(5.8-6.6)mm. **Conclusions**: the appropriate cutoff point in cancellation tests should be >0 for LCT and >2 for the SCT to consider USN in a Brazilian population, and the failure rate increases with ageing. Higher education levels correspond to lower midline deviation in LBT, and the median value used to consider USN should be above 6.6 mm.

Keywords: Unilateral spatial neglect; standardization; diagnostic tests.

Background

Unilateral spatial neglect (USN) is characterized by the inability of the patient to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain in the absence of motor or sensory deficits (Plummer, Morris, & Dunai, 2003; Tanaka, Ifukube, Sugihara, & Izumi, 2010). Often, USN is associated with lesions in the right hemisphere, particularly in the posterior parietal lobe (Halligan & Marshall, 2001; de Haan, Karnath, & Driver, 2012; Kerkhoff, 2001). It has also been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers, all of which predispose patients to falls and to semipermanent or permanent wheelchair use. These outcomes can in turn reduce the quality of life of patients with USN compared to stroke patients who do not have USN (Chen, Hreha, Fortis, Goedert, & Barrett, 2012; Gottesman et al., 2008; Harvey et al., 2010).

Unilateral spatial neglect is commonly assessed using either the line bisection (Schenkenberg, Bradford, & Ajax, 1980) or the target cancellation task (Halligan, Burn, Marshall, & Wade, 1992) in the clinic. USN tests were first proposed by Albert in 1973. During the test, the individual was requested to find and cancel random lines on a sheet of paper (Line Cancellation Test). The author concluded that the test is sensitive in detecting spatial changes in both brain hemispheres (Albert, 1973).

Performance on visuospatial tasks change based on the presence of distractor symbols. Halligan et al. (1992) thus proposed the star cancellation test (SCT), which uses non-target distractor stimuli that should be ignored by the individual during the test. The authors of this study concluded that the SCT test may be a more sensitive method for USN detection. Another test for the detection of USN is the line

bisection test (LBT), during which the subject is asked to find the midpoint of a horizontal line displayed on a sheet of paper. Schenkenberg et al. (1980) concluded that the LBT is sensitive in detecting unilateral neglect (UN) in patients with right hemisphere lesions with an accuracy of 81%.

All tests described here were performed using standard A4 sheets of paper. Although several different tests are described here, none has been used to generate normalized data in the Brazilian population. USN is associated with lower functional performance and is a major contributor to the slowing of neurological recovery. We thus examined the effects of demographic variables that may predict performance on USN tests. We obtained normative data in a healthy sample, which can then be used for the diagnosis of USN in patients with right hemisphere lesions in the clinic.

Patients and Methods

This cross-sectional study included graduate students, professionals and patients at the Clinics Hospital of Botucatu (UNESP) between March 2013 to July 2015. The persons were recruited through direct contact with the researcher followed by invitation to participate in the study.

The study was approved by the Ethics in Human Research Committee, as recorded in opinion 122/2011. The study participants had no history of neurological disorder (including but not limited to head trauma with loss of consciousness, multiple sclerosis, Parkinson's disease, cerebrovascular disease, epilepsy, meningitis, mental retardation, or anoxic injury that may affect brain functioning); no history of substance abuse or dependence (as assessed by history, record review, and serum toxicology); no use of medications with central nervous system effects;

and no history of learning disability, and no visual deficits. The participants were aware of the tests they performed, were hemodynamically stable, and had scores above 24 on the Mini-Mental State Examination (MMSE) (Almeida, 1998). They had no signs of discomfort at the time of evaluation.

Variables

We obtained and analyzed information on the following socio-demographic variables from the study participants by direct interview: age (years), sex (male or female), race (white or non-white), body mass index (BMI, kg/m^2), and years of education.

We standardized USN tests using the cancellation and bisection tasks following the procedures described below:

a) Cancellation Tests

- Line cancellation test (LCT): subjects were given a single sheet of paper containing 40 lines with a length of approximately 2.5 cm. The lines were drawn in 6 different orientations. The sheet contained 18 lines on each side (right or left) and 4 at midline (Figure 1). The examiner asked the following question from the subject once the test was finished: "Have all the lines been crossed?". The test was terminated when the answer was affirmative. The participant's score was the proportion of lines omitted relative to the total number of lines (Albert, 1973).

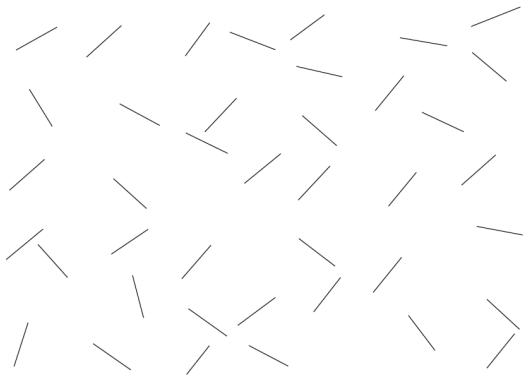

Figure 1. Line cancellation test

- SCT: the test was carried out using a sheet containing 52 big stars, 13 letters, and 10 words randomly interspersed with 56 smaller stars (Figure 2). The individual was asked to find and delete (cancel) only the smaller stars after the examiner demonstrated the procedure by striking out two stars in the center of the sheet. The number of omitted stars was subtracted from the total number of stars presented in the test (Halligan, Burn, Marshall, & Wade, 1992).

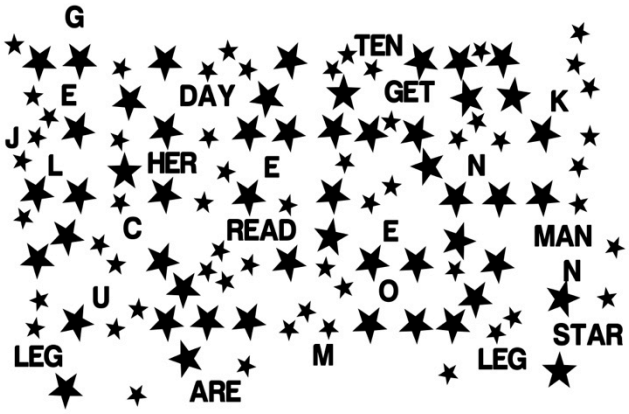

Figure 2: Star cancellation test

b) Bisection test

- LBT: The subjects were presented with 18 transverse lines arranged in six rows of three columns (right, center, and left) with a line at the upper end of the sheet. The lines are 100 mm, 120 mm, 140 mm, 150 mm, 160 mm, 180 mm, or 200 mm wide and are organized in different positions (Figure 3). Patients were requested to mark the middle of each line. After the test was completed, we determined the value in millimeters of the scratched portion in relation to the rest of the line using the formula: % = left half - middle x 100, divided by half for each line, as described by Schenkenberg et al. (Schenkenberg, Bradford, & Ajax, 1980). In this study, we also analyze the absolute value of the deviation (VAD), which is obtained by adding all of the deviations and dividing the resulting value by the total number of test lines.

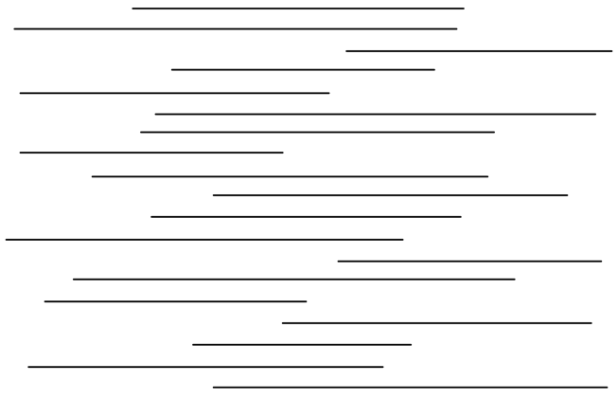

Figure 3: Line bisection test

In all USN tests, the examiner used A3 paper and put it in front of the patient so that there was a distance of 50 cm from the glabella to the center of the paper.

Statistical analyses

Since we are using a sample representative of the target population, our sampling is considered to be intentional and non-probabilistic. We needed a minimum of 150 subjects to obtain a maximum sampling error of 7.5% and a confidence level of 95%. We estimated odds ratios for the numbers of omissions in the LCT and the SCT based on sociodemographic variables. We used an ROC curve study the relationship between performance on these tests and age. The association between deviation from the center in the LBT and sociodemographic variables was investigated using the Mann-Whitney test and Spearman correlation. All associations and areas under the ROC curve were treated as significant if $p < 0.05$. Analyses were performed using SPSS software (version 21.0, SPSS, Chicago, IL, USA).

Results

We evaluated and screened 250 individuals, but only 150 met the inclusion criteria for the study (Figure 4), and sociodemographic characteristics and performance of subjects in USN testing are presented in Table 1.

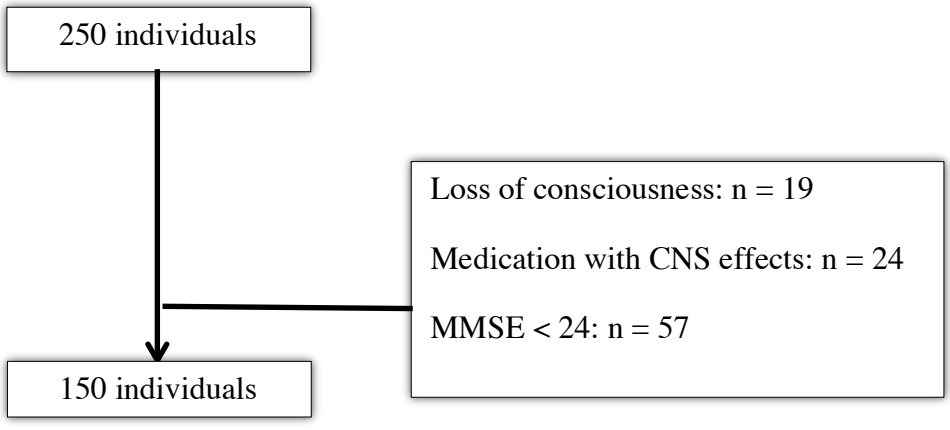

Figure 4 - Screening of patients excluded for the study

Table 1 – Sociodemographic characteristics and performance of subjects in USN testing (n=150).

Variable	Summary
Sociodemographic variables	
Sex	
Male : Female	76 (51%) : 74 (49%)
Age (years) [(1)]	31.5 (18 – 87)
BMI (Kg/m^2) [(1)]	22.8 (11.7 – 35.9)
Race	
Caucasian : Non-Caucasian	112 (75%) : 38 (25%)
Years of Education [(1)]	11 (6 – 16)
USN performance	
Line Cancellation Test	
Total number of omissions	
0	143 (95.3%)
1	6 (4.0%)
4	1 (0.7%)
Omission (Total of lines not canceled > 0)	7 (4.7%)
Star Cancellation Test	
Total number of omissions	
0	123 (82.0%)
1	16 (10.6%)
2	6 (4.0%)
> 2	5 (3.4%)
Omission (Total of lines not canceled > 0)	27 (18.0%)
Line Bisection Test	
Center deviation (AVD in mm) [(1)]	6.2 (2.1 – 6.6)

Summary in median (min-max);

AVD = absolute value of the deviation

Table 2 shows that the chance of failure in the LCT was significantly associated with age (OR = 1.1 (1.02 to 1.2); p = 0.012). The ROC curve identified 49.5 years as the cutoff age (sensitivity = 71% and specificity = 74%) (Figure 5).

Table 2 – Estimated odds ratios for the numbers of omissions in the LCT based on sociodemographic variables

Variable	**OR (95% CI)**	**p**
Sex (male)	7.9 (0.6 – 99.5)	0.109
Age (years)	1.1 (1.02 – 1.2)	0.012
BMI (km/m^2)	0.9 (0.7 – 1.1)	0.543
Race (non-white)	3.4 (0.4 – 27.6)	0.256
Years of education	1.0 (0.7 – 1.4)	0.889

BMI = body mass index; OR = odds ratio; CI = confidence interval

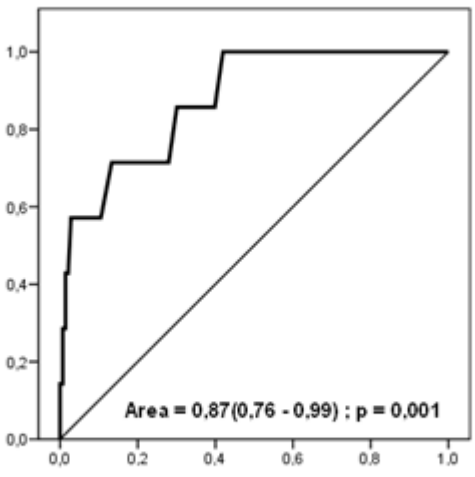

Figure 5. ROC curve relating age to the number of omissions in the LCT

Table 3 shows that the chance of failure in the SCT was significantly associated with increasing age (OR = 1.07 (1.03 to 1.11), p < 0.001). The ROC curve identified 45.5 years old as the cutoff age (sensitivity = 73% and specificity = 78%) (Figure 6).

Table 3 – Estimated odds ratios for the number of omissions in the SCT based on sociodemographic variables

Variable	**OR (95% CI)**	**p**
Sex (male)	1.01 (0.34 – 2.00)	0.983
Age (years)	1.07 (1.03 – 1.11)	0.000
BMI (kg/m^2)	0.88 (0.78 – 1.05)	0.062
Race (non-white)	2.10 (0.67 – 6.54)	0.203
Years of education	0.88 (0.75 – 1.02)	0.094

BMI = body mass index; OR = odds ratio; CI = confidence interval

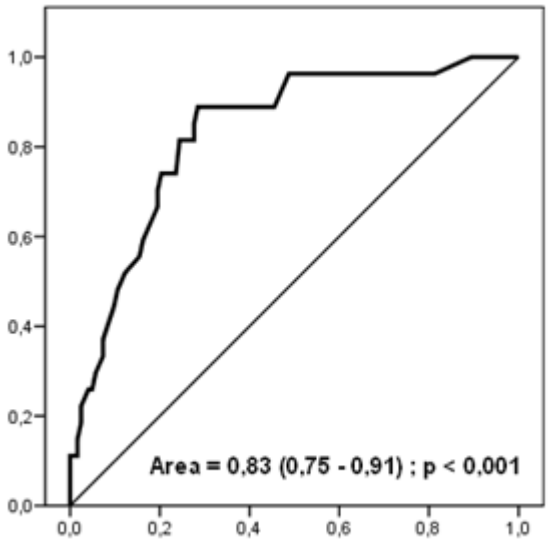

Figure 6. ROC curve relating age to the number of omissions in the SCT

Table 4 and Figure 7d show that deviation from the center was lower among subjects with the highest education levels (r = 0.20; p = 0.015). We also observe a greater variance in women compared to men. Specifically, the kurtosis was significantly higher among women (k = 13.6) compared to men (k = 3.3).

