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**Non-pharmacological intervention for posterior cortical atrophy**

Weill-Chounlamountry A *et al*. Non-pharmacological intervention for PCA

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**Abstract**

Posterior cortical atrophy (PCA) is a rare neurodegenerative condition characterized by progressive visual-perceptual deficits. Although the neurocognitive profile of PCA is a growing and relatively well-established field, non-pharmacological care remains understudied and to be widely established in clinical practice. In the present work we review the available literature on non-pharmacological approaches for PCA such as cognitive rehabilitation including individual cognitive exercises and compensatory techniques to improve autonomy in daily life, and psycho-education aiming to inform people with PCA about the nature of their visual deficits and limits of cognitive rehabilitation. The reviewed studies totalized 7 patients. There is a scarcity of the number of studies, consisting mostly of case studies. Results suggest non-pharmacological intervention to be a potentially beneficial approach for the partial compensation of deficits, improvement of daily functionality, and improvement of quality of life. Clinical implications and future directions are also highlighted for the advancement of the field, in order to clarify the possible role of non-pharmacological interventions, and its extent, in PCA.

**Key words**: Posterior cortical atrophy; Non-pharmacological intervention; Neuropsychological rehabilitation; Alzheimer’s disease; Cognitive rehabilitation

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**Core tip**: Non-pharmacological interventions remains scarcely explored as therapies for posterior cortical atrophy (PCA). Preliminary evidence suggests the potential of cognitive rehabilitation and psychoeducation. There is a need for randomized controlled trials evaluating the efficacy and cost-effectiveness of non-pharmacological approaches in PCA.

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# INTRODUCTION

Posterior cortical atrophy (PCA) or Benson’s syndrome[1] is a rare neurodegenerative syndrome mainly characterized by progressive visual-perceptual deficits. The precise prevalence and incidence of PCA are yet to be established, due to an overall lack of knowledge of this syndrome[2,3]. However Snowden has reported a 5% prevalence of PCA in a population of Alzheimer’s disease (AD) subjects[4]. PCA is often described as a visual variant of AD in which there are predominant neurovisual impairments[5] with the presence of common AD brain changes such as senile and neurofibrillary plaques[6]. This latter classification is controversial because PCA can also occur as a result of other neurodegenerative diseases such as cortico-basal degeneration, Lewy body dementia or prion disease[7-9]. In those individuals with PCA with underlying Alzheimer pathology, the distribution of plaques and tangles differs from the common amnestic AD variant due to their predominance in posterior cerebral regions, sparing the middle regions of the temporal lobes[10] and also involving the white matter lateralized on the right along visual pathways[11].

The course of PCA is characterized by insidious and progressive impairment of cognitive functions, primarily consisting of central visual deficits and excluding peripheral visual deficits or acquired focal lesion[5]. PCA patients typically present with a mean age of onset of 60 years and an average diagnostic delay of 4 years[12].

Homonymous lateral hemianopsia is often reported anecdotally in PCA, whereas this sign could be an early indicator in some patients[13]. Praxic and spatial disorders (dressing apraxia, constructional apraxia, or ideomotor apraxia) are often associated[5,11,12,14]. Some studies report the presence of a significant reduction in verbal fluency as well as an anomia[10,15,16] related to anatomical and functional abnormalities of the left temporal-parietal junction in some patients[10,16] and deficits in working memory[15]. In the early stage of PCA, episodic memory and executive functions are relatively preserved when comparing to typical/amnestic AD[5,11].

Daily life is severely affected by impairments in visuospatial orientation or visual recognition, and in the beginning of the disease, complaints of subjects with PCA encompass daily functioning. Difficulties in reading are the most frequently reported complaints[3,9,17-25] occurring in 80% of PCA patients[26]. In this regard, reading of texts is more impaired than isolated words or letters, with patients losing lines while reading and overlapping words, failing in using a “letter by letter” strategy[26] and sometimes not even being able to read their own writing[17,25]. As it can be inferred, visuospatial impairments might lead to the inability to perform simple activities of daily life [dressing[9,19,20,23,25] (how to orientate clothes to dress)], and instrumental activities such as finding the handle of a car[21], using a telephone[18], or looking at an analogue watch[18,22]. Patients can experience limitations such as be hesitating on how to sit[19], difficulties to find a way in unfamiliar surroundings[9,20,27], or even sometimes, in familiar surroundings[25,28]. Gradually, PCA patients lose the ability to draw or write[20,24] and to drive a car[9,11,24,25], which might contribute to losing their job[9,18,28] when patients are of working age.

