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Neurovascular Neuropsychology

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Chapter 19
Pharmacological Treatment of Post-stroke Cognitive Deficits

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19.1 Introduction

Stroke is defined as a dysfunction of the brain due to an interruption of the cerebral blood flow. According to the World Health Organization 15 million people suffer stroke worldwide each year, and of these, 5 million die. The financial repercussion associated with stroke and the subsequent disability is substantial, summing over 30 billion dollars annually (Roger et al., 2012). Nevertheless, since the mortality rate of stroke victims is falling steadily (Towfighi & Saver, 2011), the focus of scientific and medical attention has shifted to the long-lasting disabilities that survivors suffer after stroke. It is estimated that around 30% of all stroke survivors are left with residual disabilities affecting physical, cognitive, behavioral functions, and quality of life. Therefore, in addition to medical management after acute stroke to prevent further cerebral damage, therapeutic interventions (rehabilitation, pharmacological

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treatment) are initiated with the ultimate goal of achieving better recovery in terms of disability and affliction during the years that follow (Hachinski, Donnan, Gorelick, et al., 2010). Rehabilitation of physical motor impairment is extensively investigated, with studies indicating significant advances on recovery following medical treatments, physiotherapeutic therapy, and non-invasive brain stimulation (NIBS) (Chollet et al., 2014; Liepert, 2016; Van Peppen et al., 2004). However, strategies for restoration of cognitive functions in post-stroke cognitive deficits (PSCD) have received less attention with cognitive rehabilitation arguably considered to be the "lost dimension" of stroke rehabilitation (Cumming, Marshall, & Lazar, 2013; Mellon et al., 2015).

Post-stroke motor, cognitive, and behavioral impairments are evident in the immediate aftermath of stroke, with many deficits resolving spontaneously in the ensuing months (Cassidy & Cramer, 2017). Estimating the persistence of PSCD in the chronic period is challenging, given the myriad of possible sequelae. Hence, reported longitudinal estimations have varied from 30% to 50% (Mellon et al., 2015; Pendlebury & Rothwell, 2009; Rist, Chalmers, Arima, et al., 2013), showing the heterogeneity on the prevalence of PSCD. Therefore, heterogeneity of impairment at the individual level seems to be the rule, determined by the abovementioned factors and others such as previous medical conditions, age of onset, educational level, severity of stroke, lesion size and location, and genetic polymorphisms (Chang, Chang, Cragg, & Cramer, 2013). Importantly, patients with moderate PSCD are six times more likely to transition to incident dementia, compared with those without cognitive impairment, with up to a quarter of patients with cognitive impairment diagnosed with dementia in the 3 years following stroke (Merriman, Sexton, Donnelly, et al., 2018). Given this high prevalence of PSCD and their potential to evolve into dementia, expanding research on rehabilitation is crucial.

19.1.1 Principles Underlying Recovery Promoted by Cognitive Rehabilitation and Drugs

Recovery from stroke deficits is mainly supported by neuroplasticity, which can be guided and boosted through different interventions (Cramer & Riley, 2008; Cumming et al., 2013; Dobkin & Dorsch, 2013). Neuroplasticity provides to the brain an innate capacity of changing, allowing it to adjust to adverse circumstances (brain injury). Neural plasticity is sustained by neuroanatomic and neurochemical changes such as the growth of synapses and dendrites (Zhang, Zhang, & Chopp, 2008), axonal remodeling and angiogenesis (Ding et al., 2008), and increased expression of growth-related genes and proteins (Li & Carmichael, 2006). After a stroke, these brain changes take place during three different stages of evolution (Berthier et al., 2011; Cassidy & Cramer, 2017). The initial stage arises soon after the stroke wherein brain tissue and networks could be salvaged by reperfusion or

neuroprotection (Hillis & Heidler, 2002). The second stage covers from days to weeks after stroke onset and coincides with the start of brain repairing mechanisms (Hillis & Heidler, 2002). Spontaneous recovery is accentuated during this period. Finally, the third stage is confined to the chronic phase in which spontaneous recovery is no longer expected and a tendency to stabilization occurs in regard to intrinsic repair-related events. In this vein, the election and implementation of therapeutic interventions that modulate neural plasticity even several years after stroke onset take a special relevance in order to improve clinical outcomes. Improvement of PSCD relies on both the repair of dysfunctional networks and the recruitment of spared neural networks (Dobkin & Dorsch, 2013; Small, Buccino, & Solodkin, 2013) which can be stimulated through different interventions such as cognitive training, drugs, or NIBS administered alone or combined between them.

Drug treatment improves PSCD, even when given unpaired with behavioral treatments (Berthier et al., 2009; Chen et al., 2010; Hong, Shin, Lim, Lee, & Huh, 2012; López-Barroso et al., 2018). However, there is evidence that drug action is boosted when combined with behavioral interventions. Importantly, it seems that drugs combined with intensive training are associated with better outcomes than when combined with distributed therapies (Berthier, Dávila, García-Casares, & Moreno-Torres, 2014). The contribution of adding behavioral interventions to drug treatment results from harnessing *experience-dependent plasticity*, a label used to reflect wiring and rewiring changes in synapses and entire networks in response to experience (Kleim & Jones, 2008; Kolb & Gibb, 2014). Therefore, it seems that drug treatment can prime cortical and subcortical excitability, optimizing learning process promoted by cognitive rehabilitation. This would lead to obtain more pronounced and durable benefits, presumably by converting short-term benefits in long-lasting gains, which may show little decrements even after stopping drug treatment (Berthier et al., 2003; Berthier, Higueras, Fernández, Hinojosa, & Martín, 2006; Berthier, Hinojosa, Martín Mdel, & Fernández, 2003).

In this chapter, we review the pharmacological treatment of PSCD. It the past few years, there have been several tutorial reviews (Berthier, García-Casares, et al., 2011; Llano & Small, 2016) and book chapters (Flanagan & Gordon, 2009; Berthier & Dávila, 2015) on the pharmacotherapy of PSCD. Nearly all this body of work has examined the impact of pharmacological approaches in animal and human studies, focusing on the neurotransmitter systems affected by the stroke and the drugs targeting them to improve outcomes. Therefore, in this chapter besides briefly updating the state-of-the-art and the theoretical rationale for using drugs to treat PSCD, we briefly review the impact of drug treatment on key PSCD such as aphasia, neglect, and cognitive impairment. We also provide some guidelines for refining and expanding the use of efficacy measures and responder analysis methods. Finally, we dedicate a few words to the emerging strategy of combining drugs to further augment and speed up recovery and the manner in which cognition-enhancing drugs modulate neural network reorganization and activity.

19.1.2 Drug Treatment: The State-of-the-Art

Neurorehabilitation is the cornerstone treatment of PSCD, and the complementary role of pharmacotherapy is to prime the brain for enhancing the benefits provided by behavioral interventions. Nevertheless, drug trials aimed to improve cognition in Alzheimer's disease (AD) (Ferris & Farlow, 2013), Parkinson's disease (Emre et al., 2004), and vascular cognitive impairment (VCI) (Guekht et al., 2013; Leijenaar et al., 2018; Perng, Chang, & Tzang, 2018) have been straightforwardly designed, overlooking the key role of neurorehabilitation in augmenting the benefits. The "drug alone" strategy has been conceived in the requirement of proving or disproving the beneficial action of the sole drug, but it disregards the potential action of combined interventions in clinical practice. Even more, the reluctance of evaluating the effects of drugs combined with neurorehabilitation jeopardizes the possibility of revealing a synergistic effect, perhaps not fully observed with the drug-only strategy. Several trials of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine unpaired with neurorehabilitation have been performed in heterogeneous groups of patients with vascular dementia (VaD) and VCI with mixed results. Small benefits in cognition were achieved, but there was a variable success in behavior and activities of daily living (Birks & Craig, 2006; Birks, McGuinness, & Craig, 2013; Erkinjuntti, Román, & Gauthier, 2004; Farooq, Min, Goshgarian, & Gorelick, 2017; Levine & Langa, 2011), thus restricting their use in clinical practice. By contrast, preliminary evidence from stroke patients with aphasia or neglect indicates that when drug treatment is paired with behavioral interventions, there are benefits in cognitive, behavioral, and quality of life domains (Berthier, 2012; Paolucci, Bureca, Multari, Nocentini, & Matano, 2010; Walker-Batson, Mehta, Smith, & Johnson, 2016).

The neurorehabilitation of PSCD has greatly benefited from neuroscience and neuropsychology insights (Berthier & Pulvermüller, 2011; Llano & Small, 2016), yet clinical translation of positive drug trials continues to lag behind. There are two main reasons that may account for the existent difficulty to overcome the gap between the laboratory research and the application of rehabilitation for PSCD. First, no large-scale randomized controlled trials (RCTs) into the use of pharmaceutical interventions to enhance benefits of cognitive rehabilitation have taken place and, hence, there has been no regulatory approval for any drug to treat such disorders. Second, there are no profit incentives to initiate new clinical trials to generate additional data for regulatory agencies to expand indications of already existent drugs (Berthier, 2014). In part, this is due to the expiration of marketed drug licenses in several countries.

In spite of these restrictions, drug interventions in clinical practice are being increasingly used in both acute in-hospital stroke settings (Barrett et al., 2011) and outpatient rehabilitation units in nearly 40% of cases (Barrett, Levy, & Gonzalez Rothi, 2007; Engelter et al., 2012; Engelter, Frank, Lyrer, & Conzelmann, 2010). Results from a recent prospective, explorative, multicenter study revealed that half of the patients received antidepressant medications to alleviate post-stroke mood

and anxiety disorders, whereas in one-third of the cases drugs were exclusively used with the aim of augmenting rehabilitation gains (Engelter et al., 2010, 2012). While depression is the most frequently treated psychiatric condition, aphasia and neglect are the most commonly treated cognitive disorders. Importantly, patients treated with levodopa, acetylcholinesterase inhibitors (e.g., donepezil, galantamine), and other agents such as antidepressants and stimulants achieved greater improvement in a functional independence measure than untreated patients (Engelter et al., 2010, 2012). Adverse events depend upon the agent used, but in general are temporary (Engelter et al., 2010). Although more studies are needed, the prescription of these drugs in clinical practice as "off-label" medications is supported by the results of several well-designed clinical trials. For example, there is moderate evidence (Level 1b) based on "proof-of-concept" RCTs that the use of levodopa, donepezil, galantamine, and memantine significantly improves aphasia severity, deficits in speech production (naming) and comprehension in patients with chronic stroke (see Berthier, Pulvermüller, Dávila, Casares, & Gutiérrez, 2011; Salter, Teasell, Bhogal, Zettler, & Foley, 2012; Teasell et al., 2012). Finally, an important aspect to consider before implementing drug treatment for PSCD is to avoid, whenever feasible, the prescription of compounds for the treatment of comorbid disorders (e.g., topiramate for seizures and migraine) (see Cappa, Ortelli, Garibotto, & Zamboni, 2007; Llano & Small, 2016) which can deleteriously impact on cognitive functions (Falchook, Heilman, Finney, Gonzalez-Rothi, & Nadeau, 2014; Goldstein, 1995, 1998).