Table 4 - Association between deviations from the center obtained in the LBT and sociodemographic variables.

Variable	**Summary**	**p**
Age (years)	r = 0.16	0.052
BMI (kg/m^2)	r = 0.05	0.572
Years of Education	r = -0.20	0.015
Sex [(1)]		
Female (n = 76)	6.3 (3.0 – 38.3)	0.955
Male (n = 74)	6.1 (2.1 – 23.8)	
Race [(1)]		
Non-white (n = 112)	6.2 (3.0 – 27.0)	0.506
White (n = 38)	6.8 (2.1 – 38.3)	

(1) Median (min-max)

(2) Spearman correlation

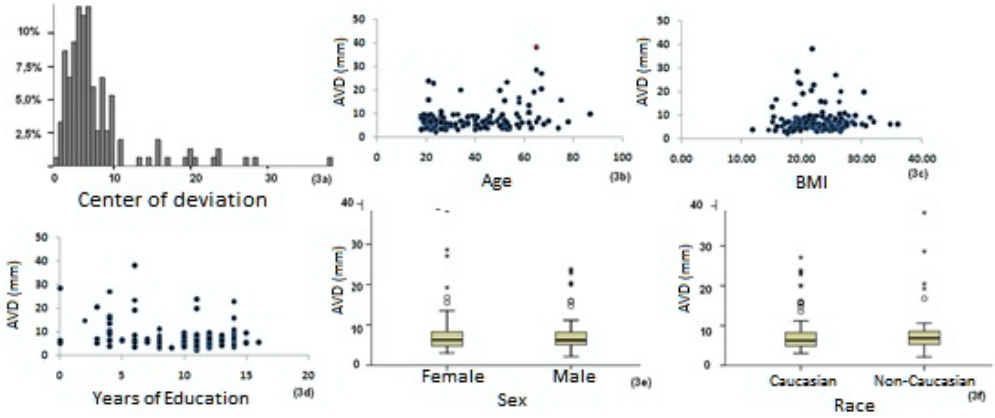

Figure 7. Histogram of the deviations from the center obtained in the LBT (7a). Scatterplot of the offset from the center in relation to age (7b), BMI (7c), and years of education (7d). Boxplot of the deviations values in relation to sex (7e) and race (7f).

In the LBT, we observed median deviations from the center of 6.2 and a range of 5.8 to 6.6 mm using a 95% confidence interval.

Discussion

This study aims to standardize USN tests in a Brazilian population without neurological disorders. The subjects in our study demonstrated a higher frequency of omissions in the SCT compared with the LCT. Initial normative studies in other populations suggest that none of the LCT lines should be omitted, and the authors found that the most common error in this test was the omission of the lower left quadrant in patients with right posterior parietal lesions. Some authors believe that the clearing of up of 51 stars or the omission of less than 3 stars should be used as a benchmark in the SCT. This test is influenced by distractors that hinder attention and is indicated for diagnosing mild cases of USN (Wilson, Cockburn, & Halligan, 1987; Azouvi et al., 1996).

Cancellation tasks that employ a random arrangement of complex symbols are more difficult and subsequently more sensitive in detecting neglect than similar tests that are arranged in organized rows and columns. Cancellation tests are most frequently used to detect USN and are more sensitive for this purpose (Mesulam, 2000; Ferber & Karnath, 2001). The line bisection tasks involve marking the midpoint of one or more horizontal lines. Patients with left neglect tend to make errors in the area right of the true center. The average deviation from the center in the LBT in this study was 6.2 (5.8 to 6.6) mm. A greater deviation indicates USN. Previous studies have shown that this test has a lower sensitivity compared to cancellation tests. It is thus used as a complementary test in USN diagnosis. A battery of tests is therefore more sensitive to the presence of neglect than one single task (Gainotti, Messerli, & Tissot, 1972; Lindell et al., 2007).

These two USN tests activate the same underlying cortical processes. The patients who have problems on the line bisection task have more posterior lesions (occipitotemporal extrastriate areas). Verdon et al. (2010) found that lesions in the right inferior parietal lobule were more associated with problems on the line bisection task and lesions in the right dorsolateral prefrontal cortex were more associated with problems on the cancellations task. However, in a recently study, the authors concluded that USN is a disorder usually associated with right parietal damage to the angular gyrus and can be tested in the clinical setting with both cancellation and line bisection tasks (Zihl, Sämann, Schenk, Schuett, & Dauner, 2009; Baier, Mueller, Fechir, & Dieterich, 2010; Molenberghs & Sale, 2011; Verdon & Vuilleumier, 2010).

The main factor that affects performance in the lines and stars cancellation tests is age. The older the patient is, the worse their performance in the tests is likely to be. Several studies have reported factors that may affect performance on USN tests, and the age is a well-discussed factor in the literature. The authors aimed to correlate age with performance in USN tests in a cross-sectional study of ischemic stroke patients in the acute phase at Johns Hopkins Hospital. They found that USN occurs more frequently in elderly individuals regardless of the size of injury or the severity of neurological symptoms. One of the proposed hypotheses is that older patients have greater attention deficits and difficulty in neural adaptations following central nervous system injury. In addition, total brain volume tends to decrease with age, which may lead to cognitive impairment (Bailey, Riddoch, & Crome, 2000; Agrell, Dehlin, & Dahlgren, 1997).

Azouvi et al. (2006) observed that in healthy individuals, the higher age associated with lower educational levels can lead to more errors in USN tests. The level of education affected the numbers of omissions on left vs. the right. Specifically, subjects with higher education levels had more mistakes on the right and subjects with less schooling made more mistakes on the left. There is a possibility that these differences are due to the fact that school subjects are taught to write from left to right, making it more likely that individuals with high levels of education have reduced omissions on the left side (Feinberg, Haber, & Stacy, 1990; Azouvi et al., 2006; Bowers & Heilman, 1980).

In the line bisection test, the main confounding factor related to the absolute value of deviation from the center was educational level. Azouvi et al. (2006) reported that factors such as education, age, and dominant hand should be taken into account in the diagnosis of USN. In a meta-analysis of the LBT, the authors concluded that young people make mistakes to the left, while older individuals tend to err to the right of center. There is inconsistency in reports on the influence of sex on deviation from the midline. Different stages of the menstrual cycle in a woman have modulating effects on the location of the sagittal-median plane, but there are no significant reports on gender differences (Silva, Cardoso, & Fonseca, 2012; Jewell & McCourt, 2000; McCourt, Mark, Radonovich, Willison, & Freeman, 1997).

The main limitations of the study relate to the testing of individuals within a single center. We also did not compare our results to those obtained other existing assays in the literature, such as the Behaviour Inattention Test, which uses 9 tests and is the gold standard for the detection of USN. Our aim was to establish objectives and practical and rapidly implemented tests that are useful in clinical

practice to facilitate the timely diagnosis of USN in acute neurological conditions arising from stroke, tumors, or trauma.

Based on our results, we can conclude that the cutoff points for USN diagnosis in the cancellation tests are more than 0 in the LCT and more than 2 in the SCT. We also found that the numbers of omissions in these tests are greater with increasing age. In the LBT, the absolute deviation from the median used as the maximum confidence interval to consider USN should be above 6.6 mm. In this test, the deviation from the median was higher with less education.

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Artigo científico 3

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Low haemoglobin levels increase unilateral spatial neglect in acute phase of stroke.

Running title: Low haemoglobin levels and neglect in stroke.

Gustavo José Luvizutto[1], Tamiris Aparecida Monteiro[1], Gabriel Pereira Braga[2], Silméia Garcia Zanati Bazan[3], Luiz Antônio de Lima Resende[4], Rodrigo Bazan[5].

1 – Physiotherapist in Rehabilitation Department; 2 – Assistant Doctor in Stroke Unit; 3 – Professor Doctor of the Clinical Medicine Department; 4 – Professor of Neurology; 5 - Assistant Professor of Neurology. Botucatu School of Medicine Neurology Service, University Estadual Paulista Júlio de Mesquita Filho, São Paulo, Brazil.

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Author for correspondence:

Gustavo José Luvizutto.

Botucatu School of Medicine Neurology Service. District of Rubião Júnior, no number, Botucatu, SP 18618-970, Brazil.

Email: gluvizutto@fmb.unesp.br.

Telephone: +55 (14) 38116049

Abstract

Objective: The objective of this study was to evaluate the relationship between unilateral spatial neglect (USN) and Haemoglobin (Hb) level in acute phase of stroke. **Methods:** Cross-sectional study was performed after right hemisphere ischemic stroke. Independent variable: Hb level (mg/dL); Outcome: USN; Potential confounding factors: Age, National Institutes of Health Stroke Scale (NIHSS)**,** and glycaemia (mg/dL); Characterization variables were obtained from electronic medical records, Hb, mean corpuscular volume (MCV) and glycaemia by laboratory exams, and USN by cancellation and bisection tasks. The relationship between Hb and USN was assessed by Spearman correlation and linear regression model. **Results:** 40 individuals were evaluated; it was observed that the higher the Hb level, the better the USN test performance, with negative correlation between them. There was no significant correlation between VCM level and USN performance. **Conclusion:** a lower Hb level worsens performance on the USN tests in acute phase of stroke.

Keywords: Stroke, perceptual disorders, haemoglobins.

Introduction

Low Haemoglobin (Hb) is a common condition in the elderly population and is associated with increased mortality and worsening functional performance, independent of cause (1,2). Many people in acute phase of stroke present low haematocrit levels, which are associated with higher mortality and worsening long-term results; but the importance of low haemoglobin in stroke clinical presentation has not been clearly established (3-7).

Currently, interest is growing in the effects of Hb concentration on cognitive decline. Critical Hb levels, high or low, have been associated with worsening cognitive performance in the elderly, but their mechanisms are poorly understood, with the hypothesis on the presence of ischemia, hypoxia or central nervous system oxidative stress (8,9). Based on the results of several studies, there is speculation that reduced aerobic capacity and cerebral vascular dysfunction could also contribute to cognitive decline, and that normal haematocrit levels reduce the transfer velocity within cerebral capillaries, improve oxygen extraction by cerebral tissue, and have a positive effect on cortex functions (10,11).

In the present study, we evaluated the relationship between Unilateral Spatial Neglect (USN) by means of cognitive with perception tests, haemoglobin (Hb) and mean corpuscular volume (MCV) level in acute phase of stroke. The study hypothesizes that low haemoglobin values are associated with poorer performance on tests of unilateral spatial neglect, being that anaemia may influence the performance of activities that place high demands on the perceptual system, increasing errors on tests of cancelling and bisection of lines.

Methods

This was a cross-sectional study of ischemic stroke patients of both sexes with right hemisphere lesion – confirmed by cranial computerized tomography (CT) or magnetic resonance imaging (MRI) – of anterior circulation origin, with defined aetiology, in the acute ictus phase (in the first 48 hours after ictus), under conservative treatment and admitted to the Stroke Unit at Botucatu Medical School University Hospital - UNESP. Patients were excluded if they presented at least one of the following conditions: haemorrhagic or posterior circulation stroke, left hemisphere ischemia, previous Modified Rankin Scale (mRS) ≥1, pre-existing dementia, aphasia, visual deficits, other neurological diseases, as were patients who had undergone surgical procedures, thrombolytic treatment, blood transfusion or presented a history of alcohol abuse, hypothyroidism, chronic obstructive pulmonary disease, liver disease, kidney failure or marked leukocytosis on laboratory exams.

Procedures

Individuals were evaluated by three USN exams, two for cancellation and one for bisection: a) Cancellations tests: Line Cancellation Task (LCT), scored by lines cancelled in relation to a total number of 40 lines on a sheet of paper (12); Star Cancellation Task (SCT), scored by 52 stars cancelled in between distractors (13); b) Bisection test: Line Bisection Task (LBT), based on absolute value of deviation to the right in relation to middle of line marked by patient on each line of the sheet (14). In all USN tests the examiner placed the test sheet in front of the patient with the centre of the sheet 50 cm from the glabella, the objective being to measure USN severity.

Hb level (in g/dL), MCV (in fL) and other laboratory exams were performed through a standard protocol by nurses trained in vein puncture to collect blood samples using a sterile technique. The blood sample was collected in a 10ml tube on the same day that USN tests were applied, and transferred to the clinical laboratory for automated processing. After analysis of the exams, anaemia was defined as Hb <12 g/dL in women and Hb <13 g/dL in men (15). The individuals classified as anaemic were divided into microcytic (MCV < 80 fL), normocytic (MCV = 80-100) or macrocytic (MCV > 100 fL) (16).

The National Institutes of Health Stroke Scale (NIHSS) and mRS were applied at same time as the USN tests to define neurological deficit severity and functional independence; demographic and anthropometric data were obtained from electronic hospital records on the same USN test date.

Statistical Analysis

The relationship between potential confounding factors (age, neurological deficit severity, functional independence and glycaemia) and USN was assessed by the Spearman correlation and Mann-Whitney test, whereas the relationship between Hb level, MCV and NSU was explored by the Spearman correlation and linear regression model.

Ethics

The study was approved by Human Research Ethics Committee of UNESP/Botucatu. All individuals or relatives consented to participate in the study.