Despite a relatively well-known neurocognitive profile, non-pharmacological intervention in PCA is still rarely described or implemented even though recommended[29,30] since its benefits are encouraging for PCA patients’ daily life[25,31-33].

In the available literature, two types of intervention approaches have been reported previously: (1) cognitive rehabilitation programs, aiming at maximizing patient cognition and functionality[25,31,32]; and (2) psycho-educative programs[33] which consist of a didactic and therapeutic approach for people with PCA and their caregivers in order to facilitate coping, understanding of the disease, and to reduce its impact in daily life.

Cognitive rehabilitation aims to address impaired cognitive functions (memory, executive functions, attention...) and can be performed individually or in group. Cognitive rehabilitation is a therapeutic intervention approach which aims to improve functioning of patients in daily life, whether in limitation of activities or in restriction of participation, as referenced by the international classification of functioning, disability and health (ICF). Furthermore, cognitive rehabilitation requires identifying individual needs and goals with suitable assessments in order to implement restorative or compensatory interventions.

Cognitive rehabilitation has shown evidence of efficacy in the treatment of cognitive disorders acquired after stroke[34,35]. Indeed, this intervention approach has also shown some evidence of efficacy in people with AD[36-39]. In a pilot study, Clare *et al*[38] has previously shown that people with early-stage dementia could benefit from cognitive rehabilitation and these subjects could personally identify individual goals of daily life. It was a single blind, randomized controlled study in which the three following interventions (during eight sessions) were applied to 69 subjects with dementia at an early stage: (1) cognitive rehabilitation (*n* = 23); (2) relaxation therapy, as a placebo condition (*n* = 24); and (3) treatment as usual (mainly pharmacological) (*n* = 22). Goal performance improved for subjects who received cognitive rehabilitation with maintenance beyond six months without any intervention. Conversely, no change was noticed for the other two groups.

# CURRENT STATE OF ART

## Cognitive rehabilitation

Presently, only three case studies on three patients[25,31,32] fall within the scope of cognitive rehabilitation approaches. They described similar comprehensive approaches, which included: (1) improving autonomy in daily life as a goal; (2) individual cognitive training exercises aimed at reducing cognitive deficits; (3) introduction of compensatory techniques; and (4) a psycho-educational aspect aiming to explain to people with PCA the nature of their visual deficits and to inform them about the limits of cognitive rehabilitation as a comprehensive remediation in degenerative diseases. The first case was reported by Roca *et al*[32] and involved a 64 years old man, with PCA characterized by visual agnosia with a complete Balint’s syndrome (simultagnosia, optic ataxia and oculomotor disorders). Namely, there was a dorsal simultagnosia responsible for difficulties such as in discerning more than one object at the same time due to an attentional limitation (so that visual recognition was focusing on an isolated part of the object), optic ataxia, as well as oculomotor disorders and reading difficulties. A second case was reported by Weill-Chounlamountry *et al*[25] and involved a 60 years old woman presented with progressive visual disorders since she was 54 years old. She presented with visual agnosia, simultagnosia, visual-constructive apraxia, left spatial neglect, impaired visuo-spatial working memory, and her reading and writing abilities were also affected. The third case was reported by Alves *et al*[31] and involved a 57 years old man who presented progressive decline of visuo-spatial and perceptive abilities, with praxic deficits and also impairment in written language. An early-stage of visual variant of AD had been diagnosed, two years earlier in this patient, following difficulties in driving, writing or reading. As it can be inferred, for these three patients, difficulties were predominantly visual whereas memory and executive abilities were comparatively more preserved in agreement with previous descriptions[5].

Indeed there were many similarities between those three patients. They shared a common semiology of occipitoparietal dorsal visual pathway conjugated with visual agnosia due to a disturbance of the occipitotemporal ventral visual pathway and also a relative preservation of cognitive performance without major executive functions disorder or memory impairment. For patients SS and LO, the beginning of their clinical history was marked by various ophthalmological consultations before consulting neurologists. All three had preserved awareness of their disorders, likely responsible for some of the anxiety, as it is often described in PCA subjects[2,22,40].