19.1.3 Theoretical Justification for Using Drugs in Post-stroke Cognitive Disorders

Stroke lesions may disrupt the activity of various neurotransmitter systems at the level of selected basal forebrain, brainstem and deep grey nuclei, and cerebral cortex (Berthier & Pulvermüller, 2011; Bohnen, Müller, Kuwabara, Constantine, & Studenski, 2009; Husain & Mehta, 2011). This would imply that when damage to one neurotransmitter system is not significant, there exists the possibility of rescuing salvaged components of this system by modulating its spared receptors with drugs. Similarly, theoretical and applied research indicates that the justification for using pharmacological agents to treat PSCD is to leverage the activity of specific neurotransmitters in dysfunctional but not completely infarcted tissue. Circumscribed or diffuse brain lesions affect the activity of several neurotransmitters; thus, normalizing their availability at synapses with drugs is an useful strategy to boost cognition in brain-damaged patients (Berthier & Pulvermüller, 2011). In addition, since stroke decreases integration and information capacity in several networks (Adhikari et al., 2017), it may be desirable that the beneficial effect of drug treatment is exerted in (dysfunctional and healthy) brain tissue nearby and distant to the lesion that are part of one or more neural networks with specific functions (Wirsich et al., 2018). In the case that perilesional areas share multiple receptor fingerprints with the damaged

ones, it is tempting to speculate that drugs acting on perilesional tissue can play a key role in restoring function (Berthier et al., 2017), a mechanism termed "direct restoration" (Small et al., 2013). It is also possible that after the stroke, areas distant to the damaged region are recruited and remodeled to instantiate the original function, a mechanism known as "indirect restoration" (Small et al., 2013). If these remote areas belong to the same functional network, they may have the same transmitter receptor density (Hiraoka et al., 2009; Palomero-Gallagher & Zilles, 2017), so that drug treatment can render them more adaptable to comply with new task demands. Based on the connectivity of two distant brain areas, one neurotransmitter system (i.e., acetylcholine) can interact with others (i.e., glutamate, dopamine) (Mena-Segovia & Bolam, 2017). Therefore, pharmacological agents used with the aim of modulating the activity of a single neurotransmitter to enhance a cognitive process probably also influence the function of other neurotransmitters (Froudist-Walsh, López-Barroso, Torres-Prioris, Croxson, & Berthier, 2017; Furey, 2011; Mena-Segovia & Bolam, 2017). Altogether, these arguments suggest that future pharmacological studies aimed to enhance cognition in stroke with a drug need to consider its role in modulating more than a single transmitter system. This action can be boosted further by combining two agents, predominantly acting on different neurotransmitters (Berthier, Dávila, & Torres-Prioris, 2015; Froudist-Walsh et al., 2017). Combined therapies wherein one drug is added to an ongoing treatment with another agent (i.e., add-on therapy with memantine in patients already receiving donepezil or galantamine) are regularly used for the symptomatic treatment of severe AD (Atri et al., 2013; Peters et al., 2012; Tariot et al., 2004) and this approach is being translated to treat PSCD (Walker-Batson et al., 2016; López-Barroso et al., 2018—see Sect. 19.1.9). Although several PSCD have been treated with drugs, in the next sections we analyze the status of drug treatment in the most commonly investigated PSCD (aphasia, neglect, and cognitive impairment).

19.1.4 Aphasia

Aphasia, defined as the partial or complete loss of language function after acquired brain damage, is amenable to pharmacological treatment (Albert, Bachman, Morgan, & Helm-Estabrooks, 1988; Berthier, 2005; Llano & Small, 2016). Aphasia is the most frequent PSCD after left hemisphere lesions and it is independently associated with increased length of stay and complications during the acute stroke admission (Boehme, Martin-Schild, Marshall, & Lazar, 2016). Aphasia represents the PSCD most commonly treated with single (Chen et al., 2010; Hong et al., 2012) or combined drugs (Engelter et al., 2010, 2012) alongside language therapy (Berthier et al., 2009). Table 19.1 shows pharmacological studies carried out in aphasia (only recent data are shown in the text). Several agents have been used with variable results (see Berthier & Pulvermüller, 2011; Llano & Small, 2016), probably because until now there are no guidelines for selecting the period after the stroke when the drug provides greatest benefits (Zhang, Wei, Chen, & Luo 2016) or the "right" drug

Table 19.1 Clinical trials of pharmacotherapy of post-stroke aphasia

Agent	Mechanism of action	Study design	Number of studies/authors	Outcomes
Bromocriptine	Dopamine agonist	Single cases Case series Group studies Open label RCT(cross-over designs)	15 Albert et al. (1988) Bachman and Morgan (1988) MacLennan, Nicholas, Morley, et al. (1991) Gupta and Mlcoch (1992) Sabe, Leiguarda, and Starkstein (1992) Sabe, Salvarezza, Cuerva, Leiguarda, and Starkstein (1995) Gupta, Mlcoch, Scolaro, and Moritz (1995) Ozeren, Sarica, Mavi, and Demirkiran (1995) Berthier (1999) Bragoni et al. (2000) Gold, VanDam, and Silliman (2000) Hughes, Jacobs, and Heilman (2000) Raymer et al. (2001) Ashtary, Janghorbani, Chitsaz, Reisi, and Bahrami (2006) Galling, Goorah, Berthier, and Sage (2014)	Positive effects in single cases, cases series, and open-label trials mainly in transcortical motor aphasia, dynamic aphasia, and Broca's aphasia of mild to moderate severity. Improvement on production tasks in chronic patients. Lack of improvement in non-verbal cognitive abilities. Variable outcomes in moderate Broca's aphasia and lack of positive effects in severe cases. Three of four RCTs are negative. Only three trials combined bromocriptine with speech-language therapy. Limited response to speech-language therapy improves with the addition of bromocriptine. Improvement in apathy and depression is possible. Beneficial effects on functions dependent upon dopaminergic activity with little impact on other language and cognitive deficits
Levodopa	Dopamine agonist	RCT Group studies Open label RCT (parallel and cross-over designs)	4 Hacki, Kenklies, Hofmann, and Haferkamp (1990) Seniów, Litwin, Litwin, Leśniak, and Członkowska (2009) Leemann, Laganaro, Chetelat-Mabillard, and Schnider (2011) Breitenstein et al. (2015)	Anecdotal evidence of improvement of dysarthria and aphonia. Positive effects in chronic patients when given just before each session of speech-language therapy on naming and repetition especially in patients with frontal lobe damage. However, levodopa does not augment the positive response to high-intensity language therapy in subacute and chronic aphasia
Amantadine	Dopamine agonist, Uncompetitive NMDA receptor antagonist. Possible anti-cholinergic effects	Single case Open label	1 Barrett and Eslinger (2007)	Useful in transcortical aphasias. Improvement of verbal fluency in two transcortical motor aphasic patients with left putaminal hemorrhage and right anterior cerebral artery infarction when paired with speech-language therapy. Anti-cholinergic effects of this drug may negatively affect attention and memory functioning

(continued)

Table 19.1 (continued)

Agent	Mechanism of action	Study design	Number of studies/authors	Outcomes
Dexamphetamine	Catecholamine uptake inhibition	Single cases Case series Open label RCT (parallel and cross-over designs)	8 Benson (1970) Walker-Batson et al. (1992) McNeil et al. (1997) Walker-Batson et al. (2001), Walker-Batson et al. (2016) Whiting, Chenery, Chalk, and Copland (2007) Spiegel and Alexander (2011) Keser et al. (2017)	Positive effects on overall performance in communication in subacute stroke with variable efficacy at chronic stages. Negative effect on lexical-semantic deficits. Variable outcomes on naming performance when paired with model-based (semantic plus phonological) naming therapy in chronic stages. Combined therapy with amphetamine and donepezil improved language and communication deficits. Positive effects when paired with transcranial direct current stimulation and melodic intonation therapy in subjects with chronic nonfluent aphasia
Piracetam	Neuronal and vascular unspecific effects	RCT	7 Herrschaft (1988) Enderby, Broeckx, Hospers, Schildermans, and Deberdt (1994) Huber, Willmes, Poeck, Van Vleymen, and Deberdt (1997) Kessler, Thiel, Karbe, and Heiss (2000) Szelies, Mielke, Kessler, and Heiss (2011) Güngör, Terzi, and Onar (2011) Hamzei-Moghaddam, Shafa, Nazari, and Akbari (2014)	Short-lived positive effects in the acute aphasia on overall language measures, spontaneous speech, and written language. It only benefits written language at the end of the trials (see Zhang et al., 2016). Language deficit improvement correlates with both an increase in blood flow in the left peri-Sylvian cortex and shift in alpha-rhythm from frontal to occipital regions. Lack of long-term benefits in cases with large infarcts
Physostigmine	IAChE	Open label	1 Jacobs et al. (1996)	Positive effects in combination with lecithin on chronic anomia, but not on other cognitive and mood variables. Not used in clinical practice

Bifemelane	IAChE	RCT	2 Kabasawa et al. (1994) Tanaka, Miyazaki, & Albert (1997)	Positive effects on naming, comprehension, and repetition, but not in fluency. Language improvements correlate with an increase in blood flow in the left peri-Sylvian cortex
Donepezil	IAChE	Single cases Case series Group studies Open label RCT (parallel and cross-over designs)	9 Hughes et al. (2000) Tsz-Ming and Kaufer (2001) Berthier, Hinojosa, et al. (2003), Berthier, Pujol, et al. (2003) Berthier et al. (2006) Chen et al. (2010) Berthier et al. (2014) Yoon, Kim, An, and Kim (2015) Berthier et al. (2017) Woodhead et al. (2017)	Positive effects on aphasia severity and everyday functional communication. Significant benefits on spontaneous speech, comprehension, and naming in chronic aphasia. Efficacy maintained at long-term follow-up. Beneficial effects on acute aphasia. Beneficial effect when combined with intensive sentence-repetition and audiovisual repetition-imitation training and in Wernicke aphasia associated with bitemporal lesions. Negative outcome in subjects with chronic receptive phonological impairments associated with Wernicke and global aphasias, but positive response with behavioral training
Galantamine	Competitive IAChE with dual action (allosteric modulation of the α4β42 and α-7nAChR)	Open-label case-control study	1 Hong et al. (2012)	Positive effects on aphasia severity. Significant benefits on spontaneous speech, comprehension, and naming in chronic aphasia. Good responsiveness to drug in patients with possible cholinergic involvement at subcortical sites
Memantine	Moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage-dependency and fast kinetics	RCT Group study	1 Berthier et al. (2009)	Positive effects on aphasia severity and everyday functional communication. Significant benefits on spontaneous speech, comprehension, and naming. Better results pairing memantine with intensive speech-language therapy. Efficacy maintained at long-term follow-up (6 months)
Fluvoxamine	SSRI	RCT	1 Tanaka and Bachman (2007)	Positive effects on anomia

(continued)

Table 19.1 (continued)

Agent	Mechanism of action	Study design	Number of studies/authors	Outcomes
Moclobemide	IMAO-A	RCT	1 Laska et al. (2005)	Negative effect
Zolpidem	GABA agonist interacting with Ω_1 receptor	Single case	1 Cohen et al. (2003)	Positive reversible effect on verbal fluency in Broca's aphasia
Propranolol	β-blocking agent	RCT	1 Beversdorf et al. (2007)	Positive effect on naming in chronic Broca's aphasia
Vasopressin	Neurotrophic effect mediated by the V1 receptor	RCT	1 Belokoskova, Tsikunov, and Klement'ev (2002)	Positive effect on expressive and receptive language functions
Cerebrolysin	Mimics endogenous neurotrophic factors	RCT	1 Jianu et al. (2010)	Positive effect on spontaneous speech, repetition, and naming in acute Broca's aphasia

Note: Only clinical trials providing a neuroscientifically motivated rationale for the selected treatment of post-stroke aphasia are included. Other agents (haloperidol, thiazide, chlordiazepoxide) lacking a theoretical rationale were excluded. *IAChE* acetylcholinesterase inhibitor; NMDA: *N*-methyl-D-aspartate; SSRI: selective serotonin reuptake inhibitor; IMAO-A: inhibitor monoaminoxidase A; GABA: γ-aminobutyric acid; RCT: randomized controlled trial; SLT: speech-language therapy.

to improve speech production, comprehension, or both (Berthier et al., 2015). For example, the effects of piracetam on language deficits are short-lived with no long-term benefits (Güngör et al., 2011) and the outcomes of dopamine agonists (bromocriptine, levodopa) are mixed (Berthier, 2005; Gill & Leff, 2014). Regarding dopamine agonists, negative outcomes in group studies are likely to have resulted from an inadequate inclusion of candidates (global aphasias, large lesions) (Ashtary et al., 2006; Gupta et al., 1995; Sabe et al., 1995). The wrong selection of some candidates may have masked positive effects to dopaminergic manipulation in patients with a suitable profile. At present, the best candidates for dopaminergic stimulation seem to be patients with reduced drive to generate spontaneous speech (e.g., nonfluent transcortical aphasias) secondary to frontal and/or basal ganglia lesions (Cahana-Amitay, Albert, & Oveis, 2014; Gill & Leff, 2014; Raymer, 2003). The beneficial action of dopaminergic stimulation in such cases is the improvement of speech initiation, pauses in conversation, paraphasias, and naming (Albert et al., 1988; Galling et al., 2014). The action of dopaminergic stimulation to improve aphasia is through modulation of motor control, incentive reward, memory, attention, problem-solving, and learning via restoring dopaminergic activity in frontal-basal ganglia circuits (Berthier, García-Casares, et al., 2011; Berthier, Pulvermüller, et al., 2011; Cahana-Amitay et al., 2014; Gill & Leff, 2014; Seniów et al., 2009). Adding speech-language therapy to dopaminergic stimulation seems to be effective for bromocriptine (Bragoni et al., 2000; Galling et al., 2014), but it is controversial for levodopa, with one study reporting beneficial effects when levodopa was given soon before starting each daily session of aphasia therapy (Seniów et al., 2009), whereas others found that levodopa did not augment the benefit provided by intensive language therapy (Breitenstein et al., 2015; Leemann et al., 2011).