Results

Between June and December 2012, a total of 40 patients were included in present data. The general demographic data and baseline characteristics are displayed in Table 1, and the potential confounders are presented in Table 2.

Table 1. Sample Description

Variables*	**Values**
Age, y	66 (34 - 87)
Sex, male	25 (62.5%)
Race, White	23 (57.5%)
Weight (Kg)	72.4 (43.8 - 99.0)
Height (m)	1.69 (1.50 - 1.78)
BMI (Kg/m^2)	23.5 (16.4 - 38.2)
NIHSS	5 (3 - 12)
mRS	3 (0 - 4)
Laboratory Exams	
Glycaemia, mg/dL	101.5 (69.0 - 237.0)
Urea, mg/dL	20 (12.0 - 37.0)
Creatinine, mg/dL	0.8 (0.5 – 1.2)
Haemoglobin, mg/dL	14.1 (8.6 - 16.9)
MCV, fl	91.4 (66.9 – 116.0)
USN exams	
Score on LCT	15.5 (0 - 36)
Score on SCT	33.5 (4 - 51)
Score on LBT	
Deviation from centre line	64.4 (14.3 - 90.9)

BMI indicates Body Mass Index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MCV, mean corpuscular volume; USN – Unilateral Spatial Neglect.

*Numbers are mean (SD) or counts (percentages).

Table 2 – Relationship between age, neurological deficit and glycaemia as potential confounders for NSU.

Variable*		LCT	SCT	LBT
Age, y	r	0.20	0.18	0.19
	p(1)	0.339	0.391	0.375
NIHSS	r	-0.19	-0.22	-0.32
	p(1)	0.402	0.332	0.155
mRS	r	0.32	0.35	0.30
	p(1)	0.134	0.090	0.155
Glycaemia (mg/dL)	r	-0.07	-0.11	0.06

NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin Scale LCT, Line Cancellation Test; SCT: Star Cancellation Test; LBT: Line Bisection Test.

*Numbers are mean (SD) or counts (percentages).

(1) p – value associated with Spearman's correlation

r : estimate of Spearman's correlation

Figures 1 and 2 show the negative correlation between Hb and LCT (r= -0.35; p = 0.02) and SCT (r=- 0.27; p=0.09). The relationship between Hb level and USN evaluated by LBT (Figure 3) reveals a negative correlation with absolute deviation value (r=-0.27; p=0.11), number of deviations to the right (r = -0.36; p=0.03), mean percentage of deviations to the right (r= - 0.15; p = 0.35), and mean percentage of deviations to the left (r= - 0.15; p=0.35). These associations were independent of age, neurological deficit, incapacity level or blood glucose.

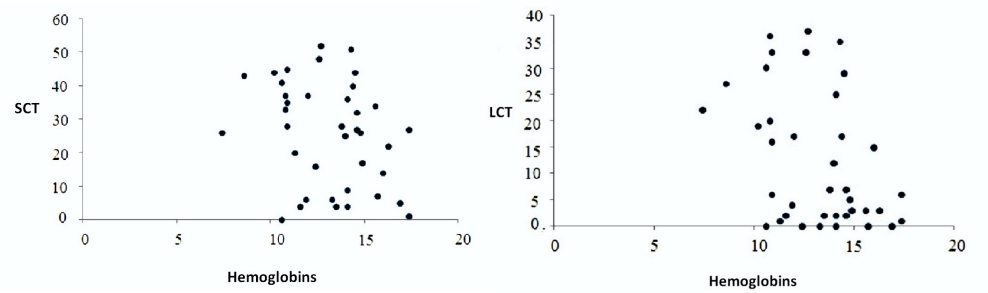

Figure 1 – (A) Correlation between Hb level and LCT; (B) Correlation between Hb level and SCT.

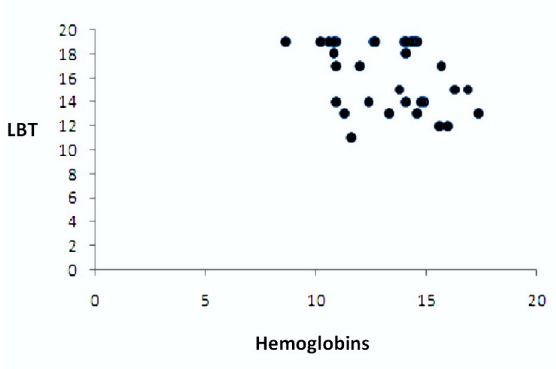

Figure 3 - Correlation between Hb level and LBT.

In the linear regression model, it was demonstrated that the higher the Hb level, the fewer lines and stars were cancelled, with an average of around three lines (β = -3.1) and three stars (β = -3.2) left un-cancelled for each unit increase in Hb (tables 3 and 4).

Table 3. Adjusted linear regression models to explain the number of lines cancelled in LCT as a function of haemoglobin.

	β	Standard error	p	CI (β: 95%)
Constant	56.2	15.1	0.001	(24.9 - 87.4)
Haemoglobin (mg/dL)	-3.1	1.1	0.010	(-5.4 - -0.8)

Residual analysis: p=0.591 (Shapiro-Wilk);

Table 4. Adjusted linear regression models to explain the number of stars cancelled in SCT as a function of haemoglobin.

	β	Standard error	p	CI (β: 95%)
Constant	71.3	17.3	0.001	(35.6 - 107.0)
Haemoglobin (mg/dL)	-3.2	1.3	0.018	(-5.9 - -0.6)

Residual analysis: p=0.829 (Shapiro-Wilk);

Table 5 demonstrates an absence of a statistically significant correlation between the VCM level and the degree of unilateral spatial neglect by means of LCT (r=-0.089; p = 0.616), SCT (r = 0.001; p = 0.997) and LBT (r=0.063; p=0.723).

Table 5. Correlation between MCV and scores of tests for unilateral spatial neglect.

		LCT	SCT	LBT
MCV	r	-0.089	0.001	0.063
	p	0.616	0.997	0.723

MCV, mean corpuscular volume; LCT, Line Cancellation Task; SCT, Star Cancellation Task; LBT, Line Bisection Task.

Discussion

In our study we found a relationship between Hb level and the presence or absence of USN, and that age, severity (NIHSS), incapacity (mRS) and glycaemia are not confounding factors in the final NSU result. This result is consistent with a physiological mechanism, as the much lower haemoglobin levels reduce cerebral oxygen, and thus worsen USN in the acute phase by establishing a larger area of ischemic penumbra and delimiting the lesion area much earlier (8). Studies have shown that erythropoietin levels have neuroprotective properties that can regulate

some caspases, and therefore prevent neuron death, which is important for reducing the ischemic area and improving neurological deficits (17).

In the first study where this association was found, a “U” pattern was suggested in the correlation between Hb and USN, where the critical levels, high or low, had determined worse USN (3). Our results highlight the drop in Hb in the acute phase as a factor of severity and cognitive decline through the USN tests. In an observational study (6), the authors reported that anaemia in stroke acute phase results in worse functional performance in the first three months and that this association is associated with increased penumbra area and cerebral infarct (7). An association was demonstrated between the Hb level and the all USN tests, with poor correlation with LBT, because this test has a relatively poor sensitivity for detecting USN. The other tests applied (LCT and SCT) are generally the most sensitive in perceptual disorders (18,19). This information is important because the association of Hb with LBT can be influenced by the sensitivity of the test to detect USN.

The results of MCV did not show a statistical correlation with performance on NSU tests. In a descriptive analysis of our data, the patients with macrocytic anaemia presented worse performance on tests of cancelling of lines and stars. This datum has been little explored in the literature, where worsening has been reported only in patients with a deficit in the spatial attention network and cognitive decline in patients with macrocytic anaemia (20-21). This finding presents little consistency with our study in which only 4 patients presented macrocytic anaemia.

The limitations of the present study were small sample size, the fact that individuals could have received electrolyte replacement therapy, and other confounding factors, such as tobacco smoking. However, our results not onlyconsistently demonstrate a negative association between Hb and USN severity, bu also demonstrate the importance of the research objective of establishing ideal haemoglobin levels in the

acute phase to avoid cognitive and perceptual decline and improve functional prognosis. We recommend that longitudinal follow-up studies be performed to observe long-term functional outcome and verify whether USN is reduced with haemoglobin replacement. To conclude, the lower the haemoglobin level, the worse the development in USN cancellation tests in acute phase of stroke.

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Artigo científico 4

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Pharmacological interventions for unilateral spatial neglect after stroke

Gustavo José Luvizutto[1], Gabriel Pereira Braga[2], Silméia Garcia Zanati Bazan[3], Luiz Antônio de Lima Resende[4], Rodrigo Bazan[5], Regina El Dib

1 – Physiotherapist in Rehabilitation Department; 2 – Assistant Doctor in Stroke Unit; 3 – Professor Doctor of the Clinical Medicine Department; 4 – Professor of Neurology; 5 - Assistant Professor of Neurology. Botucatu School of Medicine Neurology Service, University Estadual Paulista Júlio de Mesquita Filho, São Paulo, Brazil.

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Author for correspondence:

Gustavo José Luvizutto.

Botucatu School of Medicine Neurology Service. District of Rubião Júnior, no number, Botucatu, SP 18618-970, Brazil.

Email: gluvizutto@fmb.unesp.br.

Telephone: +55 (14) 38116049

Abstract

Background: Unilateral spatial neglect (USN) is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain and has been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers. Pharmacological interventions (medical interventions only, use of drugs to improve the health condition), such as dopamine and noradrenergic agonists or pro-cholinergic treatment, have been used in people affected by USN after stroke, and effects of these treatments could provide new insights for health professionals and policy makers. **Objectives**: To evaluate the effectiveness and safety of pharmacological interventions for USN after stroke. **Search methods:** We searched the Cochrane Stroke Group Trials Register (April 2015), the Cochrane Central Register of Controlled Trials (April 2015), MEDLINE (1946 to April 2015), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to April 2015), EMBASE (1980 to April 2015), PsycINFO (1806 to April 2015) and Latin American Caribbean Health Sciences Literature (LILACS) (1982 to April 2015). We also searched trials and research registers, screened reference lists, and contacted study authors and pharmaceutical companies (April 2015). **Selection criteria:** We included randomized controlled trials (RCTs) and quasi-randomized controlled trials (quasi-RCTs) of pharmacological interventions for USN after stroke. **Data collection and analysis:** Two review authors independently assessed risk of bias in the included studies and extracted data. **Main results:** We included in the review two studies with a total of 30 randomly assigned participants. We rated the quality of the evidence as very low as the result of study limitations, small numbers of events, and small sample sizes, with imprecision in the confidence interval (CI). We were not able to perform meta-analysis because of heterogeneity related to the different interventions evaluated between included studies. Very low-quality evidence from one trial (20 participants) comparing effects of rivastigmine plus rehabilitation versus rehabilitation on overall USN at discharge showed the following: Barrage (mean difference (MD) 0.30, 95% confidence interval (CI) -0.18 to 0.78); Letter Cancellation (MD 10.60, 95% CI 2.07 to 19.13); Sentence Reading (MD 0.20, 95% CI -0.69 to 1.09), and the Wundt-Jastrow Area Illusion Test (MD -4.40, 95% CI -8.28 to -0.52); no statistical significance was observed for the same outcomes at 30 days' follow-up.

In another trial (10 participants), study authors showed statistically significant reduction in omissions in the three cancellation tasks under transdermal nicotine treatment (mean number of omissions 2.93 ± 0.5) compared with both baseline (4.95 ± 0.8) and placebo (5.14 ± 0.9) (main effect of treatment condition: F (2.23) = 11.06; P value < 0.0001). One major adverse event occurred in the transdermal nicotine treatment group, and treatment was discontinued in the affected participant. None of the included trials reported data on several of the prespecified outcomes (falls, balance, depression or anxiety, poststroke fatigue, and quality of life). **Authors' conclusions:** The quality of the evidence from available RCTs was very low. The effectiveness and safety of pharmacological interventions for USN after stroke are therefore uncertain. Additional large RCTs are needed to evaluate these treatments.

Background

Various non-pharmacological rehabilitation techniques have been explored for unilateral (restricted to one side of the body) spatial neglect (USN). The aim of these techniques has been to facilitate the recovery of perception and behavior. These techniques have included right half-field eye-patching (Tsang 2009), mirror therapy (Thieme 2013), prism adaptation (Mizuno 2011), left-hand somatosensory stimulation with visual scanning training (Polanowska 2009), contralateral transcutaneous electrical nerve stimulation and optokinetic stimulation (Schröder 2008), trunk rotation (Fong 2007), repetitive transcranial magnetic stimulation (Cazzoli 2012), galvanic vestibular stimulation (Nakamura 2015), and dressing practice (Walker 2011). These studies demonstrated a positive effect on visuospatial neglect after stroke, but their results do not support use of these techniques in isolation for improvement of secondary outcomes such as performance and sensorimotor functions, activities of daily living, or quality of life (Cazzoli 2012; Turton 2010; Thieme 2013).

Most recently, pharmacological interventions, such as use of dopamine or noradrenergic agonists, have been shown to improve perception as measured by the Line Bisection task (Schenkenberg 1980) and the Line Cancellation task (Albert 1973) in people affected by USN, and they seem to represent a promising approach to treatment of patients with this condition (Bartolomeo 2012; Luauté 2006; Malhotra 2006).

Description of the condition

Stroke is the second leading cause of death worldwide and the primary cause of chronic disability in adults (Bonita 1992). In the United States, it is the fourth leading cause of death overall (Jauch 2013). Each year in the UK, 110,000 people suffer a stroke (Bray 2013), and in Asia the incidence is two to three times higher than in Europe (Hata 2013). In Brazil, stroke is the leading cause of death overall (Pontes-Neto 2008). Among people who survive a stroke, USN is the most frequent disorder for right hemisphere lesions (Gorgoraptis 2012). The incidence of USN varies widely from 10% to 82% (Chen 2012; Stone 1993; Vanier 1990).