SS, Roca’s patient[32], received a cognitive intervention whose goals were selected in collaboration with the patient and his family. They aimed to improve the functioning of activities in daily life which they had considered important, such as being able to find nearby objects, diminishing difficulties in pouring drinks, and being able to read messages left by his family. The cognitive rehabilitation programme contained psycho-educative intervention, cognitive rehabilitation selected to reinforce preserved functions (*e.g.*, recognition of objects and visual exploration strategies) and also compensatory intervention (*e.g.*, use of tactile afferents to offset some visual problematic situations, like pouring a liquid in a glass). Weill-Chounlamountry’s patient, LO, benefited from similar interventions in a multidisciplinary approach (speech therapy, occupational therapy, and physiotherapy), in terms of reinforcement of residual visual abilities, and compensation strategies and also a psycho-educative intervention[25]. The reinforcement of residual visual abilities contained training of visual recognition (objects, pictures, and scenes) and of visual exploration (where to look and how to explore, in various tasks with light pursuit for an example), with the additional aim of decreasing simultagnosia. One of the major complaints of LO was the loss of reading, which was regained once simultagnosia and inabilities in visual exploration decreased. In addition, compensation strategies were also used in those exercises, such as the use of a rule and “finger-cursor” in order to guide the visual exploration when reading or sewing back labels on the clothes of the patient to recover autonomy of dressing. Further activities have been conducted to provide a more comprehensive intervention and transfer of training to daily life, such using public transport, as well as planning and organizing projects. Similarly, Alves *et al*[31] have proposed a cognitive rehabilitation programme with specific cognitive training sessions for written language and numbers, temporal, and spatial orientation, and promotion of autonomy in daily life. These were complemented by psycho-educative intervention. After an intensive intervention of 3 sessions per week (totalling 60 h), this patient showed small neuropsychological improvements and a modest improvement in daily functioning, with the patient being more able to resort to environmental cues, such as daylight, for temporal orientation.

## Psychoeducation

Regarding psycho-educational interventions, Videaud *et al*[33] has proposed a psycho-educative programme to four patients with PCA and their caregivers. There were six, two-hour sessions every two months during one year. The program included, in order of the sessions: (1) information about the disease to enhance the understanding of PCA subjects and their caregivers; (2) an assessment of repercussion of the PCA on the activities of daily life; (3) a speaking time; (4) a use of technical aids to improve the quality of life; and (5) strengthening the knowledge and information about available help (financial and human aids). After the programme, results were generally positive: the quality of life appeared unchanged, but knowledge about the disease and exchanges between participants reduced the anxiety of caregivers.

## Motor interventions and vision training

Lastly, to our best knowledge, no studies are available that focus on other non-pharmacological interventions, such as vision therapy supervised by orthoptists or single-component physical therapy, or physical exercise for PCA patients.

**CONCLUSION**

# *Summary of findings*

Cognitive rehabilitation programs have been successful at partially remediating cognitive impairments and improving functionality in PCA, whereas the contribution of isolated psycho-educative intervention was moderate. Many studies have already shown efficacy of cognitive rehabilitation in brain injury[34,35,41] and a recent study shows that such interventions may benefit people exhibiting initial to moderate dementia[38], as is the case with these three clinical case studies of patients with PCA[25,31,32]. Strengthening residual abilities might contribute to decreased errors in daily life and profiled above to enhance the quality of life. It was possibly an awareness of some of their preserved abilities and incitement to use them that have allowed these patients to regain some autonomy. Following their respective interventions, they have thus learned to understand their disease, and to develop compensatory strategies (and use them) when they were needed with a consequent improvement of the goals they have set. It is our understanding that cognitive rehabilitation intervention can be beneficial as long the overall cognitive abilities are preserved and may, thus, allow for a transfer to daily life.