In recent years, the pharmacologic armamentarium to treat post-stroke aphasia has been expanded to incorporate anti-dementia drugs with action on the cholinergic and glutamatergic neurotransmitter systems (Berthier, García-Casares, et al., 2011; Berthier, Pulvermüller, et al., 2011) (Table 19.1). The cholinesterase inhibitor donepezil is safe and well tolerated for the treatment of acute stroke (Barrett et al., 2011), and single cases, open-label trials, and RCTs of this agent in patients with acute and chronic post-stroke aphasia showed improvements in aphasia severity, picture naming, comprehension, and everyday communication (Berthier et al., 2006; Berthier, Hinojosa, et al., 2003; Berthier, Pujol, et al., 2003; Chen et al., 2010; Yoon et al., 2015). Recent data raise the possibility that donepezil is more effective to treat production than comprehension deficits (Woodhead et al., 2017). Some support for this hypothesis comes from the study of patients with conduction aphasia and deficits in speech production (Berthier et al., 2014, 2017) and from patients with comprehension deficits associated with Wernicke's or global aphasias (Woodhead et al., 2017; Yoon et al., 2015). On one hand, donepezil significantly improved speech production in patients with chronic conduction aphasia and its action was better when it was combined with massed sentence-repetition training (40 h in 8 weeks) than with a more distributed therapy (40 h in 16 weeks) (Berthier et al., 2014). In addition, the combination of donepezil with intensive audiovisual,

repetition-imitation training improved speech production and everyday communication deficits in a patient with chronic, crossed, conduction aphasia by inducing structural plasticity in right hemisphere white matter tracts partially affected or spared by the lesion (Berthier et al., 2017). On the other hand, the extant data on the role of donepezil in aphasic patients with receptive deficits is divergent. Donepezil treatment improved auditory comprehension and other language deficits in a patient with extensive damage to the left temporal and parietal lobes sustained 8 years before and who incurred a new right temporal infarction causing severe Wernicke's aphasia (Yoon et al., 2015). Comprehension improvements with donepezil after the new stroke were associated with increased metabolic activity in bilateral perilesional areas and left cerebellum (Yoon et al., 2015). Nevertheless, donepezil led only to short-lived improvements in a patient with severe chronic Wernicke's aphasia (case 11 in Berthier, 2005). In the same vein, a recent RCT of donepezil in patients with chronic moderate-to-severe Wernicke's and global aphasias was negative in improving speech comprehension abilities (Woodhead et al., 2017). It remains to be determined whether large lesions such as those occurring in global and Wernicke's aphasia markedly deplete cortical cholinergic receptors, making these cases less responsive to cholinergic modulation. Note that in the only RCT of galantamine performed in chronic stroke aphasic patients, improvements in language performance were found mainly in cases with left subcortical involvement affecting the trajectory of the lateral cholinergic pathway (Hong et al., 2012). The potential role of rivastigmine in post-stroke aphasia has not yet been explored.

The NMDA receptors antagonist memantine given in the absence of speech-language therapy improved aphasia severity and communication deficits, and synergistic effects were obtained when intensive aphasia therapy was added (Berthier et al., 2009). The beneficial effects of the drug administered alone and in combination with behavioral training were associated with bilateral neural reorganization and the obtained gains persisted on long-term follow-up. (Barbancho et al., 2015; Berthier et al., 2009). The potential role of other pharmacological agents is included in Table 19.1**.**

19.1.5 Neglect

Post-stroke neglect is a condition characterized by a difficulty to attend, orient, or respond to stimuli presented in the hemispace contralateral to the brain lesion, usually the left side (Heilman, Bowers, Valenstein, & Watson, 1987). It is a complex syndrome with multiple underlying mechanisms and profiles, and a reported incidence ranging from 48% (Buxbaum et al., 2004) to 82% (Stone, Halligan, & Greenwood, 1993) of patients with right hemisphere strokes. Patients with different profiles of neglect often show concomitant motor deficits (hemiparesis/hemiplegia) and behavioral disorders (e.g., anosognosia for motor and cognitive deficits, somatoparaphrenia) (Orfei et al., 2007; Vallar & Ronchi, 2009). Importantly, reduced insight for neglect, expressed as either anosognosia, overestimation of spatial abili-

ties or confabulation, may impact on rehabilitation (Chen & Toglia, 2018; Starkstein, este Jorge se ha colado aqui & Robinson, 2010) and daily life functioning (Kortte & Hillis, 2011). The abnormal cognitive processes underpinning visuospatial neglect involve attention and/or sensory processing. Behavioral therapies such as prism adaptation (Rossetti, Rode, Pisella, et al., 1998) and visual scanning training are the most frequent behavioral interventions. Other promising techniques in the rehabilitation of neglect have emerged in the last decades such as virtual reality training and NIBS (Fasotti & van Kessel, 2013; Kortte & Hillis, 2011), but recovery is not always complete and mild symptoms persist (~1 year) in a large percentage (40–75%) of patients (Buxbaum, Ferraro, Whyte, et al., 2007; Nijboer, Kollen, & Kwakkel, 2013). Therefore, the use of other interventions to augment gains provided by neurorehabilitation such as pharmacotherapy is advisable.

Experimental treatments of neglect in animals with brain lesions have generally focused on dopaminergic agonists and progesterone, proving positive effects in neglect symptomatology (e.g., somatosensory neglect) (Corwin et al., 1986; Goss, Hoffman, & Stein, 2003; Wali, Ishrat, Won, Stein, & Sayeed, 2014; Yousuf, Atif, Sayeed, Tang, & Stein, 2014). In humans, pharmacological approaches have been implemented as adjuvant therapy for visuospatial neglect but the role of drug treatment for co-occurring awareness syndromes (e.g., anosognosia, confabulation) has not been examined so far. Even though neglect is the common signature of large right hemisphere strokes, there is limited research on its pharmacological treatment (ten studies) when compared with the number of drug studies carried out in aphasia (55 studies) after left hemisphere stroke (Tables 19.1 and 19.2).

Three classes of drugs have been tested for neglect: dopaminergic, noradrenergic and cholinergic (see Table 19.2). Several compounds, including bromocriptine, guanfacine, apomorphine, rotigotine, levodopa, nicotine, and rivastigmine, have been investigated with variable outcomes. Dopaminergic drugs are the agents most investigated for the treatment of neglect. The first human investigation used bromocriptine in an open-label study in two patients with visuospatial neglect secondary to large ischemic strokes in the right frontal-temporal-parietal area (Fleet et al., 1987). Daily administration of bromocriptine (3–4 weeks) improved performance in both basic reaction time tests and classical paper-and-pencil neglect tests, although there were some individual differences in response to treatment and long-term maintenance of gains. Nevertheless, a single low dose (2.5 mg) of bromocriptine given to seven patients with right hemisphere strokes worsened latent visuospatial neglect, as manifested by a decrement of the time dedicated to exploration of the left hemispace (Grujic et al., 1998). The use of a single low dose of bromocriptine in such study limits reaching conclusions for clinical practice.

The use of traditional dopaminergic drugs (levodopa and bromocriptine) is flawed by several contraindications and adverse events, thus jeopardizing treatment continuity. Therefore, there is an implicit expectation that modern dopaminergic drugs, like rotigotine and ropirinole, with better efficacy and tolerance profiles than levodopa and bromocriptine may enhance the benefits and adherence to treatment in patients with PSCD (Galling et al., 2014; Gill & Leff, 2014). Recently, a pharmacological intervention in post-stroke neglect and unilateral motor deficit was

Table 19.2 Clinical trials of pharmacotherapy of post-stroke neglect

Agent	Mechanism of action	Study design	Number of studies	Outcomes
Bromocritptine	Dopamine agonist acting in D2 postsynaptic dopamine receptors	Single case Case series Open label	4 Fleet, Valenstein, Watson, et al. (1987) Grujic et al. (1998) Hurford, Stringer, and Jann (1998) Barrett, Crucian, Schwartz, and Heilman (1999)	Positive and negative effects have been reported in acute and chronic post-stroke patients. Studies revealing worsening of neglect have reported increase in the amount of time dedicated to explore the left side of the space, decrease in measures of spatial bias (e.g., line bisection), and slight increase in left side auditory extinction. Positive effects include improvement in basic reaction time tests and pen-and-paper neglect tests (line and shape cancellation, and line bisection), as well as in social interaction and kinesis measures. Right putamen damage might be related with detrimental effect of the drug
Methylfenidate	Dopamine agonist	Single case Open label	1 Hurford et al. (1998)	Clinical improvement of neglect symptoms in perceptual (visual and auditory) and perceptual-motor tasks. However, administration of bromocriptine in the same patient induced better outcomes
Rotigotine	Dopamine agonist	Group study RCT	1 Gorgoraptis et al. (2012)	Significant improvement in the number of targets identified on the left side revealed by different objective tests in acute and chronic right hemisphere stroke patients with neglect. Positive effects were not related to prefrontal cortex preservation. No motor improvement was found
Levodopa	Dopamine agonist	Single case Open label	1 Mukand et al. (2001)	Beneficial effects in 3 out of 4 patients after 1 week of carbidopa L-dopa. Significantly improvement on the performance of standardized test of neglect and in functional status

(continued)

Table 19.2 (continued)

Agent	Mechanism of action	Study design	Number of studies	Outcomes
Apomorphine	Dopamine agonist acting on dopamine D1 and D2 receptors	Case series Open label	1 Geminiani, Bottini, and Sterzi (1998)	Significant improvement in three patients in two modalities of a search task, targeting perceptual and perceptual-motor components of neglect. Greater improvement in the perceptual-motor condition
Guanfacine	Noradrenergic agonist acting on noradrenergic alpha-2A agonist	RCT Group study	2 Malhotra, Parton, Greenwood, and Husain (2006) Dalmaijer et al. (2018)	Single dose of the drug induces significant improvement in leftward space exploration with increment in target detection. No effect on performance in sustained attention or spatial working memory tasks. Drug seems to act on dorsolateral prefrontal areas. Patients showing benefits had a spared dorsolateral prefrontal cortex
Rivastigmine	Dual inhibitor of acetylcholines-terase and butyrylcholi-nesterase	Group study Open label	1 Paolucci et al. (2010)	Drug alone has positive effect on neglect symptoms. However, significantly better results were seen when applied together with a therapy (physical therapy, swallowing, occupational therapy, and specific neglect therapy) (5–6 days/week)
Nicotine	Cholinergic agonist acting on nicotine receptors	Case series RCT	2 Vossel, Kukolja, Thimm, Thiel, and Fink (2010) Lucas et al. (2013)	Single dose of nicotine treatment facilitates attentional reorienting, improving target detection and progressive exploration of the contralesional space. A reduced reaction time in attentional paradigms (location-cueing paradigm) was found although no changes were seen in other tasks (e.g., line bisection). Improvements seem to be mediated by increased general attentional capacity, without effect in other mechanisms impaired in neglect (e.g., perceptual). The beneficial effects may be associated with intact right parietal cortex, basal forebrain, and medial temporal lobe

RCT randomized controlled trial, *IAChE* inhibitor of acetylcholinesterase

performed using rotigotine in a RCT with three phases (A_1: pretreatment; B: transdermal patches of rotigotine, 9 mg; A_2: drug withdrawal) in 16 patients. Treatment with rotigotine, administered for 7–11 days, significantly increased the number of targets identified on the left and decreased the rightward spatial bias on a shape cancellation task.