USN is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain, when this symptom cannot be accounted for by motor or sensory deficits (Plummer 2003;Tanaka 2010). Diagnoses are made by paper-and-pen tests, for example, cancellation and bisection tests (Agrell 1997) and, in subacute or chronic stages of neglect, after stroke diagnosis is made on the basis of behavioral measures derived from assessment of functional abilities in everyday life (Azouvi 2003). USN has been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers, all of which predispose patients to the risk of falls and to semi permanent or permanent wheelchair use (Chen 2012; Gottesman 2008; Tanaka 2010), which can reduce their quality of life compared with that of other stroke patients who do not have USN (Harvey 2010). Furthermore, USN decreases a patient's work productivity, which has a socioeconomic impact, thus affecting a community's public health status (Brown 2006; Treger 2007).

Description of the intervention

Pharmacological intervention has been used in people affected by USN after stroke to enhance their performance on neglect tests and assessment of daily life functions. Some studies aiming to explain the effects of dopamine and noradrenergic agonists, which have been shown to modulate cognitive function, have shown that they most likely act via postsynaptic α2 receptors in the dorsolateral prefrontal cortex (a region of the brain responsible for working memory) (Malhotra 2006). Dopamine agonists have been shown to improve tests of visuospatial neglect such as line bisection, letter cancellation, and reading (Fleet 1987; Geminiani 1998; Hurford 1998; Mukand 2001), and to act in perceptual attentional systems and premotor components of visuospatial neglect (Mukand 2001). Noradrenergic agonists showed improvement on paper-and-pencil tasks as well as on visual exploration in participants who had a lesion that spared the dorsolateral prefrontal cortex (Malhotra 2006). Other pharmacological approaches for USN after stroke include pro-cholinergic drugs, which also work to modulate the activity of the attention system in the brain (Thiel 2005).

How the intervention might work

Dopamine is a biological amine synthesized in the hypothalamus, the basal ganglia, and many areas of the central and peripheral nervous system. Dopamine and its agonists play an important role in central nervous system regulation through stimulation of α- and β-adrenergic and dopaminergic receptors. Dopaminergic agonists, which cross the blood-brain barrier, have neurological and endocrine central effects and act directly at postsynaptic receptors within the basal ganglia, increasing the availability of dopamine in the synaptic cleft (Velasco 1998). Dopamine-selective D1 agonists are one type of pharmacological intervention that have been used for USN. Dopamine D1 receptors can have an effect on visual areas of attention and could provide a possible mechanism for facilitating spatial attention and working memory (Castner 2000; Funahashi 1994). Noradrenergic agonists have been associated with increased output from the locus coeruleus (a part of the brainstem) to both inferior parietal and frontal lobes of the cortex (the outer covering of the brain) via the thalamus (portion of the diencephalon), which may be involved in USN (Singh-Curry 2011). Cholinergic drugs work to increase levels of acetylcholine and subsequently enhance the function of neural cells; they can modulate activity in the frontoparietal attention system of the brain and working memory tasks (Thiel 2005), and may increase selective attention during spatial exploration (Witte 1997).

Why it is important to do this review

Stroke is a prevalent disease that has high morbidity and mortality worldwide; it is characterized as a serious public health problem. People who develop USN after stroke have major functional disabilities, as well as decreased rates of adherence to rehabilitation programs (Paolucci 2001; Wee 2008). Understanding the effects of a pharmacological intervention, given alone or in combination with non-pharmacological strategies for rehabilitation, could provide new insights for health professionals and policy makers.

Objectives

To evaluate the effectiveness and safety of pharmacological interventions for unilateral spatial neglect (USN) after stroke.

Methods

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi-randomized controlled trials (quasi-RCTs).

Types of participants

Adults over 18 years of age, regardless of gender and ethnicity, with USN after stroke diagnosis measured by clinical examination or radiographically by computed tomography (CT) or magnetic resonance imaging (MRI), regardless of whether they were included after evaluation by a paper-and-pencil test**.** We included people diagnosed with any type of stroke (ie, ischemic or hemorrhagic) from the acute phase (the first 24 to 72 hours (Furlan 2012)) until one year after the stroke.

Types of interventions

We included trials that compared:

a) drug A versus placebo or control;

b) drug A + rehabilitation versus rehabilitation; and

c) drug A versus drug B (with or without rehabilitation).

We considered any non-pharmacological therapy provided with the aim of improving USN as rehabilitation therapy, such as right half-field eye-patching, mirror therapy, prism adaptation, left-hand somatosensory stimulation, visual scanning training, contralateral transcutaneous electrical nerve stimulation, optokinetic stimulation, trunk rotation, repetitive transcranial magnetic stimulation, galvanic vestibular stimulation, and dressing practice.

Types of outcome measures

Primary outcomes

Test of neglect

Overall USN measured by any paper-and-pencil tests, such as the Line Cancellation task (Albert 1973), the Line Bisection test (Schenkenberg 1980), or the Star Cancellation Test (Halligan 1992); and by any validated specific instrument, such as the Catherine Bergego Scale (Azouvi 2003) and the Behavioural Inattention Test (Wilson 1987).

Secondary outcomes

a) Disability in neurological and functional abilities as measured by any validated specific instrument, such as the National Institutes of Health Stroke Scale and the Modified Rankin Scale (Cincura 2009), the Box and Block Test (Mathiowetz 1985), or the Fugl-Meyer Assessment (Sanford 1993) after treatment and over the long term.
b) Daily life functions as measured by any validated measurement scale, such as the Barthel Index (Cincura 2009).
c) Number of reported falls as measured by diaries of falls, by the Morse Fall Scale (Morse 1989), or by the Hendrich II Fall Risk Model (Hendrich 2003) after treatment and over the long term.
d) Balance as measured by the Berg Balance Scale, the balance subscale of the Fugl-Meyer test, and the Postural Assessment Scale for Stroke Patients (Mao 2002) after treatment and over the long term.
e) Depression or anxiety as measured by the Beck Depression Inventory, the Hospital Anxiety and Depression Scale, Symptom Checklist-90 (SCL-90), and the Hamilton Depression Rating Scale (Aben 2002) after treatment and over the long term.
f) Evaluation of poststroke fatigue by the Fatigue Severity Scale (Lerdal 2011) after treatment and over the long term.

g) Quality of life (however defined by the study authors) after treatment and over the long term.

h) Adverse events (eg, euphoria, hallucinations, orthostatic hypotension, nausea, insomnia, dizziness, syncope) after treatment and over the long term.

i) Death.

Search methods for identification of studies

See the "Specialized register" section of the Cochrane Stroke Group module. We searched for trials in all languages and when possible arranged for translation of relevant articles.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (April 2015) and the following electronic databases and trials registers.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2015, April issue) (Appendix 1).

- MEDLINE (Ovid) (1948 to April 2015) (Appendix 2).

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ebsco) (1982 to April 2015) (Appendix 3).

- EMBASE (Ovid) (1980 to April 2015) (Appendix 4).

- PsycINFO (Ovid) (1806 to April 2015) (Appendix 5).

- Latin American and Caribbean Health Sciences Literature (LILACS) (1982 to April 2015) (Appendix 6).

- ClinicalTrials.gov (April 2015) (www.clinicaltrials.gov/).

- Stroke Trials Registry (April 2015) (www.strokecenter.org/trials/).

- International Standardized Randomized Controlled Trial Number (ISRCTN) Registry (June 2015) (http://www.isrctn.com/).

- European Union (EU) Clinical Trials Register (June 2015) (www.clinicaltrialsregister.eu).

- World Health Organization (WHO) International Clinical Trials Registry Platform (June 2015) (http://www.who.int/ictrp/en/).

- Australian-New Zealand Clinical Trials Registry (June 2015) (www.anzctr.org.au/).

We developed search strategies for CENTRAL, MEDLINE, CINAHL, EMBASE and PsycINFO with the help of the Cochrane Stroke Group Trials Search Co-ordinator, and we adapted the MEDLINE strategy for LILACS and the trials registers.

Searching other resources

In an effort to identify additional published, unpublished and ongoing trials, we: screened the reference lists of identified studies; contacted the following pharmaceutical companies: Aché, Boehringer Ingelheim, Novartis, Sanofi-Aventis, GlaxoWellcome, and Pfizer (July 2015); contacted study authors and experts; and used Science Citation Index Cited Reference Search for forward tracking of important articles.

Data collection and analysis

Selection of studies

Two review authors (GJL and RB) independently screened titles and abstracts of records obtained through electronic database searches and excluded obviously irrelevant reports. We retrieved full-text articles for the references that remained; two review authors (GJL and RB) independently screened the articles to identify studies for inclusion, and identified and recorded the reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted a third person (RED). We collated multiple reports on the same study, so that each study, not each reference, was the unit of interest in the review. We recorded the selection process and completed a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Data extraction and management

Two review authors (GJL and GPB) independently extracted data from the included studies. We resolved discrepancies by discussion and used a standard data extraction form based on the one recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to extract the following information: characteristics of the study (design, methods of randomization); participants; interventions; and outcomes (types of outcome measures, adverse

events). We contacted the authors of the included studies for clarification about missing data, or for further information.

Assessment of risk of bias in included studies

Two review authors (GJL and RB) independently assessed the risk of bias for each study, using the criteria outlined in the¬*Cochrane Handbook for Systematic Reviews of Interventions*¬(Higgins 2011). We resolved disagreements by discussion or by consultation with another review author (RED). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report, together with justification for our judgment, in the "Risk of bias" tables.

Measures of treatment effect

Binary outcomes

For dichotomous data, we planned to use risk ratio (RR) as the effect measure, along with the 95% confidence interval (CI).

Continuous outcomes

For continuous data, we presented the results as mean differences (MDs) with 95% CIs. We planned to use the standardized mean difference (SMD) to combine trials that measured the same outcome but used different measures.

Unit of analysis issues

The unit of analysis was each participant recruited into the trial.

Dealing with missing data

An intention-to-treat analysis (ITT) is one in which all participants in a trial are analyzed according to the intervention to which they were allocated, whether or not they received the intervention. We assumed that participants who dropped out were non-responders. For each trial, we reported whether investigators stated if the analysis was performed according to the ITT principle. If participants were excluded after allocation, we reported in full any details provided. Therefore, we planned to perform the analysis on an ITT basis (Newell 1992) when possible. Otherwise, we planned to adopt the per-protocol analysis.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We classified heterogeneity by using the following I^2 values.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: shows considerable heterogeneity.

If considerable heterogeneity existed (ie, > 75%), we did not combine the studies but provided a descriptive summary of results.

Assessment of reporting biases

Apart from assessing the risk of selective outcome reporting, considered under the assessment of risk of bias in included studies, we planned to assess the likelihood of potential publication bias by using funnel plots if we identified at least eight trials. If small studies in a meta-analysis appear to show larger treatment effects, we considered other possible causes, including selection bias, poor methodological quality, heterogeneity, artifact, and chance.

Data synthesis

When we considered studies to be sufficiently similar, we conducted a meta-analysis by pooling appropriate data using RevMan 5.3 (RevMan 2014). We used the fixed-effect model to analyze data. In future updates of this review, when we identify substantial heterogeneity (eg, $I^2 > 50\%$), we will compute pooled estimates of the treatment effect for each outcome by using a random-effects model (with two or more studies).

Subgroup analysis and investigation of heterogeneity

We did not perform the subgroup analysis because clinical heterogeneity was excessive ($I^2 > 50\%$), and we used subgroup analysis to pool the results. Subgroup analyses are secondary analyses in which participants are divided into groups according to shared characteristics, and outcome analyses are conducted to determine whether any significant treatment effect occurs in response to that characteristic. We plan to carry out the following subgroup analyses in a future update of the review.

- Different ages: younger adults (18 years to 65 years) versus older adults (over 65 years).
- Different combinations of pharmacological drugs and rehabilitation, for example, dopamine plus mirror therapy versus noradrenaline versus prism adaptation.
- Different co-morbidities (ie, hypertension, cardiovascular disease, diabetes, smoking, etc - the presence of at least two co-morbidities versus no co-morbidities).

We planned to perform the Chi^2 test for subgroup differences set at a P value of 0.05.

Sensitivity analysis

As we identified an inadequate number of studies, we did not perform a sensitivity analysis for the primary outcome (ie, disability and test of neglect) to evaluate the effect on results of studies with high risk of bias, nor on data from ITT versus per-protocol analyses.

"Summary of findings" tables

In our review, we used the principles of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes (overall USN, disability, and daily life functions at both discharge and follow-up) and constructed a "Summary of findings" (SoF) table by using GRADE software. The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

The quality of the evidence for a specific outcome was altered by one level according to the performance of studies against these five factors.

- High-quality evidence: Findings are consistent among at least 75% of RCTs with low risk of bias; data are consistent, direct, and precise, and no publication biases are known or suspected. Further research is unlikely to change the estimate or our confidence in the results.
- Moderate-quality evidence: One of the domains is not met. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low-quality evidence: Two of the domains are not met. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low-quality evidence: Three of the domains are not met. We are very uncertain about the results.
- No evidence: We identified no RCTs that addressed this outcome.

Results

Description of studies

See the Characteristics of included studies table.

Results of the search

We identified a total of 1617 citations through database searches (see Figure 1 for search results). After screening by title and then by abstract, we obtained full-paper copies for 24 citations that were potentially eligible for inclusion in the review. We excluded 22 studies for the reasons described in the Characteristics of excluded studies table (Buxbaum 2007; Cho 2009; Damulin 2008; Geminiani 1998; Gorgoraptis 2012; Grujic 1998; Kakuda 2011; Kettunen 2012a; Kettunen 2012b; Krivonos 2010;Laihosalo 2011; Lehmann 2001; Losoi 2012; Mukand 2001; Nolte 2009; Pokryszko-Dragan 2008; Sato 2006; Spalletta 2003; Tobinick 2012; Toyoda 2004; Troisi 2002; Xu 2007). The remaining two studies, with a total of 30 participants, met the minimum methodological requirements, and we included them in this review (Lucas 2013;Paolucci 2010). We also found one ongoing study (EudraCT 200400050717).