## Clinical implications for current non-pharmacological care

In light of the aforementioned results, some prerequisites seem to be crucial to reach individual functional goals and focused requests of people with PCA: (1) It appears important to ensure that patients have sufficient overall cognitive functioning level to follow cognitive rehabilitation[42] and to implement strategies proposed by therapists; and (2) Cognitive rehabilitation should be focused on life plans of the patient and should also involve caregivers. A previous study indicated[38] that goal-oriented intervention can be helpful to people with AD, since they are able to identify goals and can provide information about their needs in daily life or in order to reduce memory deficits. In the same way, the definition of functional goals in daily life can be a key to success for cognitive rehabilitation in people with PCA. Subjects must, therefore, have realistic functional goals that are shared with therapists and caregivers and which concern either the activity, or the participation, in improving their quality of life and their environment, as referenced by the international classification of functioning, disability and health (ICF).

Therefore, based on our current knowledge, cognitive rehabilitation programs designed for PCA subjects could include: (1) A psycho-educative intervention component with the aim of explaining neurological mechanisms underlying the troubles experienced by the patients and their caregivers; (2) Stimulation/maximization/development of preserved abilities either in activities of daily life and/or in visual situations. Patients with PCA might underuse their residual abilities because there is sometimes a real gap between observed performance and complaints expressed. Patients should learn to reuse their skills that are still preserved, but underused. Therefore, psycho-educative intervention will clarify these residual abilities[33]. One example, of such residual ability is the gaze.  Spontaneously, patients with PCA stare and do not explore their environment, even though they retain the ability to do so. Through dedicated training of exploration with vanishing cues, patients can relearn how to explore visually, first in constrained situations and limited space (computer screen for an example), and then transfer these trainings to larger environments (“Vanishing cues” means facilitating the task being performed with cues which fade gradually until they disappear completely); (3) Dedicated, focused and intensive training determined according to the goals shared by the multidisciplinary team, patients with PCA and their families (For example, write a shopping list and be able to read it); and (4)Theuse of compensatory strategies for praxic disorders or spatial disorders. A standardised occupational therapy programme had previously been shown to produce positive effects in stroke patients[43-45]. It uses strategy control and contains three successive phases: (1) initiation and orientation, which encompasses formulating a plan of action and selecting the correct objects; (2) execution of the selected plan; and (3) control of the result, followed by correction, if necessary. Patients learn actions with verbal aids and they can use the verbalisation of the action plan during task performance. For an example, cues can be labels on clothes for dressing, or a colour card displayed on doors for orientation at home. The therapist teaches systematic spatial orientation of clothes before dressing, and then uses strategy control (*i.e.,* choice of clothes, orientation of clothes with a verbalisation by patient with PCA, dressing, and finally control if the dressing is performed correctly).

# *Future directions*

In the present work we reviewed the existing data on non-pharmacological interventions for PCA. Although evidence is scarce, preliminary findings do exist for cognitive rehabilitation and psycho-education, suggesting their potential beneficial role/impact. Moreover, present studies suggest and serve as a proof of concept for their implementation feasibility in PCA patients. These findings support related evidence in the field of dementia. For example, in a recent meta-analysis, Alves *et al*[39] showed that cognitive intervention might lead to benefits in global cognitive status. Moreover these interventions can be developed to be cost-effective and feasible options for ameliorating cognition, functionality, quality of life, and/or provide relevant experiences[46,47].

As has been observed in the global field of Alzheimer´s disease and other dementias[46,48], non-pharmacological approaches might play a pivotal/relevant role within the clear need for complementing, pharmacological management of PCA. Further studies assessing the potential of non-pharmacological intervention for PCA must rely on systematic enquiry through solid research design. In this regard, RCT’s are considered the gold standard. A concerted and systematic effort of researchers and practitioners in the field should focus on conducting clinical research with short-term applied/applicable value which would bring both clarification of scientific and potential clinical value. For example, vision therapy studies could be conducted in order to assess their specific efficacy on the compensation, or even amelioration, of neurovisual impairments of these patients and its potential impact on daily life functionality. Indeed, recent evidence suggests that visual rehabilitation might play a relevant role in the neurorehabilitation field, both in terms of aiming at promoting recovery or compensation, but also based on underlying functional and biological neuroplasticity[49,50]. Similarly, cognitive training might delay/slow cognitive dysfunction progression in early stages and should be explored for this purpose.