Noradrenergic modulators may also ameliorate neglect. Studies in monkeys demonstrated that the administration of guanfacine, a noradrenergic alpha-2A agonist, improves performance on spatial delayed-response tasks by modulating the activity of the dorsolateral prefrontal cortex (Arnstein, 1998). A large two-month placebo-controlled RCT of guanfacine extended release in children and adolescents with attention deficit hyperactivity disorder, showed beneficial effects in attention and behavior (Biederman et al., 2008). In 2010, guanfacine was licensed for the treatment of attention deficit hyperactivity disorder for people 6–17 years old but not for adults. Two studies with guanfacine in post-stroke neglect used a single dose (Dalmaijer et al., 2018; Malhotra et al., 2006). A small RCT showed benefits in two out of three patients with visuospatial neglect improving in the detection of targets on the left side of space on standard tests of neglect and in a computerized search task, probably by enhancing attentional abilities through stimulation of the dorsolateral prefrontal cortex (Malhotra et al., 2006). In fact, lesions in the two "responder" patients spared the right dorsolateral prefrontal cortex, whereas extensive damage to this region was found in the "non-responder" patient (Malhotra et al., 2006). These results have been replicated in a larger trial (Dalmaijer et al., 2018). Long-term treatment with this compound is warranted.

The activity of acetylcholine was also modulated in post-stroke neglect with two compounds, nicotine and rivastigmine. Nicotine acts in the central nervous system as an agonist of nicotinic acetylcholine receptors, thus increasing acetylcholine action. Two studies using single dose of nicotine in patients with visuospatial neglect have reported faster reaction times (Vossel et al., 2010) on different tasks of visuospatial exploration and orienting, improvement of target detection and exploration in both sides of space with greater improvement in the contralesional side and increased duration of search times (Lucas et al., 2013). The effectiveness of nicotine seems to depend on the location of the right hemisphere damage. For instance, a lesion-symptom mapping study reported that the effects of a single dose of nicotine in reorienting attention to contralesional space are better when the right parietal and temporal areas are spared (Vossel et al., 2010). Despite evidence showing that cognitive rehabilitation alone improves the performance on some neglect test, nowadays the more promising cognitive rehabilitation approaches come from the use of combined therapies. In this line, Paolucci et al. (2010) studied the beneficial effect derived from the administration of rivastigmine combined with behavioral therapy for neglect rehabilitation. They compared two groups (ten patients in each group) of subacute (>1 month post-stroke) neglect patients. One group received low therapeutic doses of rivastigmine (6 mg/day) for 8 weeks plus cognitive rehabilitation therapy for visuospatial neglect and the other group received only cognitive rehabilitation. The group that received a combined treatment significantly improved performance on the letter cancellation and Wundt–Jastrow illusion tests, and there was better

response on both tasks than that observed in patients receiving rehabilitation only. Thus, it seems that rivastigmine improves and accelerates recovery.

19.1.6 Vascular Cognitive Impairment

Several clinical subtypes of cognitive impairment due to vascular lesions exist, ranging in severity from mild cognitive impairment to dementia. The clinical profile of cognitive deficits in VCI (psychomotor slowing, dysexecutive deficits) is predominantly subcortical, which results in part from disruption of cholinergic pathways (Bohnen, Bogan, & Müller, 2009; Bohnen, Müller, et al., 2009; Grantham & Geerts, 2002; Mesulam, Siddiqe, & Cohen, 2003; Román & Kalaria, 2006). In support, magnetic resonance imaging of elderly non-demented patients usually shows periventricular frontal white matter vascular lesions interrupting the lateral cholinergic pathway. These lesions are associated with slow information processing (psychomotor retardation) linked to PET evidence of cholinergic denervation in posterior cortical sites (Bohnen, Bogan, & Müller, 2009, Bohnen, Müller, et al., 2009). Medications approved for the treatment of AD have also been investigated for the treatment of PSCD. Acetylcholinesterase inhibitors improve cognition in patients with PSCD presumably by increasing the availability of acetylcholine in the synaptic space. There is also some evidence that these medications increase cerebral blood flow (Grantham & Geerts, 2002; Mesulam et al., 2003; Román & Kalaria, 2006). Therefore, various clinical trials have assessed the efficacy of three available acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in VCI and dementia of vascular origin (Table 19.3). Other compounds, supplements and herbal medicines (actovegin, citicoline, huperzine A, and vinpocetine) have also been investigated in the VaD population, but since their therapeutic effects are inconclusive they are not further analyzed here (see Farooq et al., 2017; Jian, Shi, Tian, & Ni, 2015) (see Table 19.3).

Donepezil demonstrated significant cognitive improvements on patients with mild to moderate VaD (Black et al., 2003; Chen, Zhang, Wang, Yuan, & Hu, 2016; Román et al., 2010; Wilkinson et al., 2003), although some cognitive deficits were not responsive to drug administration (Black et al., 2003). Intriguingly, significant improvement in global function was observed in patients receiving low doses (5 mg/day) (Black et al., 2003; Wilkinson et al., 2003). Donepezil has also been tried in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (Dichgans et al., 2008). Donepezil treatment resulted in no improvement in the primary outcome measure (V-ADAS-cog, a vascular disease version of Alzheimer's Disease Assessment Scale cognitive subscale-ADAS-Cog), but improvements were noted on other measures of executive function in a secondary analysis (Dichgans et al., 2008). Overall, the results of these trials indicate that donepezil may have a greater impact on cognitive than global function and activities of daily living in patients with VaD. Donepezil was well tolerated, and

Table 19.3 Clinical trials of pharmacotherapy of vascular cognitive impairment

Agent	Mechanism of action	Study design	Number of studies	Outcomes
Memantine	Moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage-dependency and fast kinetics	RCTs	2 Orgogozo et al. (2002) Wilcock et al. (2002)	Positive effects on cognition in patients with mild to moderate VaD, but there was no significant improvement in global functioning. Overall, memantine was well tolerated
Donepezil	IAChE	RCTs	4 Wilkinson et al. (2003) Black et al. (2003) Dichgans et al. (2008) Román et al. (2010)	Positive effects on cognition in patients with mild to moderate VaD, although some items on the cognitive battery did not improve. Significant improvement in global function was observed in patients receiving 5 mg/day. In CADASIL, patients' measures of executive function were improved. Donepezil was well tolerated
Rivastigmine	Dual inhibitor of acetylcholinesterase and butyrylcholinesterase	RCT Open-label controlled study	3 Moretti et al. (2002) Ballard et al. (2008) Narasimhalu et al. (2010)	Positive effects on cognitive performance in patients with VaD or probable VaD. Improvement on verbal fluency in VCI patients, and executive functions in subcortical VaD patients. No differences on global assessment, activities of daily living, or behavioral measures in VaD patients. Overall, rivastigmine was well tolerated
Galantamine	Dual action: reversible and competitive IAChE and allosteric modulator of nicotine receptors	RCT	2 Erkinjuntti et al. (2002) Auchus et al. (2007)	Positive effects on language and memory, and executive function (Auchus et al., 2007's trial) in VaD patients. Mixed results on activities of daily living and global functioning. Benefits on behavioral symptoms
Citicoline	Enhances brain phosphatidylcholine and acetylcholine synthesis, both important for cell membranes reparation	RCT	1 Cohen et al. (2003)	Lack of effect. Overall, the administration of citicoline in patient with VaD did not show beneficial effects on cognition in comparison to the placebo control group. Significant decline in cognitive performance was observed in both groups at 12 months of follow-up

Huperzine A	IAChE and NMDA receptor antagonist	RCT	1 Xu et al. 2012 Zhou & Sheng (2013)	Positive effects on cognition in VaD patients compared to the vitamin C control group with significant improvements on general cognition, activities of daily living, and in dementia rating scores. Huperzine A was well tolerated
Ginkgo biloba extract (EGb761®)	Antioxidant and anti-inflammatory effects. Increases cerebral blood flow and antiplatelet effects	RCTs	2 Demarin et al. (2017) Napreyeyenko et al. (2007)	Overall small positive effects on changes in cognition were present by slowing down decline in patients with VaD, but not in the placebo group. No changes in global functioning compared to control group. Beneficial changes in neuropsychiatric symptoms and activities of daily living in one trial (Napreyeyenko et al., 2007). Small adverse reactions were reported
Folic acid (vitamin B^9)	Reduces elevated plasma levels of homocysteine	RCT	1 Jian et al. (2013)	Positive effects on cognition after 24 weeks as measured by a multimodal cognitive assessment scale. Folic acid supplementation for 3 years seems to improve cognitive domains that usually tend to decline with age
Nimodipine	Calcium antagonist	RCT	3 Besson et al. (1988) Pantoni et al. (2000) Pantoni at al. (2005)	Small positive effects on cognition in patients with small vessel VaD but not for multi-infarct dementia. Patients scored higher in lexical production and less frequently showed cognitive or global deterioration compared to placebo patients. Data on longer-term outcomes are lacking. Nimodipine was well tolerated with few side effects
Nicardipine	Calcium antagonist	RCT Open-label	2 Spanish Group of Nicardipine Study in Vascular Dementia (1999) González-González (2000)	Positive effect on cognitive decline of vascular origin. Six months administration of the drug slows the rate of cognitive decline, especially in females

RCT randomized controlled trial, *VaD* vascular dementia, *IAChE* acetylcholinesterase inhibitor

withdrawals due to side effects were relatively low (Black et al., 2003; Román et al., 2010; Wilkinson et al., 2003).

Rivastigmine has also improved cognitive performance in patients with VaD (Ballard et al., 2008), semantic verbal fluency on VCI patients (Narasimhalu et al., 2010), and executive functions in subcortical VaD patients (Moretti et al., 2002). However, no differences were observed on global assessment, activities of daily living or behavioral measures in VaD patients. Exploratory analyses showed that improvement in cognition was more pronounced in older subjects, which likely points to the well-known drug effect on concomitant AD in this age group (Ballard et al., 2008). Overall, rivastigmine was well tolerated. Finally, galantamine seems to improve cognition in VaD patients, particularly executive functions, but it does not have a documented global clinical benefit (Chen et al., 2016).

Like acetylcholinesterase inhibitors, memantine has been demonstrated to be safe and effective in the symptomatic treatment of AD. This drug is a NMDA receptor antagonist with strong voltage-dependency and fast kinetics. These properties allow memantine to block the excessive activity of glutamate without interfering with physiological glutamatergic neurotransmission (Parsons, Stöffler, & Danysz, 2007) eventually contributing to improvement (Rogawski & Wenk, 2003). Otherwise, cortical neuronal loss in patients with ischemia may be related to glutamate toxicity through excessive NMDA stimulation, and memantine blocking pathological stimulation of NMDA receptors may be helpful to protect against further damage in VaD. Thus, memantine could theoretically protect against weak excitotoxicity, while sparing synaptic responses required for normal behavioral functioning, cognition, and memory. Findings suggest that memantine could have a positive effect on cognition in patients with mild to moderate VaD, but there was no significant improvement in global functioning. In any case, beneficial effects on cognition were maintained at the 28 weeks of follow-up (Orgogozo et al., 2002; Wilcock et al., 2002). Also, there was a small reduction in a behavioral disturbance scale in subjects with mild to moderately advanced VaD (Orgogozo et al., 2002).

In summary, acetylcholinesterase inhibitors and memantine may have modest beneficial effects on cognitive symptoms of VaD, although without a concomitant global or clinical benefit in most cases. This would explain why no drug has been licensed for VaD. Moreover, some studies did not entirely rule out the possibility that a proportion of enrolled patients had concomitant AD with vascular disease, and that the beneficial effect of the drug was due to its activity directed at AD-related neuropathology rather than at pathological changes underlying VaD. Future studies need to take into consideration the specific location of vascular lesions in VCI (Grysiewicz & Gorelick, 2012). Although this key issue has not been explored in pivotal drug trials of VCI and VaD, donepezil was effective in improving cognitive failure (executive functions and goal-directed behaviors) in a case with a single strategic left-thalamic infarct (Riveros, Chabriat, Flores, Alvarez, & Slachevsky, 2011). Moreover, amnesia after basal forebrain lesions secondary to surgical repair of anterior communicating artery aneurysms (Benke, Köylü, Delazer, Trinka, & Kemmler, 2005) and general cognitive function after right hemisphere stroke (Chang et al., 2011) also improved with donepezil treatment.