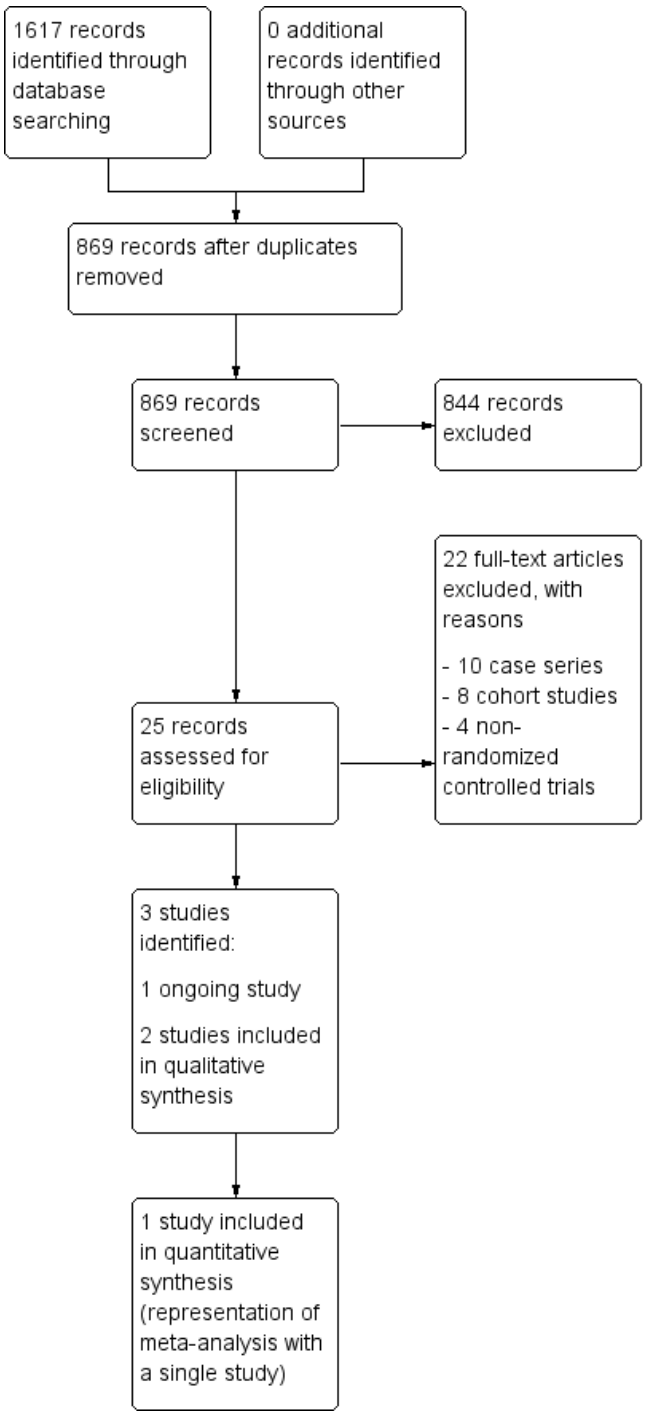


Figure 1: Study flow diagram.

Included studies

We included two studies with a total of 30 randomly assigned participants (Lucas 2013; Paolucci 2010).

Lucas 2013 assessed transdermal nicotine compared with placebo in an elderly stroke population with a single focal lesion to the right hemisphere involving the middle cerebral artery and partial or full visual hemifield cuts. The methodological quality of this study revealed high risk of bias for random sequence generation and other bias, and low risk of bias for blinding of participants and personnel, incomplete outcome data, and selective reporting. The outcome used in this study - USN - was measured by shape, letter, and Bells' cancellation, and subsidiary analysis showed no systematic influence of hemifield defects on performance or treatment response. The number of participants per group was uncertain.

Paolucci 2010 evaluated rivastigmine plus rehabilitation versus rehabilitation, also in an elderly population with a single focal lesion to the right hemisphere involving the middle cerebral artery. The overall risk of bias of this study was low, as all domains were adequately performed except allocation concealment, which we classified as having unclear risk of bias. The outcome used in this study - USN - was measured by the Barrage Test, the Letter Cancellation Test, a Sentence Reading Test, and the Wundt-Jastrow Area Illusion Test.

It was possible to present some of the data from Paolucci 2010 graphically (meta-analysis representation), but it was not possible to combine the results of both included studies because of the diversity of the outcomes reported and the interventions used.

Design of the studies

Lucas 2013 was a quasi-randomized trial; Paolucci 2010 was an RCT.

Type of intervention and follow-up

Lucas 2013 allocated participants to a pro-cholinergic agent (Nicorette, 10 mg) administered by patch or placebo (patch). Follow-up occurred four days after the intervention.

Paolucci 2010 randomly assigned participants to physiotherapy, cognitive training and rivastigmine 1.5 mg twice a day versus physiotherapy and cognitive training. Follow-up occurred one month after therapy was completed.

Type of study participants

Participants in Lucas 2013 were right-handed (except one), hemodynamically stable, conscious, and sufficiently co-operative to undergo a testing session of 45 minutes, and showed stable symptoms of neglect. The study excluded current smokers who smoked one or more cigarettes per day, and investigators systematically quantified and registered any past history of smoking.

Paolucci 2010 assessed right-hemisphere stroke. We excluded people with stroke due to hemorrhagic lesions, the presence of sequelae of previous cerebrovascular accidents and/or of other chronic disabling pathologies, and a score under the established cutoff of 22 on the Mini Mental State Examination.

Type of outcomes measures

Lucas 2013 evaluated USN by Shape Cancellation, Letter Cancellation, and Bells' Cancellation, and by brain lesion analysis.

Paolucci 2010 measured USN by Letter Cancellation, Barrage Test, Sentence Reading Test, Wundt-Jastrow Area Illusion Test, and functional evaluation (length of stay in rehabilitation, independence in daily living, mobility status, Barthel Index, Rivermead Mobility Index).

Excluded studies

We excluded 22 studies for the reasons described in the Characteristics of excluded studies table (Buxbaum 2007; Cho 2009; Damulin 2008; Geminiani 1998; Gorgoraptis 2012; Grujic 1998; Kakuda 2011; Kettunen 2012a; Kettunen 2012b; Krivonos 2010;Laihosalo 2011; Lehmann 2001; Losoi 2012; Mukand 2001; Nolte 2009; Pokryszko-Dragan 2008; Sato 2006; Spalletta 2003; Tobinick 2012; Toyoda 2004; Troisi 2002; Xu 2007).

Studies awaiting assessment

Five studies are awaiting assessment, as they were published in languages other than English or Portuguese (Bruckner 1979; Ibadullaev 2004; Itoh 1998; Pilkowska 2002; Zhou 2004).

Risk of bias in included studies

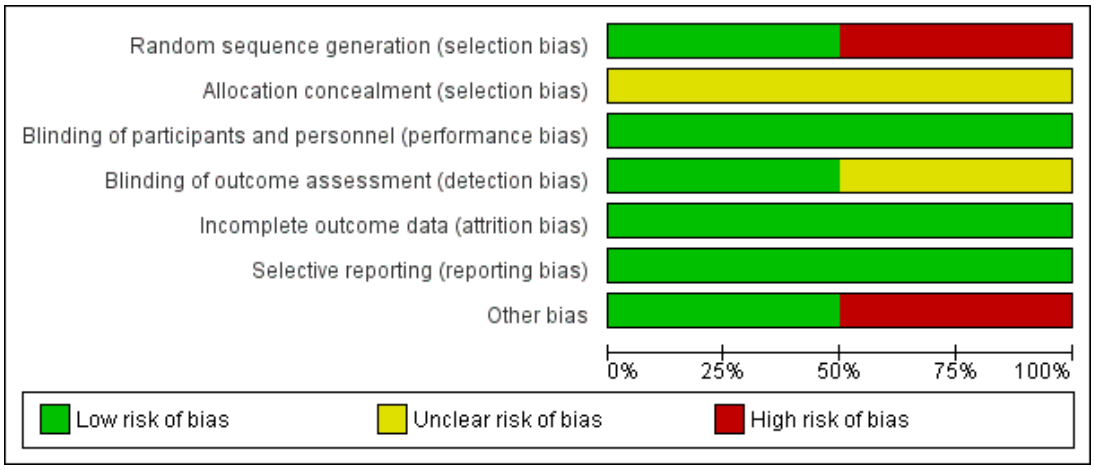


Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

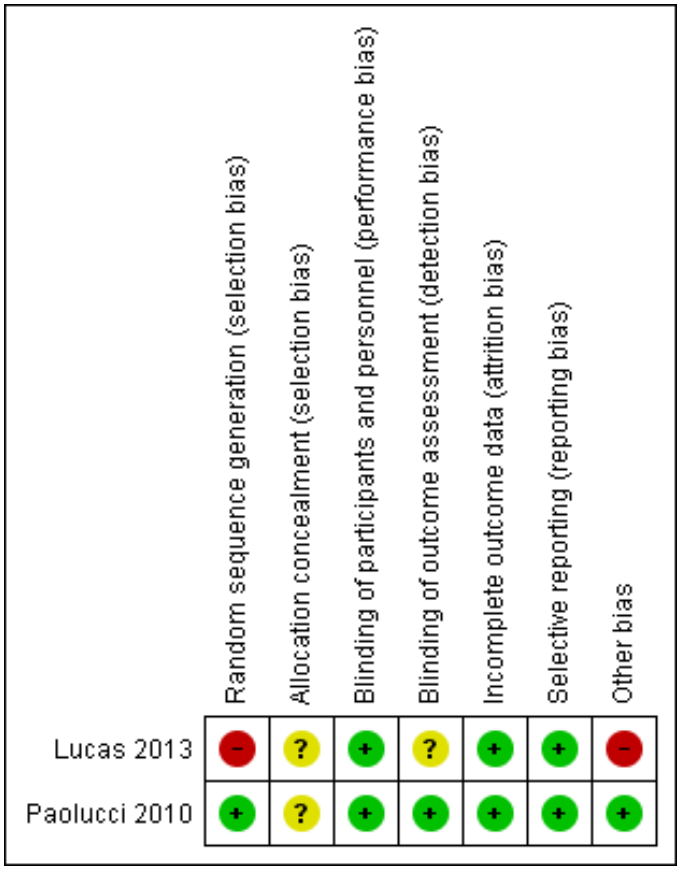


Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation (selection bias)

In Paolucci 2010, randomization was performed using an electronically produced randomization list. Therefore, we classified this domain as having low risk of bias. With regard to allocation concealment, Paolucci 2010 did not report this, and so we classified it as unclear.

Lucas 2013 is a quasi-randomized trial, as study authors assigned participants in a successive manner; therefore, we classified it as having high risk of bias for this domain. With regards to allocation concealment, no description regarding allocation concealment was provided, so we ranked the study as having unclear risk of bias.

Blinding (performance bias and detection bias)

In Paolucci 2010, blinding was provided with regard to outcome assessors and the investigator; therefore, we ranked this study as having low risk of bias. However, with regard to blinding of participants, researchers provided no information, so we ranked this study as having unclear risk of bias.

In Lucas 2013, blinding with regard to participants and personnel was provided; therefore, we ranked this study as having low risk of bias. However, with regard to outcome assessors, investigators provided no information, so we ranked this study as having unclear risk of bias.

Incomplete outcome data (attrition bias)

The two studies performed intention-to-treat analysis.

Paolucci 2010 reported no withdrawals or dropouts, so we classified this study as having low risk of bias.

In Lucas 2013, only one participant was lost (10%), so we classified this study as having low risk of bias.

Selective reporting (reporting bias)

We noted no evidence of selective reporting in either of the included studies (Lucas 2013; Paolucci 2010); therefore, we ranked both studies as having low risk of bias for this domain.

Other potential sources of bias

We found no evidence of other biases in Paolucci 2010; therefore, we ranked this study as having low risk of bias for this domain. However, in Lucas 2013, a pharmaceutical company provided the intervention drugs; therefore, we ranked this study as having high risk of bias for this domain. The two studies included in this review did not report the sample size calculation.

Effects of interventions

Transdermal nicotine treatment (Nicorette) versus placebo or control

Lucas 2013 reported this comparison; however, it was not clear how many participants were evaluated in each group. Therefore, we could provide no additional data.

Overall USN

Lucas 2013 reported on this outcome. The number of omissions (number of targets identified by the participant) in the three cancellation tasks (shape, letter, and Bells' cancellation) showed statistical significance that was reduced under transdermal nicotine treatment (mean number of omissions 2.93 ± 0.5) compared with both baseline (4.95 ± 0.8) and placebo (5.14 ± 0.9) (main effect of treatment condition: F (2.23) = 11.06; P value < 0.0001). Investigators did not assess the following outcomes in this trial: disabilities, daily life functions, number of reported falls, balance, depression or anxiety, poststroke fatigue, quality of life, and death.