Taking in to account the current state of the field, we propose the following steps: (1) To conduct group studies for interventions showing promising results, such as cognitive rehabilitation. This would also aid in clarifying possible differential effects of each therapy; (2) Whenever RCT’s or other group studies are not possible, due to participant number or other constraints, case studies[51] should be used, or quasi-experimental (*e.g*., ABAB designs with statistical methods, such as Significant Change); (3) Likewise, case studies can provide a feasible option for exploring the potential role of “experimental” non-pharmacological therapies, such as vision therapy and efforts should be developed for testing each of the available non-pharmacological therapies; and (4) Studies should, therefore, sequentially focus on assessing implementation feasibility, efficacy, cost-effectiveness, and differential/compared efficacy for symptoms/difficulties/functionality.

In sum, current research in the field of dementia suggests that PCA patients show relative preserved insight in the early and moderate stages, and preliminary evidence showing promising effects for non-pharmacological interventions in PCA, warrant future research.

# REFERENCES

1 **Benson DF**, Davis RJ, Snyder BD. Posterior cortical atrophy. *Arch Neurol* 1988; **45**: 789-793 [PMID: 3390033 DOI: 10.1001/archneur.1988.00520310107024]

2 **Crutch SJ**, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. *Lancet Neurol* 2012; **11**: 170-178 [PMID: 22265212 DOI: 10.1016/S1474-4422(11)70289-7]

3 **Vighetto A**. Towards an earlier diagnosis of Alzheimer's disease presenting with visuospatial disorders (posterior cortical atrophy). *Rev Neurol* (Paris) 2013; **169**: 687-694 [PMID: 24035594 DOI: 10.1016/j.neurol.2013.08.001]

4 **Snowden JS**, Stopford CL, Julien CL, Thompson JC, Davidson Y, Gibbons L, Pritchard A, Lendon CL, Richardson AM, Varma A, Neary D, Mann D. Cognitive phenotypes in Alzheimer's disease and genetic risk. *Cortex* 2007; **43**: 835-845 [PMID: 17941342 DOI: 10.1016/S0010-9452(08)70683-X]

5 **McMonagle P**, Deering F, Berliner Y, Kertesz A. The cognitive profile of posterior cortical atrophy. *Neurology* 2006; **66**: 331-338 [PMID: 16476930 DOI: 10.1212/01.wnl.0000196477.78548.db]

6 **Ross SJ**, Graham N, Stuart-Green L, Prins M, Xuereb J, Patterson K, Hodges JR. Progressive biparietal atrophy: an atypical presentation of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1996; **61**: 388-395 [PMID: 8890778 DOI: 10.1136/jnnp.61.4.388]

7 **Alves J**, Soares JM, Sampaio A, Gonçalves OF. Posterior cortical atrophy and Alzheimer's disease: a meta-analytic review of neuropsychological and brain morphometry studies. *Brain Imaging Behav* 2013; **7**: 353-361 [PMID: 23690254 DOI: 10.1007/s11682-013-9236-1]

8 **Caine D**. Posterior cortical atrophy: a review of the literature. *Neurocase* 2004; **10**: 382-385 [PMID: 15788276 DOI: 10.1080/13554790490892239]

9 **Mendez MF**. Visuospatial deficits with preserved reading ability in a patient with posterior cortical atrophy. *Cortex* 2001; **37**: 535-543 [PMID: 11721864 DOI: 10.1016/S0010-9452(08)70592-6]

10 **Migliaccio R**, Agosta F, Rascovsky K, Karydas A, Bonasera S, Rabinovici GD, Miller BL, Gorno-Tempini ML. Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. *Neurology* 2009; **73**: 1571-1578 [PMID: 19901249 DOI: 10.1212/WNL.0b013e3181c0d427]

11 **Migliaccio R**, Agosta F, Toba MN, Samri D, Corlier F, de Souza LC, Chupin M, Sharman M, Gorno-Tempini ML, Dubois B, Filippi M, Bartolomeo P. Brain networks in posterior cortical atrophy: a single case tractography study and literature review. *Cortex* 2012; **48**: 1298-1309 [PMID: 22099855 DOI: 10.1016/j.cortex.2011.10.002]