In the next sections, we address some issues that require attention in future studies of pharmacotherapy of PSCD.

19.1.7 Refining and Expanding the Use of Efficacy Measures

A clinical intervention trial should be able not only to show a statistically significant improvement in primary efficacy endpoint(s), but also to reveal that the magnitude of the effect is clinically meaningful. Considering, for instance, post-stroke aphasia, note that commonly selected outcome measures (e.g., Western Aphasia Battery-Kertesz, 1982) to rate the impact of drug treatment in the type and severity of aphasia, are coarse-grained. Such assessment tools provide no fruitful information on the evolution of language processing deficits relevant for unveiling the restorative cognitive mechanisms guiding recovery promoted by drug treatment (Cahana-Amitay et al., 2014; Gill & Leff, 2014). In general, most trials on the pharmacotherapy of PSCD use a single primary outcome measure that, in some cases, is assessed after drug withdrawal to ensure that benefits are not short-lived (for discussion, see Small & Llano, 2009; Berthier, García-Casares, et al., 2011, Berthier, Pulvermüller, et al., 2011; Cahana-Amitay et al., 2014). This is correct, but insufficient. Patients with PSCD (e.g., aphasia, neglect) usually display multiple-domain cognitive impairments associated with motor/sensory deficits and psychiatric comorbidities (depression, apathy, anxiety), which reduce adaptability and quality of life (Berthier et al., 2015). In fact, patients with post-stroke aphasia and left hemisphere stroke lesions have one or more non-language cognitive deficits affecting abstract reasoning, visual memory, visual perception and construction, and executive functioning (El Hachioui et al., 2014). In the same vein, patients with neglect and right hemisphere stroke lesions also display other deficits, including impaired spatial working memory, impaired ability to recognize facial emotions and emotional prosody, as well as anosognosia (Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992; Toba et al., 2018). Such accompanying signs indicate that analysis of treatment outcomes should ideally be multidimensional, incorporating a variety of different measures to obtain a far-reaching understanding of the putative treatment role (Cahana-Amitay et al., 2014; Gill & Leff, 2014). Nevertheless, it remains to be explored whether increasing the number of primary outcome measures can illuminate the full impact of drug treatment and whether the selected compound has an effect on target symptoms with generalization of benefits to other cognitive, behavioral, and functional domains.

19.1.8 Responder Analysis

Drug trials typically report treatment effects for efficacy measures by comparing mean change scores between active drug and placebo groups and between baseline and endpoints. Nevertheless, since the results of drug trials are influenced by

participants' variability in the therapeutic response, this information is not fully informative for clinicians. Therefore, to assist clinicians in evaluating the impact of drug treatment in an individual patient, one proposed approach is performing a responder analysis, in which changes from baseline to endpoint in the efficacy measures are individually dichotomized into "responders" and "non-responders." For example, Van Der Meulen, Van De Sandt-Koenderman, Heijenbrok, Visch-Brink, and Ribbers (2016) used six outcome measures to evaluate changes in aphasic patients after melodic intonation therapy (Albert, Sparks, & Helm, 1973) with the aim of distinguishing between improvement on trained items, improvement on non-trained items, and generalization to functional language use. Group analysis showed improvements only in one out of the six outcome measures (repetition of both trained and untrained utterances), thus indicating that the study was negative. However, responder analysis revealed individual variation with some patients responding well to treatment. This raises the question of how many outcome measures should improve with a drug treatment in PSCD to consider that the results are positive and this study also raises the importance of determining predictors of positive versus negative response to treatment. Another relevant issue is whether a drug trial could be considered positive when only cognition, and not multiple outcome measures (behavior, functionality, quality of life), is improved.

A related key point that deserves consideration is to reach consensus on what range of improvement in a given testing scale should be adopted to classify a patient with PSCD as a responder (see Malouf & Birks, 2004). Considering, for instance, the Aphasia Quotient (AQ) of the Western Aphasia Battery (WAB) (Kertesz, 1982), a measure of aphasia severity sensitive to changes after drug treatment, there is no consensus about the criteria for a positive response. At present, the more conservative definitions of a clinically relevant improvement consider a patient as a responder with an improvement $\geq$5 points in the WAB-AQ (Berthier et al., 2009; Katz & Wertz, 1997), another study required an improvement $\geq$10 points (Walker-Batson et al., 2016) and still another $\geq$20 points (Hong et al., 2012). Consensus is needed on these matters. Finally, the identification of responders to drug therapy needs to be enhanced by the identification of non-clinical variables, which might contribute to obtain a better response to drug treatment. The analysis of surrogate markers (genetic polymorphisms, lesion location, premorbid architecture of neural organization, and so forth) can aid to understand different responses to drug treatment.

19.1.9 Combined Therapies

Drugs administered to modulate the activity of a single neurotransmitter to improve cognitive deficits, such as aphasia and neglect, probably influence the activity of other neurotransmitters (Froudist-Walsh et al., 2017; Furey, 2011). This knowledge stimulated the combined use of two pharmacological agents targeting different neurotransmitter systems to alleviate cognitive deficits (Tariot et al., 2004). Two cognitive enhancing drugs (i.e., memantine and donepezil), commonly used to treat AD,

have different yet complementary mechanisms of action and may potentially provide additional benefits. The theoretical rationale for combining two drugs to treat PSCD comes for several sources of evidence. First, stroke can modify the activity of various neurotransmitters simultaneously causing, for example, depletion of cholinergic transmission and release of glutamate, which in turn produces high cell toxicity (Berthier, García-Casares, et al., 2011; Tocco et al., 2014). Second, stimulation of the cholinergic system with donepezil may facilitate the decrease of excitotoxicity mediated by glutamate and dopamine, and the addition of memantine leverages pathological-released glutamate to more physiological levels. Chronic treatment with memantine in mice with experimental stroke reduces excitotoxicity, increased vascular density, and release of brain-derived neurotrophic factor in perilesional areas (López-Valdés et al., 2014). Third, drug trials in AD in which memantine was added to treatment in patients already receiving donepezil provided additional benefits in language and communication (Atri et al., 2013; Riepe et al., 2007; Tariot et al., 2004; Tocco et al., 2014). In support, the addition of memantine reduced deficits not mitigated by the modulation of the cholinergic system with donepezil alone in a patient with chronic post-stroke nonfluent aphasia (López-Barroso et al., 2018). A pilot study in post-stroke aphasia explored a stable treatment with donepezil plus an adjunctive low dose of dextro-amphetamine administered 30 minutes prior to aphasia therapy to facilitate recovery (Walker-Batson et al., 2016). This treatment regime significantly improved aphasia severity and communication deficit causing no adverse effects (Walker-Batson et al., 2016). Although combined drug therapies seem a promising strategy, it remains to be determined whether they can lead to better outcomes than either drug alone.

19.1.10 Neural Network Modulation and Cognition-Enhancing Drugs

There are two general approaches for neurorehabilitation. Based on the altered relationship between different networks in both cerebral hemispheres, one can posit that a broad approach to neurorehabilitation may be adopted (Geranmayeh, Chau, Wise, Leech, & Hampshire, 2017). The other approach is more focused because it targets the treatment to specific anatomical sites (e.g., arcuate fasciculus, frontal aslant tract), which may have a key role in very selective cognitive domains (verbal repetition, speech fluency) (Berthier et al., 2017; Schlaug, Marchina, & Norton, 2009). These two potential treatment strategies are based on the segregated organization of neural networks into domain-specific and domain-general (Blank & Fedorenko, 2017; Brownsett et al., 2014). Although the premises underlying these two neural networks are different, they do have complex interactions among widely distributed brain regions, but not all networks are interdependent (Blank & Fedorenko, 2017).

One important question is whether some pharmacological agents may selectively modulate the activity of domain-specific networks while other compounds with more general, widespread actions may preferentially modulate domain-general networks. Some preliminary data from drug treatments of PSCD performed in sin-

gle case studies, case series, open-label and randomized clinical trials suggest that different agents might preferentially act on different networks. Since the anatomy of white matter tracts and the cortical distribution of neurotransmitter fingerprints are increasingly being identified (Amunts & Zilles, 2012; Palomero-Gallagher & Zilles, 2017; Selden, Gitelman, Salamon-Murayama, Parrish, & Mesulam, 1998), this can provide fruitful information about the selection of a given pharmacological agent to target cognitive impairments that might reflect vascular damage to specific neurotransmitter systems. For example, since the neuroanatomy of mesocortical and mesolimbic dopaminergic pathways is well known, one can assume that patients with cognitive deficits (decreased drive to generate speech, impaired goal-directed behavior) resulting from incomplete damage to such pathways could be treated with dopamine agonists (Cahana-Amitay et al., 2014; Galling et al., 2014; Gill & Leff, 2014).

The same notion may apply for the cholinergic system. Early anatomical studies on the distribution of major cholinergic pathways (e.g., Selden et al., 1998) and recent in vivo mapping of their trajectory using diffusion tensor imaging (tractography) (Hong & Jang, 2010; Liu et al., 2017) allow the identification of cholinergic involvement after stroke lesions (Behl et al., 2007). The areas of selective binding of donepezil to acetylcholinesterase can be identified with positron emission tomography and [5-11C-methoxy] donepezil (Hiraoka et al., 2009), and changes in the pattern of connectivity under pharmacological manipulation with this drug have been identified (Wirsich et al., 2018). Preliminary data using these methodologies have shown that patients with disrupted trajectory of cholinergic pathways in the white matter can benefit with cholinesterase inhibitors (galantamine, donepezil) (Berthier et al., 2017; Hong et al., 2012). In addition, the modulation of a widely distributed neurotransmitter (glutamate) with the drug memantine showed that benefits in post-stroke aphasia are related to bilateral brain reorganization (Barbancho et al., 2015), although connectivity analysis in healthy subjects under memantine treatment failed to show changes in resting state networks (Wirsich et al., 2018).

Altogether, these findings illuminate the cortical hubs and white matter tracts participating in the recovery process from stroke deficits (Berthier et al., 2017; McKinnon et al., 2017; Piai, Meyer, Dronkers, & Knight, 2017; Wan, Zheng, Marchina, Norton, & Schlaug, 2014). Therefore, there are now clues to stimulate compensatory activity of healthy brain tissue with intensive rehabilitation and biological interventions (e.g., drugs, NIBS). In particular, the modulation of these structures with biological treatments is emerging as a promising treatment option. An exciting approach might be directing drugs to anatomic target sites or specific tissue where the concentration of specific neurotransmitters is more abundant. Up to now, attempts to modulate specific cortical regions (left superior temporal lobe) rich in cholinergic receptors (Zilles & Amunts, 2009) and presumably participating in recovery have been made using the acetylcholinesterase inhibitor donepezil (Woodhead et al., 2017). Similarly, cholinergic potentiation with donepezil alone and paired with intensive rehabilitation improved speech production and communication, and induced structural plasticity in white matter tracts important for such functions (Berthier et al., 2014, 2017).

References

Adhikari, M. H., Hacker, C. D., Siegel, J. S., Griffa, A., Hagmann, P., Deco, G., & Corbetta, M. (2017). Decreased integration and information capacity in stroke measured by whole brain models of resting state activity. *Brain, 140*(4), 1068–1085.

Albert, M. L., Bachman, D. L., Morgan, A., & Helm-Estabrooks, N. (1988). Pharmacotherapy for aphasia. *Neurology, 38*(6), 877–879.

Albert, M. L., Sparks, R. W., & Helm, N. A. (1973). Melodic intonation therapy for aphasia. *Archives of Neurology, 29*(2), 130–131.

Amunts, K., & Zilles, K. (2012). Architecture and organizational principles of Broca's region. *Trends in Cognitive Sciences, 16*(8), 418–426.