Adverse events

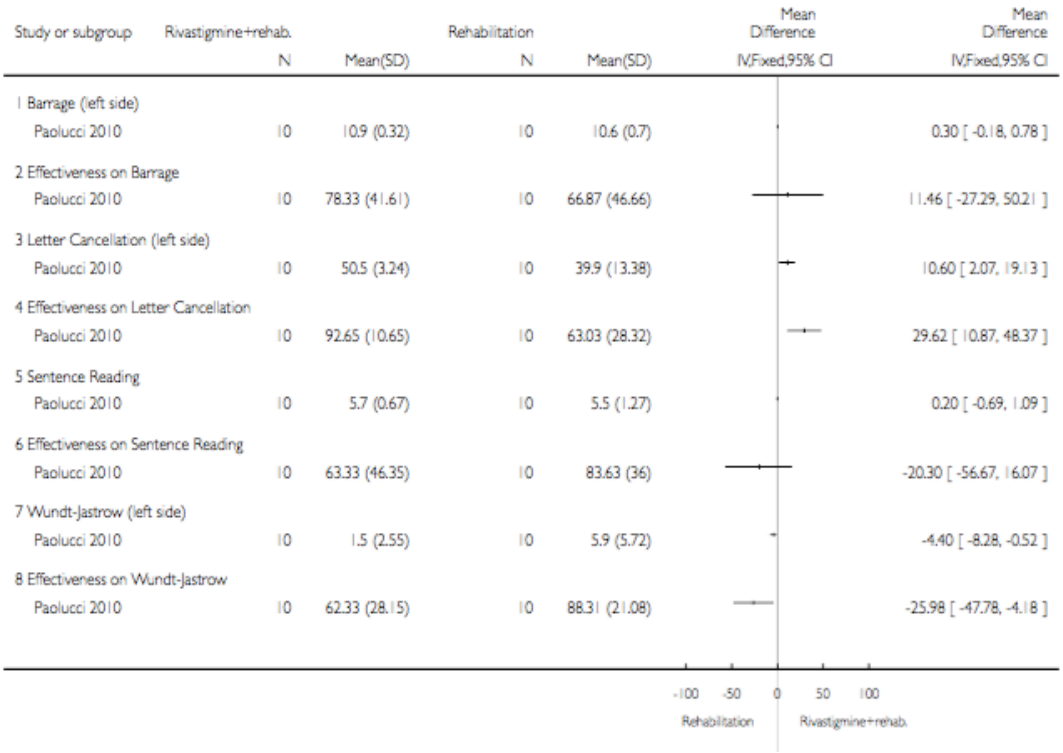
Lucas 2013 reported on this outcome. Only two participants had a positive score for one item (diarrhea) on the negative symptom checklist. For one participant with a score of 2 on this scale (major symptom), treatment was interrupted, and the participant was not included in the study. The second participant presented a score of 1 (minor symptom) in the first few hours after treatment, but the symptom soon resolved, and the participant continued in the study with no other problems. The two participants were included in the intervention arm of this study.

Rivastigmine + rehabilitation versus rehabilitation

Paolucci 2010 reported on this comparison.

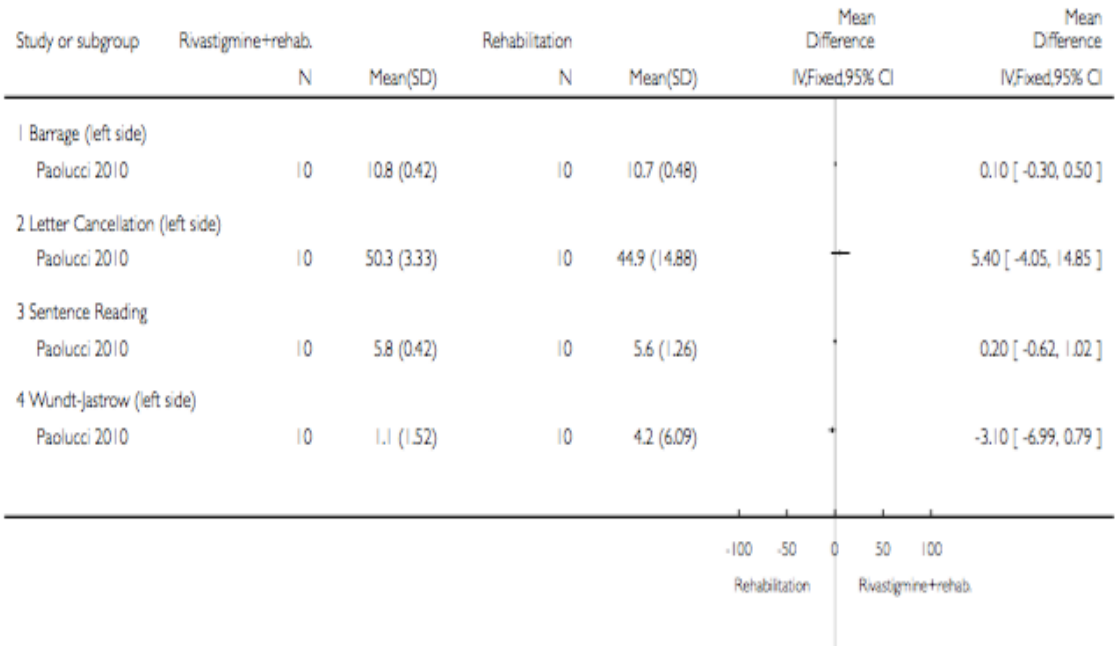
Overall USN

Paolucci 2010 reported on this outcome. A statistically significant difference favored rivastigmine plus rehabilitation regarding outcomes in the subcategory of letter cancellation (left side) at discharge (MD 10.60, 95% CI 2.07 to 19.13) and effectiveness of letter cancellation at discharge (MD 29.62, 95% CI 10.87 to 48.37). However, researchers reported no statistically significant differences between treatment groups regarding outcomes in the subcategories of barrage (left side) at discharge (MD 0.30, 95% CI -0.18 to 0.78), effectiveness of barrage at discharge (MD 11.46, 95% CI -27.29 to 50.21), sentence reading at discharge (MD 0.20, 95% CI -0.69 to 1.09), and effectiveness of sentence reading at discharge (MD -20.30, 95% CI -56.67 to 16.07). A statistically significant difference favored rehabilitation (control) in terms of outcomes in the subcategories of Wundt-Jastrow (left side) at discharge (MD -4.40, 95% CI -8.28 to -0.52) and effectiveness of Wundt-Jastrow at discharge (MD -25.98, 95% CI -47.78 to -4.18) (Analysis 1.1).



Analysis 1.1: Rivastigmine plus rehabilitation versus rehabilitation alone regarding USN at discharge

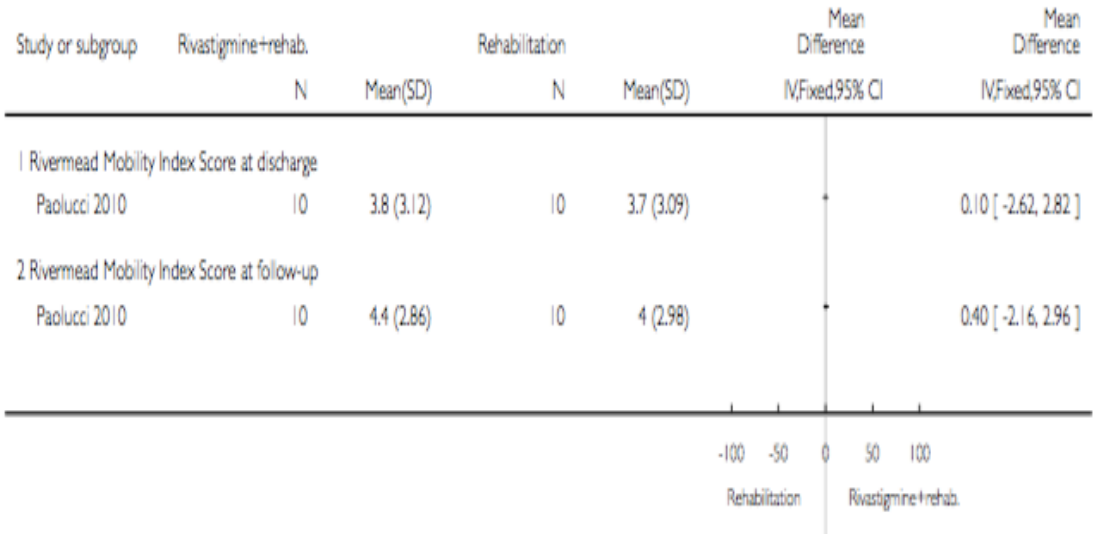
Investigators reported no statistically significant differences between treatment groups regarding outcomes at follow-up in the subcategories of barrage (left side) (MD 0.10, 95% CI -0.30 to 0.50), letter cancellation (left side) (MD 5.40, 95% CI -4.05 to 14.85), sentence reading (MD 0.20, 95% CI -0.62 to 1.02), and Wundt-Jastrow (MD -3.10, 95% CI -6.99 to 0.79) (Analysis 1.2).



Analysis 1.2: Rivastigmine plus rehabilitation versus rehabilitation alone regarding USN at follow-up

Disabilities

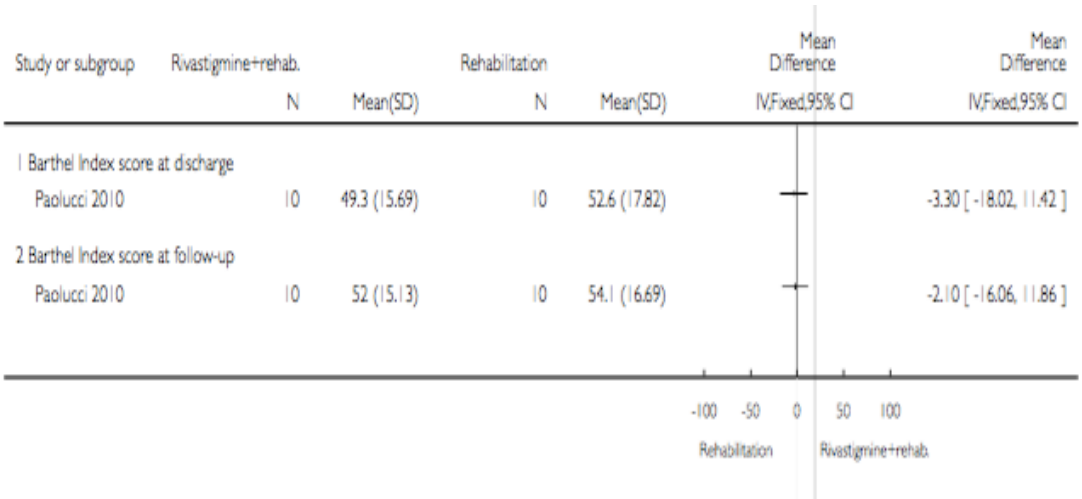
In terms of this outcome, Paolucci 2010 reported no statistically significant differences between rivastigmine plus rehabilitation and rehabilitation alone regarding disability in both of the subcategories Rivermead Mobility Index Score at discharge (MD 0.10, 95% CI -2.62 to 2.82) and Rivermead Mobility Index Score at follow-up (MD 0.40, 95% CI -2.16 to 2.96) (Analysis 1.3).



Analysis 1.3: Rivastigmine plus rehabilitation and rehabilitation alone regarding disability

Daily life functions

Paolucci 2010 reported on this outcome and described no statistically significant differences between rivastigmine plus rehabilitation and rehabilitation in terms of daily life functions in bothsubcategories of Barthel Index Score at discharge (MD -3.3, 95% CI -18.02 to 11.42) and Barthel Index Score at follow-up (MD -2.10, 95% CI -16.06 to 11.86) (Analysis 1.4).



Analysis 1.4: Rivastigmine plus rehabilitation and rehabilitation alone regarding daily life function

Investigators did not assess the following outcomes in this trial: number of reported falls, balance, depression or anxiety, poststroke fatigue, quality of life, death, and adverse events.

Discussion

Summary of main results

This systematic review offers up-to-date but limited evidence supported by only two randomized controlled trials on the effectiveness and safety of pharmacological interventions for unilateral spatial neglect (USN) after stroke (Lucas 2013; Paolucci 2010).

We presented the results of overall USN from Paolucci 2010 in a forest plot, which showed a statistically significant difference between the intervention and rehabilitation alone in the Letter Cancellation Test at discharge. The study also showed a non-significant difference between the intervention and rehabilitation alone on the Barrage Test and on a Sentence Reading Test. The Wundt-Jastrow Area Illusion Test showed a statistically significant difference favoring rehabilitation (control).

Several pharmacological approaches have been explored to determine whether some drugs, such as acetylcholinesterase inhibitors (AchEIs), might be useful in promoting recovery from USN. AchEIs have been used in treating patients with mild to moderate Alzheimer's disease (Birks 2009). They may help improve rehabilitation outcomes by enhancing cognitive functioning and reducing apathy, thereby increasing participation and enhancing the ability to learn during rehabilitation (Paolucci 2010). In Paolucci 2010, AchEIs were responsible for enhancing performance in only one test of neglect, but improvement in some USN measures was not replicated in functional outcome measures in either group. The effectiveness of rehabilitation strategies for reducing the disabling effects of neglect and increasing independence remains unproven.

The pro-cholinergic treatment was reasonably well tolerated in this setting and was associated with significantly reduced neglect in visual tasks, which tended to be more pronounced in people with severe neglect and to persist in chronic stages (Lucas 2013). Effects of pro-cholinergic treatment of USN after stroke by a single administration of transdermal nicotine induced consistent improvement in target detection and exploration behavior on visual tasks and would be mediated by increased nicotine activity in cortical arousal and facilitated processing of task-relevant information. However, nicotine activity may increase sustained attention or the general motivation factor (Knott 1999; Lucas 2013). Neuroimaging studies after pro-cholinergic treatment have demonstrated consistent modulation of parietal and

frontal activity and activation in attention-related networks into more posterior parietal regions, which are the main regions involved in USN after stroke (Ernst 2001; Thiel 2005; Vossel 2008). Results of the studies included in this review demonstrate improvement at the USN level but show no impact on functional abilities nor on the capacity of individuals for daily life functions.

Lucas 2013 reported improved performance on USN tests among participants receiving transdermal nicotine treatment, and investigators concluded that this intervention may be one rehabilitation approach that can be used to improve patient care over the long term, while enhancing functionality. In Paolucci 2010, a statistically significant difference favoring rivastigmine plus rehabilitation was observed with one of the USN tests applied at discharge, but not at follow-up. Results of this study show improved performance on USN tests in the initial phase of treatment (rivastigmine plus rehabilitation). The same results were found over the long term, showing that improvements in spatial performance were not fixed by the participant.

Overall completeness and applicability of evidence

In the two included studies, patient groups, interventions, and relevant outcomes have been addressed to prove the effectiveness of drug therapy, but the authors of this review propose use of a specific instrument, such as the Catherine Bergego Scale (Azouvi 2003) or the Behavioural Inattention Test (Wilson 1987), to clarify the effects of unilateral spatial neglect on disabilities. None of the included trials reported data on several of the prespecified outcomes (falls, balance, depression or anxiety, poststroke fatigue and quality of life).