12 **Tang-Wai DF**, Graff-Radford NR, Boeve BF, Dickson DW, Parisi JE, Crook R, Caselli RJ, Knopman DS, Petersen RC. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology* 2004; **63**: 1168-1174 [PMID: 15477533 DOI: 10.1212/01.WNL.0000140289.18472.15]

13 **Formaglio M**, Krolak-Salmon P, Tilikete C, Bernard M, Croisile B, Vighetto A. [Homonymous hemianopia and posterior cortical atrophy]. *Rev Neurol* (Paris) 2009; **165**: 256-262 [PMID: 19124140 DOI: 10.1016/j.neurol.2008.10.010]

14 **Kas A**, de Souza LC, Samri D, Bartolomeo P, Lacomblez L, Kalafat M, Migliaccio R, Thiebaut de Schotten M, Cohen L, Dubois B, Habert MO, Sarazin M. Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain* 2011; **134**: 1464-1478 [PMID: 21478188 DOI: 10.1093/brain/awr055]

15 **Crutch SJ**, Lehmann M, Warren JD, Rohrer JD. The language profile of posterior cortical atrophy. *J Neurol Neurosurg Psychiatry* 2013; **84**: 460-466 [PMID: 23138762 DOI: 10.1136/jnnp-2012-303309]

16 **Magnin E**, Sylvestre G, Lenoir F, Dariel E, Bonnet L, Chopard G, Tio G, Hidalgo J, Ferreira S, Mertz C, Binetruy M, Chamard L, Haffen S, Ryff I, Laurent E, Moulin T, Vandel P, Rumbach L. Logopenic syndrome in posterior cortical atrophy. *J Neurol* 2013; **260**: 528-533 [PMID: 23007194 DOI: 10.1007/s00415-012-6671-7]

17 **Beversdorf DQ**, Heilman KM. Progressive ventral posterior cortical degeneration presenting as alexia for music and words. *Neurology* 1998; **50**: 657-659 [PMID: 9521252 DOI: 10.1212/WNL.50.3.657]

18 **Denburg NL**, Jones RD, Tranel D. Recognition without awareness in a patient with simultanagnosia. *Int J Psychophysiol* 2009; **72**: 5-12 [PMID: 18824046 DOI: 10.1016/j.ijpsycho.2008.02.012]

19 **Gardini S**, Concari L, Pagliara S, Ghetti C, Venneri A, Caffarra P. Visuo-spatial imagery impairment in posterior cortical atrophy: a cognitive and SPECT study. *Behav Neurol* 2011; **24**: 123-132 [PMID: 21606573 DOI: 10.3233/BEN-2011-0279]

20 **Goethals M**, Santens P. Posterior cortical atrophy. Two case reports and a review of the literature. *Clin Neurol Neurosurg* 2001; **103**: 115-119 [PMID: 11516556 DOI: 10.1016/S0303-8467(01)00114-7]

21 **Josephs KA**, Whitwell JL, Boeve BF, Knopman DS, Tang-Wai DF, Drubach DA, Jack CR, Petersen RC. Visual hallucinations in posterior cortical atrophy. *Arch Neurol* 2006; **63**: 1427-1432 [PMID: 17030659 DOI: 10.1001/archneur.63.10.1427]

22 **Kennedy J**, Lehmann M, Sokolska MJ, Archer H, Warrington EK, Fox NC, Crutch SJ. Visualizing the emergence of posterior cortical atrophy. *Neurocase* 2012; **18**: 248-257 [PMID: 22026812 DOI: 10.1080/13554794.2011.588180]

23 **Koch G**, Stefani A, Panella M, Giordano A, Schillaci O, Marfia GA. Posterior cortical atrophy with unilateral occipito-temporal degeneration. *J Neurol* 2004; **251**: 1530-1531 [PMID: 15645358 DOI: 10.1007/s00415-004-0573-2]

24 **Ruis C**, van den Berg E, van Zandvoort MJ, Boshuisen K, Frijns CJ. Ophthalmic impairment or higher-order visual deficit? Posterior cortical atrophy: a case report. *Appl Neuropsychol Adult* 2012; **19**: 153-157 [PMID: 23373584 DOI: 10.1080/09084282.2012.670165]