Arnstein, A. F. (1998). Catecholamine modulation of prefrontal cortical cognitive function. *Trends in Cognitive Science, 2*(11), 436–447.

Ashtary, F., Janghorbani, M., Chitsaz, A., Reisi, M., & Bahrami, A. (2006). A randomized, double-blind trial of bromocriptine efficacy in nonfluent aphasia after stroke. *Neurology, 66*(6), 914–916.

Atri, A., Molinuevo, J. L., Lemming, O., Wirth, Y., Pulte, I., & Wilkinson, D. (2013). Memantine in patients with Alzheimer's disease receiving donepezil: New analyses of efficacy and safety for combination therapy. *Alzheimer's Research & Therapy, 5*(1), 6.

Auchus, A. P., Brashear, H. R., Salloway, S., Korczyn, A. D., De Deyn, P. P., Gassmann-Mayer, C., & GAL-INT-26 Study Group. (2007). Galantamine treatment of vascular dementia: A randomized trial. *Neurology, 69*, 448–458.

Ballard, C., Sauter, M., Scheltens, P., He, Y., Barkhof, F., van Straaten, E. C., & Lane, R. (2008). Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: The VantagE study. *Current Medicine Research and Opinion, 24*(9), 2561–2574.

Barbancho, M. A., Berthier, M. L., Navas-Sánchez, P., Dávila, G., Green-Heredia, C., García-Alberca, J. M., & Lara, J. P. (2015). Bilateral brain reorganization with memantine and constraint-induced aphasia therapy in chronic post-stroke aphasia: An ERP study. *Brain and Language, 145-146*, 1–10.

Barrett, K. M., Brott, T. G., Brown, R. D., Jr., Carter, R. E., Geske, J. R., Graff-Radford, N. R., & Meschia, J. F. (2011). Enhancing recovery after acute ischemic stroke with donepezil as an adjuvant therapy to standard medical care: Results of a phase IIA clinical trial. *Journal of Stroke and Cerebrovascular Diseases, 20*(3), 177–182.

Barrett, A. M., Crucian, G. P., Schwartz, R. L., & Heilman, K. M. (1999). Adverse effect of dopamine agonist therapy in a patient with motor-intentional neglect. *Archives of Physical Medicine and Rehabilitation, 80*(5), 600–603.

Barrett, A. M., & Eslinger, P. J. (2007). Amantadine for adynamic speech: Possible benefit for aphasia? *American Journal of Physical Medicine and Rehabilitation, 86*(8), 605–612.

Barrett, A. M., Levy, C. E., & Gonzalez Rothi, L. J. (2007). Pharmaceuticals for poststroke and brain injury rehabilitation. *American Journal of Physical Medicine and Rehabilitation, 86*(8), 603–604.

Behl, P., Bocti, C., Swartz, R. H., Gao, F., Sahlas, D. J., Lanctot, K. L., & Black, S. E. (2007). Strategic subcortical hyperintensities in cholinergic pathways and executive function decline in treated Alzheimer patients. *Archives of Neurology, 64*(2), 266–272.

Belokoskova, S. G., Tsikunov, S. G., & Klement'ev, B. I. (2002). Neuropeptide induction of compensatory processes at aphasias. *Vestnik Rossiĭskoĭ Akademii Meditsinskikh Nauk, 12*, 28–32.

Benke, T., Köylü, B., Delazer, M., Trinka, E., & Kemmler, G. (2005). Cholinergic treatment of amnesia following basal forebrain lesion due to aneurysm rupture-an open-label pilot study. *European Journal of Neurology, 12*(10), 791–796.

Benson, D. F. (1970). Presentation 10. In A. L. Benton (Ed.), *Behavioral change in cerebrovascular disease*. New York, NY: Harper and Row.

Berthier, M. L. (1999). *Transcortical aphasias*. Hove: Psychology Press.

Berthier, M. L. (2005). Poststroke aphasia: Epidemiology, pathophysiology and treatment. *Drugs and Aging, 22*(2), 163–182.

Berthier, M. L. (2012). *Pharmacological interventions boost language and communication treatment effects in chronic post-stroke aphasia. Presented in the symposium Fortschritte in Neurowissenschaft und Neurorehabilitation der Sprache, 85* (p. 23). Hamburg: Kongress der Deutschen Gesellschaft für Neurologie mit Fortbildungsakademie. Hauptprogramm.

Berthier, M. L. (2014). Editorial. Cognitive enhancing drugs in aphasia: A vote for hope. *Aphasiology, 28*(2), 128–132.

Berthier, M. L., Dávila, G., García-Casares, N., & Moreno-Torres, I. (2014). Post-stroke aphasia. In T. A. Schweizer & R. L. Macdonald (Eds.), *The behavioral consequences of stroke* (pp. 95–117). New York, NY: Springer.

Berthier, M. L., Dávila, G., & Torres-Prioris, M. J. (2015). Neuropharmacological approaches to aphasia rehabilitation. In R. H. Bahr & E. R. Silliman (Eds.), *Routledge handbook of communication disorders* (pp. 90–101). London: Routledge Handbooks Online.

Berthier, M.L., & Dávila, G. (Eds). (2015). Pharmacology and aphasia. London and New York: Routledge Taylor & Francis Group. ISBN: 978-1-138-79988-2

Berthier, M. L., De-Torres, I., Paredes-Pacheco, J., Roé-Vellvé, N., Thurnhofer-Hemsi, K., Torres-Prioris, M. J., & Dávila, G. (2017). Cholinergic potentiation and audiovisual repetition-imitation therapy improve speech production and communication deficits in a Person with crossed aphasia by inducing structural plasticity in white matter tracts. *Frontiers in Human Neuroscience, 14*(11), 304.

Berthier, M. L., García-Casares, N., Walsh, S. F., Nabrozidis, A., Ruíz de Mier, R. J., Green, C., & Pulvermüller, F. (2011). Recovery from post-stroke aphasia: Lessons from brain imaging and implications for rehabilitation and biological treatments. *Discovery Medicine, 12*(65), 275–289.

Berthier, M. L., Green, C., Higueras, C., Fernández, I., Hinojosa, J., & Martín, M. C. (2006). A randomized, placebo-controlled study of donepezil in poststroke aphasia. *Neurology, 67*(9), 1687–1689.

Berthier, M. L., Green, C., Lara, J. P., Higueras, C., Barbancho, M. A., Dávila, G., & Pulvermüller, F. (2009). Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. *Annals of Neurology, 65*(5), 577–585.

Berthier, M. L., Hinojosa, J., Martín Mdel, C., & Fernández, I. (2003). Open-label study of donepezil in chronic poststroke aphasia. *Neurology, 60*(7), 1218–1219.

Berthier, M. L., Pujol, J., Gironell, A., Kulisevsky, J., Deus, J., Hinojosa, J., & Soriano-Mas, C. (2003). Beneficial effect of donepezil on sensorimotor function after stroke. *American Journal of Physical Medicine and Rehabilitation, 82*(9), 725–729.

Berthier, M. L., & Pulvermüller, F. (2011). Neuroscience insights improve neurorehabilitation of poststroke aphasia. *Nature Reviews Neurology, 7*, 86–97.

Berthier, M. L., Pulvermüller, F., Dávila, G., Casares, N. G., & Gutiérrez, A. (2011). Drug therapy of post-stroke aphasia: A review of current evidence. *Neuropsychology Review, 21*, 302–317.

Besson, J. A., Palin, A. N., Ebmeier, K. P., Eagles, J. M., & Smith, F. W. (1988). Calcium antagonists and multi-infarct dementia: A trial involving sequential NMR and psychometric assessment. *International Journal of Geriatric Psychiatry, 3*, 99–105.

Beversdorf, D. Q., Sharma, U. K., Phillips, N. N., Notestine, M. A., Slivka, A. P., Friedman, N. M., & Hillier, A. (2007). Effect of propranolol on naming in chronic Broca's aphasia with anomia. *Neurocase, 13*(4), 256–259.

Biederman, J., Melmed, R. D., Patel, A., McBurnett, K., Konow, J., Lyne, A., & Scherer, N. (2008). A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics, 121*(1), 73–84.

Birks, J., & Craig, D. (2006). Galantamine for vascular cognitive impairment. *Cochrane Database of Systematic Reviews, 25*(4), CD004746.

Birks, J., McGuinness, B., & Craig, D. (2013). Rivastigmine for vascular cognitive impairment. *Cochrane Database of Systematic Reviews, 31*(5), CD004744.

Black, S., Román, G. C., Geldmacher, D. S., Salloway, S., Hecker, J., Burns, A., & Pratt, R. (2003). Efficacy and tolerability of donepezil in vascular dementia: Positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke, 34*, 2323–2330.

Blank, I. A., & Fedorenko, E. (2017). Domain-general brain regions do not track linguistic input as closely as language-selective regions. *Journal of Neuroscience, 37*(41), 9999–10011.

Boehme, A. K., Martin-Schild, S., Marshall, R. S., & Lazar, R. M. (2016). Effect of aphasia on acute stroke outcomes. *Neurology, 87*, 2348–2354.

Bohnen, N. I., Bogan, C. W., & Müller, M. L. (2009). Frontal and periventricular brain white matter lesions and cortical deafferentation of cholinergic and other neuromodulatory axonal projections. *European Neurology Journal, 1*(1), 33–50.

Bohnen, N. I., Müller, M. L., Kuwabara, H., Constantine, G. M., & Studenski, S. A. (2009). Age-associated leukoaraiosis and cortical cholinergic deafferentation. *Neurology, 72*(16), 1411–1416.

Bragoni, M., Altieri, M., Di Piero, V., Padovani, A., Mostardini, C., & Lenzi, G. L. (2000). Bromocriptine and speech therapy in non-fluent chronic aphasia after stroke. *Neurological Science, 21*(1), 19–22.

Breitenstein, C., Korsukewitz, C., Baumgärtner, A., Flöel, A., Zwitserlood, P., Dobel, C., &, Knecht, S. (2015). L-Dopa does not add to the success of high-intensity language training in aphasia. *Restorative Neurology and Neuroscience, 33*(2), 115–120.

Brownsett, S. L., Warren, J. E., Geranmayeh, F., Woodhead, Z., Leech, R., & Wise, R. J. (2014). Cognitive control and its impact on recovery from aphasic stroke. *Brain, 137*(Pt 1), 242–254.

Buxbaum, L. J., Ferraro, M. K., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., & Coslett, H. B. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology, 62*(5), 749–756.

Buxbaum, L. J., Ferraro, M., Whyte, J., Gershkoff, A., & Coslett, H. B. (2007). Amantadine treatment of hemispatial neglect: A double-blind, placebocontrolled study. *American Journal of Physical Medicine & Rehabilitation, 86*, 527–537.

Cahana-Amitay, D., Albert, M. L., & Oveis, A. (2014). Psycholinguistics of aphasia pharmacotherapy: Asking the right questions. *Aphasiology, 28*(2), 133–154.

Cappa, S. F., Ortelli, P., Garibotto, V., & Zamboni, M. (2007). Reversible nonfluent aphasia and left frontal hypoperfusion during topiramate treatment. *Epilepsy and Behavior, 10*(1), 192–194.

Cassidy, J. M., & Cramer, S. C. (2017). Spontaneous and therapeutic-induced mechanisms of functional recovery after stroke. *Translational Stroke Research, 8*, 33–46.

Chang, E. Y., Chang, E. H., Cragg, S., & Cramer, S. C. (2013). Predictors of gains during inpatient rehabilitation in patients with stroke. A review. *Critical Reviews in Physical and Rehabilitation Medicine, 25*(3-4), 203–221.

Chang, W. H., Park, Y. H., Ohn, S. H., Park, C. H., Lee, P. K., & Kim, Y. H. (2011). Neural correlates of donepezil-induced cognitive improvement in patients with right hemisphere stroke: A pilot study. *Neuropsycholical Rehabilitation, 21*(4), 502–514.

Chen, Y., Li, Y. S., Wang, Z. Y., Xu, Q., Shi, G. W., & Lin, Y. (2010). The efficacy of donepezil for post-stroke aphasia: A pilot case control study. *Zhonghua Nei Ke Za Zhi, 49*(2), 115–118.