Quality of the evidence

We included only two studies in this review; the overall sample size of these studies was very small, although most of the domains assessed were classified as showing low risk of bias regarding methodological quality. This would be reflected in any conclusions drawn from this review. Quality of the evidence for outcomes assessed in the two trials was very low; we downgraded quality from high to very low because of the presence of a serious risk of selection bias and imprecision (due to few events and small sample sizes). The magnitude of effect in Paolucci 2010 favored the control group in one outcome (Wundt-Jastrow Area Illusion Test), and favored the intervention group in another outcome (letter cancellation test)

(Analysis 1.1). We could not assess publication bias and could not investigate heterogeneity, as included studies were insufficient to allow these analyses.
The methodological quality of the two studies was reasonable, even though risk of selection bias was substantial (participants were assigned in a successive manner) and potential conflicts of interest were revealed (support from the pharmaceutical company Pfizer) in Lucas 2013.

Potential biases in the review process

We developed a comprehensive search strategy; we handsearched the reference lists of identified studies for additional citations and contacted experts in the field. Therefore, we are confident that we have identified most clinical trials conducted to compare pharmacological interventions for USN after stroke.

Agreements and disagreements with other studies or reviews

The study conducted by Gorgoraptis 2012 was not included in our review because it is not a properly randomized study, all participants received the intervention and control in the same order, and the sequences are too similar. Study authors used rotigotine transdermal patches (dopamine agonist) in 16 participants with hemispatial neglect following right-hemisphere stroke. People were excluded if they presented with a pre-existing neurological condition (eg, dementia, Parkinson's disease, multiple sclerosis); an acute concomitant illness (eg, infection, unstable angina, myocardial infarction, or heart, respiratory, renal, or liver failure); systolic blood pressure < 120 mmHg and/or diastolic < 70 mmHg; exposure to any other investigational drug within 30 days of enrollment in the study; presence of clinically significant drug or alcohol abuse within the previous six months; pregnancy; and breast-feeding. Results of this study showed that treatment with rotigotine was associated with a significant increase in the number of targets identified on the left side (12.8% increase in the number of targets found on the left side). No serious adverse events were noted during treatment with rotigotine. Mild adverse effects included fatigue, mild skin irritation at the site of the patch, and gastrointestinal disturbance, including nausea, vomiting, and diarrhea, which are known potential side effects of rotigotine. The study author concluded that rotigotine was reasonably well tolerated in this setting and was associated with significant improvement in one visual search task, but this trial was limited by the design and by the small sample size.

This study shows agreement with findings of the studies included in our review, in that use of dopamine agonists reduced USN after stroke and improved spatial perception during early stages of treatment, but investigators did not present long-term results.

In a systematic review of non-pharmacological interventions based on a cognitive approach (Bowen 2013), review authors concluded that evidence was still insufficient to show the effects of cognitive rehabilitation interventions on functional ability in daily life function and on standardized neglect assessments. As the effectiveness of cognitive rehabilitation for reducing disabling effects of neglect and increasing independence remains unproven, no rehabilitation approach can be supported or refuted by current randomized controlled trials.

Therefore, Bowen 2013 agrees with the data presented in our review that showno favorable effects of pharmacological interventions for improving disabilities and daily life functions.

Authors' conclusions

Implications for practice

The quality of the evidence from available randomized controlled trials was very low; therefore, we can draw no definitive conclusions on the effectiveness and safety of pharmacological interventions for unilateral spatial neglect after stroke. The applicability of these findings might be compromised, as most of the results described in this review were obtained from trials with very small sample sizes.

Implications for research

This review underlines the need to conduct well-designed trials in this field. Future trials must be adequately powered and should include standardized outcome measures, such as overall USN and disability and functional abilities measured by both validated and non-validated instruments, daily life function, quality of life, and death.

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Differences between protocol and review

We have included quasi-RCTs in the review because of the small number of RCTs identified. Disability was a prespecified primary outcome in the protocol; however, this was considered a secondary outcome in the full review because the review authors considered that the pharmacological intervention has a primary effect on modulation of the perception of the central nervous system (USN), and has a secondary effect on other functions (eg, disability).

Lucas 2013

Methods	Design: double-blind placebo-controlled within-subject design Multicenter Justification for the sample size: not reported Setting: Geneva University Hospital and Plein Soleil Foundation of Lausanne, Switzerland Follow-up period: days 1, 2, and 4
Participants	10 participants randomly assigned and 9 analyzed Mean age: 69.1 years Sex: 2 men, 8 women Inclusion criteria: right-handed (except 1), stable vigilance and sufficient co-operation to undergo a testing session of 45 minutes, and signs of stable symptoms of neglect Exclusion criteria: currently smoking ≥ 1 cigarette per day, with any past history of smoking systematically quantified and registered
Interventions	Experimental group: pro-cholinergic agent (Nicorette, 10 mg) administered by patch. Each participant was treated once (on day 2 or on day 4). The patch was applied in the morning between 7 am and 8 am and was removed around 6 pm to 7 pm Control group: placebo (patch)
Outcomes	Primary outcomes: USN (shape cancellation, letter cancellation, and Bells' cancellation) Secondary outcomes: brain lesion analysis
Notes	We contacted study authors on 24 April 2015 to request further information on both methodological and statistical data. We are awaiting their reply Topography: All participants (except 1) were right-handed and showed clinical and radiological evidence of a single focal lesion in the right hemisphere due to stroke, involving the middle cerebral artery territory in all cases Clinical status: Participants had partial (5 quadranopia) or full (3 hemianopia) visual hemifield cuts, as determined by clinical examination that includes confrontation Initial neglect severity: 5 participants presented with high initial neglect severity and 5 with low initial neglect severity Transdermal nicotine side effects (demographic data): 1 participant presented with mild diarrhea in the morning

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This is a quasi-randomized trial, as study authors assigned participants in a successive manner
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel were blinded to treatment allocation, as they used active and placebo patches that were visually identical
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	1 participant had treatment interrupted and was not included in the study
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	High risk	The intervention drug was provided by Pfizer

Paolucci 2010

Methods	Design: double-blind randomized controlled trial Single center Justification for the sample size: not reported Setting: Santa Lucia Foundation, Rome, Italy Follow-up period: 1 month after cessation of therapy
Participants	20 participants randomly assigned and 20 analyzed Mean age: drugs and rehabilitation 64.10 years; only rehabilitation 67.7 years Sex: drugs and rehabilitation: 6 men, 4 women; only rehabilitation: 4 men, 6 women Inclusion criteria: right-hemisphere stroke Exclusion criteria: stroke in left hemisphere, stroke due to hemorrhagic lesions, subarachnoid hemorrhage, presence of sequelae of previous cerebrovascular accidents and/or of other chronic disabling pathologies (eg, severe Parkinson's disease; polyneuropathy; severe cardiac, liver, or renal failure; cancer; and limb amputation), score lower than the established cutoff of 22 on the Mini Mental State Examination

Interventions	Experimental group: physiotherapy, cognitive training, and rivastigmine 1.5 mg twice a day. After the first week, the dose was increased to 3 mg twice a day for 8 weeks Control group: physiotherapy and cognitive training
Outcomes	Primary outcomes: USN (Letter Cancellation Test, Barrage Test, Sentence Reading Test, Wundt-Jastrow Area Ilusion Test) Secondary outcomes: functional evaluation (length of stay in rehabilitation; independence in daily living; mobility status; Barthel Index; Rivermead Mobility index)
Notes	We contacted study authors on 24 April 2015 to request further information on both methodological and statistical data. We are awaiting their reply Topography: In the rivastigmine plus rehabilitation group, 70% of participants had total anterior circulation infarcts and 30% had partial anterior circulation infarcts; in the rehabilitation only group (control), 80% of participants had total anterior circulation infarcts and 20% had partial anterior circulation infarcts Clinical status: At admission, the 2 subgroups had similar clinical, cognitive, and functional characteristics Initial neglect severity: no statistically significant differences in neglect severity between the 2 groups Rivastigmine side effects: 1 participant had nausea, probably due to the progressive titration of medication, but rivastigmine treatment as provided in this study was safe and feasible and did not increase the risk of adverse events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using an electronically produced randomization list"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	Personnel: "The neuropsychologist, not being involved in the study, did not know which group the patients had been assigned to" Participants: not reported
Blinding of outcome assessment (detection bias)	Low risk	"The rating scales were assessed independently by two ward physicians who were blind to the purpose of the study"
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Footnotes

USN: unilateral spatial neglect.

Characteristics of excluded studies

Buxbaum 2007

Reason for exclusion	Non-RCT

Cho 2009

Reason for exclusion	Cohort study

Damulin 2008

Reason for exclusion	Case series

Geminiani 1998

Reason for exclusion	Case series

Gorgoraptis 2012

Reason for exclusion	Non-RCT

Grujic 1998

Reason for exclusion	Case series

Kakuda 2011

Reason for exclusion	Case series

Kettunen 2012a

Reason for exclusion	Cohort study

Kettunen 2012b

Reason for exclusion	Cohort study

Krivonos 2010

Reason for exclusion	Cohort study

Laihosalo 2011

Reason for exclusion	Case series

Lehmann 2001

Reason for exclusion	Non-RCT

Losoi 2012

Reason for exclusion	Cohort study

Mukand 2001

Reason for exclusion	Case series

Nolte 2009

Reason for exclusion	Case series

Pokryszko-Dragan 2008

Reason for exclusion	Cohort study

Sato 2006

Reason for exclusion	Cohort study

Spalletta 2003

Reason for exclusion	Case series

Tobinick 2012

Reason for exclusion	Case series

Toyoda 2004

Reason for exclusion	Cohort study

Troisi 2002

Reason for exclusion	Case series

Xu 2007

Reason for exclusion	Non-RCT

Footnotes

RCT: randomized controlled trial

Characteristics of ongoing studies

EudraCT 200400050717

Study name	Effectiveness of rivastigmine treatment in poststroke patients with right brain damage and unilateral spatial neglect
Methods	Not reported
Participants	Elderly adults
Interventions	Rivastigmine
Outcomes	Improvement USN and functional status in right brain damaged participants
Starting date	10 June 2004
Contact information	Fondazione Santa Lucia
Notes	None

Footnotes

USN: unilateral spatial neglect.

Summary of findings tables

1 Summary of findings

Pharmacological interventions for unilateral spatial neglect after stroke: rivastigmine + rehabilitation vs rehabilitation			
Patient or population: unilateral spatial neglect after stroke **Settings:** Italy **Intervention:** rivastigmine 1.5 mg twice a day + physiotherapy and cognitive training **Comparison:** physiotherapy and cognitive training			
Outcomes	**Mean difference (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**
Overall USN at discharge Barrage; Letter Cancellation; Sentence Reading; Wundt-Jastrow Paolucci 2010 study Follow-up: last day of therapy (discharge)	Barrage 0.30 (-0.18 to 0.78) Letter Cancellation 10.60 (2.07 to 19.13) Sentence Reading 0.20 (-0.69 to 1.09) Wundt-Jastrow -4.40 (-8.28 to -0.52)	20 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
Overall USN at follow-up Barrage; Letter Cancellation; Sentence Reading; Wundt-Jastrow Paolucci 2010 study Follow-up: 30 days after cessation of therapy	Barrage 0.10 (-0.30 to 0.50) Letter Cancellation 5.40 (-4.05 to 14.85) Sentence Reading 0.20 (-0.62 to 1.02) Wundt-Jastrow -3.10 (-6.99 to 0.79)	20 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
Disabilities Rivermead Mobility Index Score Paolucci 2010 study Follow-up: last day of therapy (discharge)	Rivermead Mobility Index Score 0.10 (-2.62 to 2.82)	20 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
Disabilities Rivermead Mobility Index Score Paolucci 2010 study Follow-up: 30 days after cessation of therapy	Rivermead Mobility Index Score 0.40 (-2.16 to 2.96)	20 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
Daily life functions Barthel Index score Paolucci 2010 study Follow-up: last day of therapy (discharge)	Barthel Index score -3.30 (-18.02 to 11.42)	20 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**

Daily life functions Barthel Index score Paolucci 2010 study Follow-up: 30 days after cessation of therapy	Barthel Index score -2.10 (-16.06 to 11.86)	20 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate			

Footnotes

[a]It was not possible to perform meta-analysis; only 1 study could be represented graphically

[b]Quality was downgraded by 1 level because of very serious imprecision (small number of events, small sample size, and wide confidence interval)

[c]Although the confidence interval was narrow in some of the scales that evaluated the primary outcome, the magnitude of effect was controversial

[d]Quality was downgraded by 1 level for uncertainty on both publication bias and heterogeneity, as included studies were insufficient to allow this analysis

[e]Risk of bias in all domains was generally classified as low

2 Summary of findings

Pharmacological interventions for unilateral spatial neglect after stroke: transdermal nicotine (Nicorette) vs placebo or control				
Patient or population: unilateral spatial neglect after stroke **Settings:** Switzerland **Intervention:** pro-cholinergic agent (Nicorette, 10 mg) administered by patch **Comparison:** placebo				
Outcomes	**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Overall USN Shape cancellation, letter cancellation, and Bells' cancellation Lucas 2013 study Follow-up period: days 1, 2, and 4	See comment	See comment	See comment	Outcome described only qualitatively
Disabilities Lucas 2013 study	See comment	See comment	See comment	Outcome not reported
Daily life functions Lucas 2013 study	See comment	See comment	See comment	Outcome not reported
*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI) **CI:** Confidence interval; **RR:** Risk ratio				
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate				

Footnotes

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Ongoing studies

EudraCT 200400050717

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Appendices

1 Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"stroke, lacunar"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"]

#2 (stroke or poststroke or "post-stroke" or cerebrovasc* or brain next vasc* or cerebral next vasc* or cva* or apoplexy* or SAH):ti,ab

#3 ((brain* or cerebral* or cerebell* or intracran* or intracerebral) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus*)):ti,ab

#4 ((brain* or cerebral* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab

#5 [mh ^hemiplegia] or [mh paresis]