25 **Weill-Chounlamountry A**, Poncet F, Crop S, Hesly N, Mouton A, Samri D, Sarazin M, Pradat-Diehl P. Physical medicine and rehabilitation multidisciplinary approach in a case of posterior cortical atrophy. *Ann Phys Rehabil Med* 2012; **55**: 430-439 [PMID: 22771215 DOI: 10.1016/j.rehab.2012.05.001]

26 **Mendez MF**, Shapira JS, Clark DG. "Apperceptive" alexia in posterior cortical atrophy. *Cortex* 2007; **43**: 264-270 [PMID: 17405672 DOI: 10.1016/S0010-9452(08)70481-7]

27 **Delazer M**, Karner E, Zamarian L, Donnemiller E, Benke T. Number processing in posterior cortical atrophy--a neuropsycholgical case study. *Neuropsychologia* 2006; **44**: 36-51 [PMID: 15936044 DOI: 10.1016/j.neuropsychologia.2005.04.013]

28 **Liu KW**, Dai DL, Wang K, Cheung CY. A case of young-onset dementia. *Hong Kong Med J* 2011; **17**: 248-251 [PMID: 21636875]

29 **Croisile B**, Trillet M, Hibert O, Cinotti L, Le Bars D, Mauguière F, Aimard G. [Visuo-constructional disorders and alexia-agraphia associated with posterior cortical atrophy]. *Rev Neurol* (Paris) 1991; **147**: 138-143 [PMID: 2028147]

30 **Jarry D**, Rigolet MH, Rivaud S, Bakchine S. [Electrophysiologic diagnosis of 2 psycho-visual syndromes: Balint syndrome and cortical blindness. A propos of a case of Benson progressive posterior atrophy]. *J Fr Ophtalmol* 1999; **22**: 876-880 [PMID: 10572801]

31 **Alves J**, Magalhães R, Arantes M, Cruz S, Gonçalves ÓF, Sampaio A. Cognitive rehabilitation in a visual variant of Alzheimer's disease. *Appl Neuropsychol Adult* 2015; **22**: 73-78 [PMID: 25529594 DOI: 10.1080/23279095.2013.831865]

32 **Roca M**, Gleichgerrcht E, Torralva T, Manes F. Cognitive rehabilitation in posterior cortical atrophy. *Neuropsychol Rehabil* 2010; **20**: 528-540 [PMID: 20306369 DOI: 10.1080/09602011003597408]

33 **Videaud H**, Torny F, Cartz-Piver L, Deschamps-Vergara N, Couratier P. [Impact of drug-free care in posterior cortical atrophy: Preliminary experience with a psycho-educative program]. *Rev Neurol* (Paris) 2012; **168**: 861-867 [PMID: 22705230 DOI: 10.1016/j.neurol.2011.10.013]

34 **Cicerone KD**, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, Ellmo W, Kalmar K, Giacino JT, Harley JP, Laatsch L, Morse PA, Catanese J. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch Phys Med Rehabil* 2005; **86**: 1681-1692 [PMID: 16084827 DOI: 10.1016/j.apmr.2005.03.024]

35 **Cicerone KD**, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, Felicetti T, Laatsch L, Harley JP, Bergquist T, Azulay J, Cantor J, Ashman T. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Arch Phys Med Rehabil* 2011; **92**: 519-530 [PMID: 21440699 DOI: 10.1016/j.apmr.2010.11.015]

36 **Bahar-Fuchs A**, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev* 2013; **6**: CD003260 [PMID: 23740535 DOI: 10.1002/14651858.CD003260.pub2]

37 **Choi J**, Twamley EW. Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychol Rev* 2013; **23**: 48-62 [PMID: 23400790 DOI: 10.1007/s11065-013-9227-4]

38 **Clare L**, Linden DE, Woods RT, Whitaker R, Evans SJ, Parkinson CH, van Paasschen J, Nelis SM, Hoare Z, Yuen KS, Rugg MD. Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease: a single-blind randomized controlled trial of clinical efficacy. *Am J Geriatr Psychiatry* 2010; **18**: 928-939 [PMID: 20808145 DOI: 10.1097/JGP.0b013e3181d5792a]