Chen, P., & Toglia, J. (2018). Online and offline awareness deficits: Anosognosia for spatial neglect. *Rehabilitation Psychology*. https://doi.org/10.1037/rep0000207

Chen, Y. D., Zhang, J., Wang, Y., Yuan, J. L., & Hu, W. L. (2016). Efficacy of cholinesterase inhibitors in vascular dementia: An updated meta-analysis. *European Neurology, 75*(3-4), 132–141.

Chollet, F., Cramer, S. C., Stinear, C., Kappelle, L. J., Baron, J. C., Weiller, C., & Adams Jr, H. (2014). Pharmacological therapies in post stroke recovery: Recommendations for future clinical trials. *Journal of Neurology, 261*(8), 1461–1468.

Clarke, R., Harrison, G., & Richards, S. (2003). Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *Journal of Internal Medicine, 254*(1), 67–75.

Cohen, R. A., Browndyke, J. N., Moser, D. J., Paul, R. H., Gordon, N., & Sweet, L. (2003). Long-term citicoline (cytidine diphosphate choline) use in patients with vascular dementia: Neuroimaging and neuropsychological outcomes. *Cerebrovascular Diseases, 16*, 199–204.

Corwin, J. V., Kanter, S., Watson, R. T., Heilman, K. M., Valenstein, E., & Hashimoto, A. (1986). Apomorphine has a therapeutic effect on neglect produced by unilateral dorsomedial prefrontal cortex lesions in rats. *Experimental Neurology, 94*(3), 683–698.

Cramer, S. C., & Riley, J. D. (2008). Neuroplasticity and brain repair after stroke. *Current Opinion of Neurology, 21*, 76–82.

Cumming, T. B., Marshall, R. S., & Lazar, R. M. (2013). Stroke, cognitive deficits, and rehabilitation: Still an incomplete picture. *International Journal of Stroke, 8*, 38–45.

Dalmaijer, E. S., Li, K. M. S., Gorgoraptis, N., Leff, A. P., Cohen, D. L., Parton, A. D., &, Malhotra, P. A. (2018). Randomised, double-blind, placebo-controlled crossover study of single-dose guanfacine in unilateral neglect following stroke. *Journal of Neurology, Neurosurgery & Psychiatry, 89*, 593–598.

Demarin, V., Bašić Kes, V., Trkanjec, Z., Budišić, M., Bošnjak Pašić, M., Črnac, P., & Budinčević, H. (2017). Efficacy and safety of Ginkgo biloba standardized extract in the treatment of vascular cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial. Neuropsychiatric disease and treatment, 13, 483–490. https://doi.org/10.2147/NDT.S120790

Dichgans, M., Markus, H. S., Salloway, S., Verkkoniemi, A., Moline, M., Wang, Q., & Chabriat, H. S. (2008). Donepezil in patients with subcortical vascular cognitive impairment: A randomised double-blind trial in CADASIL. *Lancet Neurology, 7*, 310–318.

Ding, G., Jiang, Q., Li, L., Zhang, L., Zhang, Z. G., Ledbetter, K. A., & Chopp, M. (2008). Magnetic resonance imaging investigation of axonal remodeling and angiogenesis after embolic stroke in sildenafil-treated rats. *Journal of Cerebral Blood Flow & Metabolism, 28*(8), 1440–1448.

Dobkin, B. H., & Dorsch, A. (2013). New evidence for therapies in stroke rehabilitation. *Current Atherosclerosis Reports, 15*(6), 331.

Durga, J., van Boxtel, M. P., Schouten, E. G., Kok, F. J., Jolles, J., Katan, M. B., & Verhoef, P. (2007). Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: A randomised, double blind, controlled trial. *Lancet, 369*(9557), 208–216.

El Hachioui, H., Visch-Brink, E. G., Lingsma, H. F., van de Sandt-Koenderman, M. W., Dippel, D. W., Koudstaal, P. J., & Middelkoop, H. A. M. (2014). Nonlinguistic cognitive impairment in poststroke aphasia: A prospective study. *Neurorehabilitation and Neural Repair, 28*(3), 273–281.

Emre, M., Aarsland, D., Albanese, A., Byrne, E. J., Deuschl, G., De Deyn, P. P., & Lane, R. (2004). Rivastigmine for dementia associated with Parkinson's disease. *New England Journal of Medicine, 351*(24), 2509–2518.

Enderby, P., Broeckx, J., Hospers, W., Schildermans, F., & Deberdt, W. (1994). Effect of piracetam on recovery and rehabilitation after stroke: A double-blind, placebo-controlled study. *Clinical Neuropharmacology, 17*(4), 320–331.

Engelter, S. T., Frank, M., Lyrer, P. A., & Conzelmann, M. (2010). Safety of pharmacological augmentation of stroke rehabilitation. *European Neurology, 64*(69), 325–330.

Engelter, S. T., Urscheler, N., Baronti, F., Vuadens, P., Koch, J., Frank, M., & Jenni, W. (2012). Frequency and determinants of using pharmacological enhancement in the clinical practice of in-hospital stroke rehabilitation. *European Neurology, 68*(1), 28–33.

Erkinjuntti, T., Kurz, A., Gauthier, S., Bullock, R., Lilienfeld, S., & Damaraju, C. V. (2002). Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: A randomised trial. *Lancet, 359*, 1283–1290.

Erkinjuntti, T., Román, G., & Gauthier, S. (2004). Treatment of vascular dementia evidence from clinical trials with cholinesterase inhibitors. *Journal of the Neurological Sciences, 226*(1-2), 63–66.

Falchook, A. D., Heilman, K. M., Finney, G. R., Gonzalez-Rothi, L. J., & Nadeau, S. E. (2014). Neuroplasticity, neurotransmitters, and new directions for treatment of anomia in Alzheimer disease. *Aphasiology, 28*(2), 219–235.

Farooq, M. U., Min, J., Goshgarian, C., & Gorelick, P. B. (2017). Pharmacotherapy for vascular cognitive impairment. *CNS Drugs, 31*(9), 759–776.

Fasotti, L., & van Kessel, M. (2013). Novel insights in the rehabilitation of neglect. *Frontiers in Human Neuroscience, 7*, 780.

Ferris, S. H., & Farlow, M. (2013). Language impairment in Alzheimer's disease and benefits of acetylcholinesterase inhibitors. *Clinical Interventions in Aging, 8*, 1007–1014.

Flanagan, S., & Gordon, W. A. (2009). Pharmacological treatment for cognitive disorders of neurovascular origin. In J. R. Festa & R. M. Lazar (Eds.), *Neurovascular neuropsychology*. New York, NY: Springer.

Fleet, W. S., Valenstein, E., Watson, R. T., & Heilman, K. M. (1987). Dopamine agonist therapy for neglect in humans. *Neurology, 37*, 1765–1770.

Froudist-Walsh, S., López-Barroso, D., Torres-Prioris, M. J., Croxson, P. L., & Berthier, M. L. (2017). Plasticity in the working memory system: Life span changes and response to injury. *The Neuroscientist, 24*(3), 261–276.

Furey, M. L. (2011). The prominent role of stimulus processing: Cholinergic function and dysfunction in cognition. *Current Opinion in Neurology, 24*(4), 364–370.

Galling, M. A., Goorah, N., Berthier, M. L., & Sage, K. (2014). A clinical study of the combined use of bromocriptine and speech and language therapy in the treatment of a person with aphasia. *Aphasiology, 28*(2), 171–187.

Geminiani, G., Bottini, G., & Sterzi, R. (1998). Dopaminergic stimulation in unilateral neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 65*(3), 344–347.

Geranmayeh, F., Chau, T. W., Wise, R. J. S., Leech, R., & Hampshire, A. (2017). Domain-general subregions of the medial prefrontal cortex contribute to recovery of language after stroke. *Brain, 140*(7), 1947–1958.

Gill, S. K., & Leff, A. P. (2014). Dopaminergic therapy in aphasia. *Aphasiology, 28*(2), 155–170.

Gold, M., VanDam, D., & Silliman, E. R. (2000). An open-label trial of bromocriptine in nonfluent aphasia: A qualitative analysis of word storage and retrieval. *Brain and Language, 74*(2), 141–156.

Goldstein, L. B. (1995). Common drugs may influence motor recovery after stroke: The Sygen in Acute Stroke Study Investigations. *Neurology, 45*, 865–871.

Goldstein, L. B. (1998). Potential effects of common drugs on stroke recovery. *Archives of Neurology, 55*(4), 454–456.

González-González, J. A., & Lozano, R. (2000). A study of the tolerability and effectiveness of nicardipine retard in cognitive deterioration of vascular origin. *Revista de Neurologia, 30*(8), 719–728.

Gorgoraptis, N., Mah, Y. H., Machner, B., Singh-Curry, V., Malhotra, P., Hadji-Michael, M., & Husain, M. (2012). The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke. *Brain, 135*(8), 2478–2491.

Goss, C. W., Hoffman, S. W., & Stein, D. G. (2003). Behavioral effects and anatomic correlates after brain injury: A progesterone dose-response study. *Pharmacology, Biochemistry, and Behavior, 76*(2), 231–242.

Grantham, C., & Geerts, H. (2002). The rationale behind cholinergic drug treatment for dementia related to cerebrovascular disease. *Journal of Neurological Sciences, 203-204*, 131–136.

Grujic, Z., Mapstone, M., Gitelman, D. R., Johnson, N., Weintraub, S., Hays, A., & Mesulam, M. M. (1998). Dopamine agonists reorient visual exploration away from the neglected hemispace. *Neurology, 51*(5), 1395–1398.

Grysiewicz, R., & Gorelick, P. (2012). Key neuroanatomical structures for post-stroke cognitive impairment. *Current Neurology and Neuroscience Reports, 12*(6), 703–708.

Güngör, L., Terzi, M., & Onar, M. K. (2011). Does long term use of piracetam improve speech disturbances due to ischemic cerebrovascular diseases? *Brain and Language, 117*(1), 23–27.

Gupta, S., & Mlcoch, A. (1992). Bromocriptine treatment of nonfluent aphasia. *Archives of Physical Medicine and Rehabilitation, 73*, 373–376.

Gupta, S., Mlcoch, A., Scolaro, C., & Moritz, T. (1995). Bromocriptine treatment of nonfluent aphasia. *Neurology, 45*, 2170–2173.

Hachinski, V., Donnan, G., Gorelick, P., Hacke, W., Cramer, S. C., & Tuomilehto J. (2010). Stroke: Working toward a prioritized world agenda. *Stroke, 41*, 1084–1099.

Hacki, T., Kenklies, M., Hofmann, R., & Haferkamp, G. (1990). Pharmacotherapy of voice and articulation disorders in aphasia. *Folia Phoniatrica et Logopaedica, 42*(6), 283–288.

Hamzei-Moghaddam, A., Shafa, M. A., Nazari, M., & Akbari, M. (2014). The effect of piracetam in aphasia due to acute brain ischemic stroke: Clinical trial. *Journal of Kerman University of Medical Sciences, 21*(3), 219–229.

Hanyu, H., Hirao, K., Shimizu, S., Sato, T., Kiuchi, A., & Iwamoto, T. (2007). Nilvadipine prevents cognitive decline of patients with mild cognitive impairment. *International Journal of Geriatric Psychiatry, 22*, 1264–1266.

Heilman, K. M., Bowers, D., Valenstein, E., & Watson, R. T. (1987). Hemispace and hemispatial neglect. *Advances in Psychology, 45*, 115–150.

Herrschaft, H. (1988). The effectiveness of piracetam in acute cerebral ischemia in the human. A clinical controlled double-blind study of piracetam/10% dextran 40 versus 10% dextran 40/placebo. *Medizinische Klinik, 83*(20), 667–677.

Hillis, A. E., & Heidler, J. (2002). Mechanism of early aphasia recovery. *Aphasiology, 16*(9), 885–896.

Hiraoka, K., Okamura, N., Funaki, Y., Watanuki, S., Tashiro, M., Kato, M., &, Watabe, H. (2009). Quantitative analysis of donepezil binding to acetylcholinesterase using positron emission tomography and [5-(11)C-methoxy]donepezil. *NeuroImage, 46*(3), 616–623.