#6 (hemipleg* or hemipar* or paresis or paretic):ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 [mh ^"perceptual disorders"] or [mh ^perception] or [mh "visual perception"] or [mh ^"space perception"] or [mh ^attention] or [mh ^"functional laterality"] or [mh ^"extinction, psychological"]

#9 (hemineglect or hemi-neglect):ti,ab

#10 ((unilateral or spatial or hemispatial or hemi-spatial or visual) near/5 neglect):ti,ab

#11 (inattention or hemi-inattention or extinction):ti,ab

#12 ((perceptual or perception or visuospatial or visuo-spatial or visuoperceptual or visuo-perceptual or attention*) near/5 (disorder* or deficit* or impairment* or abilit* or problem*)):ti,ab

#13 #8 or #9 or #10 or #11 or #12

#14 [mh /DT,DE,PD]

#15 [mh "dopamine agents"]

#16 [mh "dopamine agonists"]

#17 (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine):ti,ab,kw

#18 [mh "adrenergic alpha-agonists"]

#19 [mh "adrenergic alpha-1 receptor agonists"] or [mh "adrenergic alpha-2 receptor agonists"]

#20 ((adrenergic or noradrenergic) near/5 agonist*):ti,ab

#21 (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine):ti,ab,kw

#22 [mh "adrenergic beta-agonists"] or [mh "adrenergic beta-1 receptor agonists"] or [mh "adrenergic beta-2 receptor agonists"] or [mh "adrenergic beta-3 receptor agonists"]

#23 (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine):ti,ab,kw

#24 [mh "Drug Therapy"]

#25 ((drug or pharmacol*) near/5 (therap* or treat* or effect*)):ti,ab

#26 pharmacotherap*:ti,ab

#27 {or #14-#26}

#28 #7 and #13 and #27

2 MEDLINE search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. perceptual disorders/ or perception/ or exp visual perception/ or space perception/ or attention/ or functional laterality/ or extinction, psychological/
9. (hemineglect or hemi-neglect).tw.
10. ((unilateral or spatial or hemispatial or visual) adj5 neglect).tw.
11. (perception or inattention or hemi-inattention or extinction).tw.
12. ((perceptual or visuo?spatial or visuo?perceptual or attention$) adj5 (disorder$ or deficit$ or impairment$ or abilit$ or problem$)).tw.
13. 8 or 9 or 10 or 11 or 12
14. (drug effects or drug therapy or pharmacology).fs.
15. dopamine agents/ or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/ or amantadine/ or amphetamine/ or benserazide/ or benzphetamine/ or carbidopa/ or dihydroxyphenylalanine/ or dopamine/ or fusaric acid/ or levodopa/ or memantine/ or methamphetamine/
16. dopamine agonists/ or 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1h-3-benzazepine/ or apomorphine/ or bromocriptine/ or dihydroergocornine/ or dihydroergocryptine/ or dihydroergotamine/ or dihydroergotoxine/ or fenoldopam/ or lisuride/ or metergoline/ or pergolide/ or piribedil/ or quinpirole/

17. (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine).tw,nm.
18. adrenergic alpha-agonists/ or epinephrine/ or etilefrine/ or naphazoline/ or norepinephrine/ or octopamine/ or oxymetazoline/ or phenylpropanolamine/ or synephrine/
19. adrenergic alpha-1 receptor agonists/ or ergotamine/ or mephentermine/ or metaraminol/ or methoxamine/ or midodrine/ or phenylephrine/ or adrenergic alpha-2 receptor agonists/ or clonidine/ or dexmedetomidine/ or guanabenz/ or guanfacine/ or medetomidine/ or methyldopa/ or xylazine/
20. ((adrenergic or noradrenergic) adj5 agonist$).tw.
21. (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine).tw,nm.
22. adrenergic beta-agonists/ or clenbuterol/ or epinephrine/ or isoproterenol/ or isoxsuprine/ or nylidrin/ or oxyfedrine/ or tretoquinol/ or adrenergic beta-1 receptor agonists/ or dobutamine/ or etilefrine/ or prenalterol/ or xamoterol/ or adrenergic beta-2 receptor agonists/ or albuterol/ or fenoterol/ or hexoprenaline/ or isoetharine/ or metaproterenol/ or procaterol/ or ritodrine/ or terbutaline/ or adrenergic beta-3 receptor agonists/
23. (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline).tw,nm.
24. exp Drug Therapy/
25. ((drug or pharmacol$) adj5 (therap$ or treat$ or effect$)).tw.
26. (pharmacotherap$ or fluoxetine or rivastigmine).tw.

27. or/14-26
28. Randomized Controlled Trials as Topic/
29. random allocation/
30. Controlled Clinical Trials as Topic/
31. control groups/
32. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
33. double-blind method/
34. single-blind method/
35. Placebos/
36. placebo effect/
37. cross-over studies/
38. Therapies, Investigational/
39. Drug Evaluation/
40. Research Design/
41. randomized controlled trial.pt.
42. controlled clinical trial.pt.
43. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
44. (random$ or RCT or RCTs).tw.
45. (controlled adj5 (trial$ or stud$)).tw.
46. (clinical$ adj5 trial$).tw.
47. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
48. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
49. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
50. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
51. (cross-over or cross over or crossover).tw.
52. (placebo$ or sham).tw.
53. trial.ti.
54. (assign$ or allocat$).tw.
55. controls.tw.

56. or/28-55
57. 7 and 13 and 27 and 56
58. exp animals/ not humans.sh.
59. 57 not 58

3 CINAHL search strategy

S1 .(MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases+") OR (MH "Cerebral Ischemia+") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Arterial Diseases+") OR (MH "Intracranial Embolism and Thrombosis") OR (MH "Intracranial Hemorrhage+") OR (MH "Stroke") OR (MH "Vertebral Artery Dissections")
S2 .(MH "Stroke Patients") OR (MH "Stroke Units")
S3 .TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH)
S4 .TI (brain* or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain* or cerebr* or cerebell* or intracran* or intracerebral)
S5 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)
S6 .S4 and S5
S7 .TI (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid)
S8 .TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)
S9 .S7 and S8
S10 .(MH "Hemiplegia")
S11 .TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)
S12 .S1 or S2 or S3 or S6 or S9 or S10 or S11
S13 .(MH "Unilateral Neglect") OR (MH "Unilateral Neglect (Saba CCC)") OR (MH "Unilateral Neglect (NANDA)")

S14 .(MH "Perceptual Disorders+")

S15 .(MH "Perception+")

S16 .(MH "attention")

S17 .TI (hemineglect or hemi-neglect) or AB (hemineglect or hemi-neglect)

S18 .TI (unilateral or spatial or hemi#spatial or visual) or AB (unilateral or spatial or hemi#spatial or visual)

S19 .TI (neglect) or AB (neglect)

S20 .S18 AND S19

S21 .TI (inattention or hemi-inattention or extinction) or AB (inattention or hemi-inattention or extinction)

S22 .TI (perceptual or perception or visuo#spatial or visuo#perceptual or attention*) or AB (perceptual or perception or visuo#spatial or visuo#perceptual or attention*)

S23 .TI (disorder* or deficit* or impairment* or abilit*) or AB (disorder* or deficit* or impairment* or abilit*)

S24 .S22 AND S23

S25 .S13 OR S14 OR S15 OR S16 OR S17 OR S20 OR S21 OR S24

S26 .(MH "Drug Therapy+")

S27 .MW dt or MW de

S28 .(MH "Dopamine Agents") OR (MH "Dopamine Agonists+")

S29 .TI dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine

S30 .AB dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine

S31 .MW dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine

S32 .(MH "Adrenergic Agonists") OR (MH "Adrenergic Alpha-Agonists+") OR (MH "Adrenergic Beta-Agonists+")

S33 .TI ((adrenergic or noradrenergic) N5 agonist*) or AB ((adrenergic or noradrenergic) N5 agonist*)

S34 .TI norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine

S35 .AB norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine

S36 .MW norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine

S37 .TI clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine

S38 .AB clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine

S39 .MW clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine

S40 .TI (((drug or pharmacol*) N5 (therap* or treat* or effect*))) OR AB (((drug or pharmacol*) N5 (therap* or treat* or effect*)))

S41 .TI pharmacotherap* or Ab pharmacotherap*

S42 .S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41

S43 .S12 AND S25 AND S42

4 EMBASE (Ovid) search strategy

1. stroke/ or cerebrovascular disease/ or exp basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/

2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

5. hemiparesis/ or hemiplegia/ or paresis/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp perception disorder/ or exp perception/ or exp attention/ or attention disturbance/ or visual deprivation/ or neglect/ or hemispatial neglect/ or "unilateral neglect syndrome"/

9. (hemineglect or hemi-neglect).tw.

10. ((unilateral or spatial or hemi?spatial or visual) adj5 neglect).tw.
11. (inattention or hemi-inattention or extinction).tw.
12. ((perceptual or perception or attention$ or visuo?spatial or visuo?perceptual) adj5 (disorder$ or deficit$ or impairment$ or abilit$ or dysfunction)).tw.
13. 8 or 9 or 10 or 11 or 12
14. (dt or pd).fs. or exp drug therapy/
15. exp dopamine receptor stimulating agent/
16. (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine).mp.
17. exp adrenergic receptor stimulating agent/
18. ((adrenergic or noradrenergic) adj5 agonist$).tw.
19. (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine).mp.
20. (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine).mp.
21. ((drug or pharmacol$) adj5 (therap$ or treat$ or effect$)).tw.
22. pharmacotherap$.tw.
23. or/14-22
24. Randomized Controlled Trial/
25. Randomization/
26. Controlled Study/
27. control group/
28. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/

29. Crossover Procedure/
30. Double Blind Procedure/
31. Single Blind Procedure/ or triple blind procedure/
32. placebo/
33. drug comparison/ or drug dose comparison/
34. "types of study"/
35. random$.tw.
36. (controlled adj5 (trial$ or stud$)).tw.
37. (clinical$ adj5 trial$).tw.
38. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
39. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
40. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
41. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
42. (cross-over or cross over or crossover).tw.
43. placebo$.tw.
44. sham.tw.
45. (assign$ or allocat$).tw.
46. controls.tw.
47. trial.ti. or (RCT or RCTs).tw.
48. or/24-47
49. 7 and 13 and 23 and 48
50. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
51. 49 not 50
52. (neonat$ or newborn$ or new born or pediatric or paediatric or birth or infant or infants or perinatal or peri-natal or baby or babies or child or children).ti.
53. 51 not 52

5 PsycINFO search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebrovascular accidents/ or subarachnoid hemorrhage/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiparesis/ or hemiplegia/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. sensory neglect/
9. exp perceptual disturbances/
10. exp perception/
11. exp attention/
12. "extinction (learning)"/
13. (hemineglect or hemi-neglect).tw.
14. ((unilateral or spatial or hemispatial or visual) adj5 neglect).tw.
15. (inattention or hemi-inattention or extinction).tw.
16. ((perceptual or perception or visuo?spatial or visuo?perceptual or attention$) adj5 (disorder$ or deficit$ or impairment$ or abilit$)).tw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp drugs/ or exp drug therapy/ or exp psychopharmacology/
19. exp dopamine agonists/
20. exp catecholamines/
21. exp adrenergic drugs/
22. exp sympathomimetic drugs/
23. (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine).mp.

24. ((adrenergic or noradrenergic) adj5 agonist$).tw.
25. (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyldopa or xylazine).mp.
26. (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine).mp.
27. ((drug or pharmacol$) adj5 (therap$ or treat$ or effect$)).tw.
28. pharmacotherap$.tw.
29. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 7 and 17 and 29

6 LILACS search strategy

1. (Drug Therapy or Drug Therapies or Chemotherapy or Chemotherapies or Pharmacotherapy or Pharmacotherapies)
2. (Perceptual Disorder or Somatosensory Discrimination Disorder or Somatosensory Discrimination Disorders or Sensory Neglect or Sensory Neglects or Hemisensory Neglect or Hemisensory Neglects or Hemispatial Neglect or Hemispatial Neglects)
3. (Stroke or Strokes or Apoplexy or CVA (Cerebrovascular Accident) or CVAs (Cerebrovascular Accident) or Cerebrovascular Accident or Cerebrovascular Accidents or Cerebrovascular Apoplexy or Cerebrovascular Stroke or Cerebrovascular Strokes or Brain Vascular Accident or Brain Vascular Accidents or Cerebral Stroke or Cerebral Strokes or Acute Stroke or Acute Strokes or Acute Cerebrovascular Accident or Acute Cerebrovascular Accidents)
4. 1 and 2 and 3

Aprovação do Comitê de Ética e Pesquisa

unesp
Universidade Estadual Paulista
Faculdade de Medicina de Botucatu

Distrito Rubião Junior, s/nº - Botucatu – S.P.
CEP: 18.618-970
Fone/Fax: (0xx14) 3811-6143
e-mail secretaria: capellup@fmb.unesp.br
e-mail coordenadoria: tsarden@fmb.unesp.br

Comitê de Ética em Pesquisa
Ética

Registrado no Ministério da Saúde
em 30 de abril de 1997

Botucatu, 11 de junho de 2012 Of. 306/2012

Ilustríssimo Senhor
Prof. Dr. Luiz Antônio de Lima Resende
Departamento de Cirurgia e Ortopedia da
Faculdade de Medicina de Botucatu

Prezado Dr. Luiz Antônio,

Informo que o Projeto de Pesquisa **(Protocolo CEP 4223-2012)** Investigação de hemineglig**ê**ncia após Acidente Vascular Encefálico, a ser conduzido por Gustavo José Luvizutto, orientado por Vossa Senhoria, co-orientado por Rodrigo Bazan, com a colaboração de Tamiris Aparecida Monteiro, recebeu do relator parecer favorável, aprovado em reunião de 07/05/2012.

Situação do Projeto: APROVADO. Os pesquisadores deverão apresentar ao CEP ao final da execução do Projeto o "Relatório Final de Atividades".

Atenciosamente,

Prof. Dr. Trajano Sardenberg
Coordenador do CEP