39 **Alves J**, Magalhães R, Thomas RE, Gonçalves OF, Petrosyan A, Sampaio A. Is there evidence for cognitive intervention in Alzheimer disease? A systematic review of efficacy, feasibility, and cost-effectiveness. *Alzheimer Dis Assoc Disord* 2013; **27**: 195-203 [PMID: 23314062 DOI: 10.1097/WAD.0b013e31827bda55]

40 **Everhart DE**, Highsmith JM, Davis CE. Posterior cortical atrophy: a case study of Benson's syndrome that initially presented as anxiety disorder. *Appl Neuropsychol Adult* 2012; **19**: 229-236 [PMID: 23373609 DOI: 10.1080/09084282.2012.686791]

41 **Rohling ML**, Faust ME, Beverly B, Demakis G. Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of Cicerone et al.'s (2000, 2005) systematic reviews. *Neuropsychology* 2009; **23**: 20-39 [PMID: 19210030 DOI: 10.1037/a0013659]

42 **Binetti G**, Moretti DV, Scalvini C, di Giovanni G, Verzeletti C, Mazzini F, Valent S, Ghidoni R, Benussi L. Predictors of comprehensive stimulation program efficacy in patients with cognitive impairment. Clinical practice recommendations. *Int J Geriatr Psychiatry* 2013; **28**: 26-33 [PMID: 22337339 DOI: 10.1002/gps.3785]

43 **Donkervoort M**, Dekker J, Stehmann-Saris FC, Deelman BG. Efficacy of strategy training in left hemisphere stroke patients with apraxia: A randomised clinical trial. *Neuropsychol Rehabil* 2001; **11**: 549-566 [DOI: 10.1080/09602010143000093]

44 **Geusgens C**, van Heugten C, Donkervoort M, van den Ende E, Jolles J, van den Heuvel W. Transfer of training effects in stroke patients with apraxia: an exploratory study. *Neuropsychol Rehabil* 2006; **16**: 213-229 [PMID: 16565035 DOI: 10.1080/09602010500172350]

45 **Geusgens CA**, van Heugten CM, Cooijmans JP, Jolles J, van den Heuvel WJ. Transfer effects of a cognitive strategy training for stroke patients with apraxia. *J Clin Exp Neuropsychol* 2007; **29**: 831-841 [PMID: 18030634 DOI: 10.1080/13803390601125971]

46 **Alves J**, Alves-Costa F, Magalhães R, Gonçalves OF, Sampaio A. Cognitive stimulation for Portuguese older adults with cognitive impairment: a randomized controlled trial of efficacy, comparative duration, feasibility, and experiential relevance. *Am J Alzheimers Dis Other Demen* 2014; **29**: 503-512 [PMID: 24526760 DOI: 10.1177/1533317514522541]

47 **Alves J**, Magalhães R, Machado A, Gonçalves OF, Sampaio A, Petrosyan A. Non-pharmacological cognitive intervention for aging and dementia: Current perspectives. *World J Clin Cases* 2013; **1**: 233-241 [PMID: 24340275 DOI: 10.12998/wjcc.v1.i8.233]

48 **Andrieu S**, Coley N, Lovestone S, Aisen PS, Vellas B. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. *Lancet Neurol* 2015; **14**: 926-944 [PMID: 26213339 DOI: 10.1016/S1474-4422(15)00153-2]

49 **Dundon NM**, Bertini C, Làdavas E, Sabel BA, Gall C. Visual rehabilitation: visual scanning, multisensory stimulation and vision restoration trainings. *Front Behav Neurosci* 2015; **9**: 192 [PMID: 26283935 DOI: 10.3389/fnbeh.2015.00192]

50 **Pedroli E**, Serino S, Cipresso P, Pallavicini F, Riva G. Assessment and rehabilitation of neglect using virtual reality: a systematic review. *Front Behav Neurosci* 2015; **9**: 226 [PMID: 26379519 DOI: 10.3389/fnbeh.2015.00226]

51 **Perdices M**, Tate RL. Single-subject designs as a tool for evidence-based clinical practice: Are they unrecognised and undervalued? *Neuropsychol Rehabil* 2009; **19**: 904-927 [PMID: 19657974 DOI: 10.1080/09602010903040691]

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