Hong, J. H., & Jang, S. H. (2010). Neural pathway from nucleus basalis of Meynert passing through the cingulum in the human brain. *Brain Research, 1346*, 190–194.

Hong, J. M., Shin, D. H., Lim, T. S., Lee, J. S., & Huh, K. (2012). Galantamine administration in chronic post-stroke aphasia. *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(7), 675–680.

Huber, W., Willmes, K., Poeck, K., Van Vleymen, B., & Deberdt, W. (1997). Piracetam as an adjuvant to language therapy for aphasia: A randomized double-blind placebo-controlled pilot study. *Archives of Physical Medicine and Rehabilitation, 78*(3), 245–250.

Hughes, J. D., Jacobs, D. H., & Heilman, K. M. (2000). Neuropharmacology and linguistic neuroplasticity. *Brain and Language, 71*, 96–101.

Hurford, P., Stringer, A. Y., & Jann, B. (1998). Neuropharmacologic treatment of hemineglect: A case report comparing bromocriptine and methylphenidate. *Archives of Physical Medicine and Rehabilitation, 79*(3), 346–349.

Husain, M., & Mehta, M. A. (2011). Cognitive enhancement by drugs in health and disease. *Trends in Cognitive Science, 15*(1), 28–36.

Ihl, R., Tribanek, M., & Bachinskaya, N. (2012). Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer's disease and vascular dementia: Results from a randomised controlled trial. *Pharmacopsychiatry, 2*, 41–46.

Jacobs, D. H., Shuren, J., Gold, M., Adair, J. C., Bowers, D., Williamson, D. J. G., & Heilman, K. M. (1996). Physostigmine pharmacotherapy for anomia. *Neurocase, 2*, 83–92.

Jian, W. J., Shi, J., Tian, J. Z., & Ni, J. N. (2015). Treatment of vascular dementia by Chinese herbal medicine: A systematic review of randomized controlled trials of clinical studies. *Zhongguo Zhong Xi Yi Jie He Za Zhi, 35*(1), 46–52.

Jianu, D. C., Muresanu, D. F., Bajenaru, O., Popescu, B. O., Deme, S. M., Moessler, H., & Petrica, L. (2010). Cerebrolysin adjuvant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artery. *Journal of Medicine and Life, 3*(3), 297–307.

Jiang, B., Ding, C., Yao, G., Yao, C., Zhang, Y., Ge, J., & Qiu, E. (2013). Intervention effect of folic acid and vitamin B12 on vascular cognitive impairment complicated with Hyperhomocysteinemia. *Journal of Medical Biochemistry. 33*. https://doi.org/10.2478/jomb-2013-0033

Kabasawa, H., Matsubara, M., Kamimoto, K., Hibino, H., Banno, T., & Nagai, H. (1994). Effects of bifemelane hydrochloride on cerebral circulation and metabolism in patients with aphasia. *Clinical Therapeutics, 6*(3), 471–482.

Kanowski, S., Herrmann, W. M., Stephan, K., Wierich, W., & Hörr, R. (1996). Proof of efficacy of the ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry, 29*, 47–56.

Katz, R. C., & Wertz, R. T. (1997). The efficacyof computer-provided reading treatment for chronic aphasic adults. *Journal of Speech, Language, and Hearing Research, 40*, 493–507.

Kertesz, A. (1982). *Western aphasia battery test manual*. Winchester, VA: Grune & Stratton.

Keser, Z., Dehgan, M. W., Shadravan, S., Yozbatiran, N., Maher, L. M., & Francisco, G. E. (2017). Combined dextroamphetamine and transcranial direct current stimulation in poststroke aphasia. *Amercian Journal of Physical Medicine & Rehabilitation, 96*(10), 141–145.

Kessler, J., Thiel, A., Karbe, H., & Heiss, W. D. (2000). Piracetam improves activated blood flow and facilitates rehabilitation of poststroke aphasic patients. *Stroke, 31*(9), 2112–2116.

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependant neural plasticity: Implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research, 51*, S225–S239.

Kolb, B., & Gibb, R. (2014). Searching for the principles of brain plasticity and behavior. *Cortex, 58*, 251–260.

Kortte, K. B., & Hillis, A. E. (2011). Recent trends in rehabilitation interventions for visual neglect and anosognosia for hemiplegia following right hemisphere stroke. *Future Neurology, 6*(1), 33–43.

Laska, A. C., von Arbin, M., Kahan, T., Hellblom, A., & Murray, V. (2005). Long-term antidepressant treatment with moclobemide for aphasia in acute stroke patients: a randomised, double-blind, placebo-controlled study. Cerebrovascular diseases (Basel, Switzerland), 19(2), 125–132. https://doi.org/10.1159/000083256.

Le Bars, P. L., Velasco, F. M., Ferguson, J. M., Dessain, E. C., Kieser, M., & Hoerr, R. (2002). Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGb 761 in Alzheimer's disease. *Neuropsychobiology, 45*(1), 19–26.

Leemann, B., Laganaro, M., Chetelat-Mabillard, D., & Schnider, A. (2011). Crossover trial of subacute computerized aphasia therapy for anomia with the addition of either levodopa or placebo. *Neurorehabilitation and Neural Repair, 1*, 43–47.

Leijenaar, J. F., Groeneveld, G. J., van der Flier, W. M., Scheltens, P., Klaassen, E. S., Weinstein, H. C., & Prins, N. D. (2018). Symptomatic treatment of vascular cognitive impairment (STREAM-VCI): Protocol for a cross-over trial. *JMIR Research Protocol, 7*(3), e80.

Levine, D. A., & Langa, K. M. (2011). Vascular cognitive impairment: Disease mechanisms and therapeutic implications. *Neurotherapeutics, 8*(3), 361–373.

Li, S., & Carmichael, S. T. (2006). Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. *Neurobiology of Disease, 23*(2), 362–373.

Liepert, J. (2016). Update on pharmacotherapy for stroke and traumatic brain injury recovery during rehabilitation. *Current Opinion in Neurology, 29*(6), 700–705.

Liu, Q., Zhu, Z., Teipel, S. J., Yang, J., Xing, Y., Tang, Y., & Jia, J. (2017). White matter damage in the cholinergic system contributes to cognitive impairment in subcortical vascular cognitive impairment, no dementia. *Frontiers in Aging Neuroscience, 27*(9), 47.

Llano, D. A., & Small, S. L. (2016). Pharmacotherapy for aphasia. In G. Hickok & S. L. Smalls (Eds.), *Neurobiology of language* (pp. 1067–1082). London: Academic Press.

López-Barroso, D., Torres-Prioris, M. J., Beltrán-Corbellini, A., Roé-Vellvé, N., Paredes-Pacheco, J., Edelkraut, L., Dávila, G., & Berthier M. L. (2018). *Beneficial effects of pharmacological treatment in post-stroke dynamic aphasia: A behavioural and neuroimaging study*. Bressanone: Presented at the European Workshop on Cognitive Neuropsychology.

López-Valdés, H. E., Clarkson, A. N., Ao, Y., Charles, A. C., Carmichael, S. T., Sofroniew, M. V., & Brennan, K. C. (2014). Memantine enhances recovery from stroke. *Stroke, 45*(7), 2093–2100.

Lucas, N., Saj, A., Schwartz, S., Ptak, R., Thomas, C, Conne, P.,...&, Vuilleumier, P. (2013). Effects of pro-cholinergic treatment in patients suffering from spatial neglect. *Frontiers in Human Neuroscience, 7*, 1–15.

MacLennan, D. L., Nicholas, L. E., Morley, G. K., & Brookshire, R. H. (1991). The effects of bromocriptine on speech and language function in a man with transcortical motor aphasia. In T. E. Prescott (Ed.), *Clinical aphasiology*. Boston, MA: College Hill.

Malhotra, P. A., Parton, A. D., Greenwood, R., & Husain, M. (2006). Noradrenergic modulation of space exploration in visual neglect. *Annals of Neurology, 59*(1), 186–190.

Malouf, R., & Birks, J. (2004). Donepezil for vascular cognitive impairment. *Cochrane Database of Systematic Reviews, 1*, CD004395.

Mazza, M., Capuano, A., Bria, P., & Mazza, S. (2006). Ginkgo biloba and donepezil: A comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *European Journal of Neurology, 13*(9), 981–985.

McCarney, R., Fisher, P., Iliffe, S., van Haselen, R., Griffin, M., van der Meulen, M. J., & Warner, J. (2008). Ginkgo biloba for mild to moderate dementia in a community setting: A pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. *International Journal of Geriatric Psychiatry, 23*, 1222–1230.

McKinnon, E. T., Fridriksson, J., Glenn, G. R., Jensen, J. H., Helpern, J. A., Basilakos, A., & Bonilha, L. (2017). Structural plasticity of the ventral stream and aphasia recovery. *Annals of Neurology, 82*(1), 147–151.

McNeil, M. R., Doyle, P. J., Spencer, K. A., Goda, A. J., Flores, D., & Small, S. L. (1997). A double-blind, placebo-controlled study of pharmacological and behavioral treatment of lexical-semantic deficits in aphasia. *Aphasiology, 11*, 358–400.

Mellon, L., Brewer, L., Hall, P., Horgan, F., Williams, D., & Hickey, A. (2015). Cognitive impairment six months after ischemic stroke: A profile from the ASPIRE-S study. *BMC Neurology, 15*, 31.

Mena-Segovia, J., & Bolam, J. P. (2017). Rethinking the pedunculopontine nucleus: From cellular organization to function. *Neuron, 94*(1), 7–18.

Merriman, N. A., Sexton, E., Donnelly, N. A., McCabe, G., Walsh, M.E., Rohde, D., & Hickey, A. (2018). Managing cognitive impairment following stroke: Protocol for a systematic review of non-randomised controlled studies of psychological interventions. *BMJ Open, 8*, e019001.

Mesulam, M., Siddiqe, T., & Cohen, B. (2003). Cholinergic denervation in a pure multi-infarct state: Observations on CADASIL. *Neurology, 60*(7), 1183–1185.

Moretti, R., Torre, P., Antonello, R. M., Cazzato, G., & Bava, A. (2002). Rivastigmine in subcortical vascular dementia: An open 22-month study. *Journal of Neurological Sciences, 204*, 141–146.

Mukand, J. A., Guilmette, T. J., Allen, D. G., Brown, L. K., Brown, S. L., Tober, K. L., & Vandyck, W. R. (2001). Dopaminergic therapy with carbidopa L-dopa for left neglect after stroke: A case series. *Archives of Physical Medicine and Rehabilitation, 82*(9), 1279–1282.

Napryeyenko, O., & Borzenko, I. (2007). GINDEM-NP Study Group. Ginkgo biloba special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittel-Forschung, 57*(1), 4–11.

Narasimhalu, K., Effendy, S., Sim, C. H., Lee, J. M., Chen, I., Hia, S. B., & Tan, E. K. (2010). A randomized controlled trial of rivastigmine in patients with cognitive impairment no dementia because of cerebrovascular disease. *Acta Neurologica Scandinavica, 121*, 217–224.

Nijboer, T. C. W., Kollen, B. J., & Kwakkel, G. (2013). Time course of visuospatial neglect early after stroke: A longitudinal cohort study. *Cortex, 49*, 2021–2027.

Orfei, M. D., Robinson, R. G., Prigatano, G. P., Starkstein, S., Rüsch, N., Bria, P., & Spalletta, G. (2007). Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: A systematic review of the literature. *Brain, 130*(12), 3075–3090.

Orgogozo, J. M., Rigaud, A. S., Stoffler, A., Mobius, H. J., & Forette, F. (2002). Efficacy and safety of memantine in patients with mild to moderate vascular dementia: A randomized, placebo-controlled trial (MMM 300). *Stroke, 33*(7), 1834–1839.

Ozeren, A., Sarica, Y., Mavi, H., & Demirkiran, M. (1995). Bromocriptine is ineffective in the treatment of chronic nonfluent aphasia. *Acta Neurologica Belgium, 95*, 235–238.

Palomero-Gallagher, N., & Zilles, K. (2017). Cortical layers: Cyto-, myelo-, receptor- and synaptic architecture in human cortical areas. *Neuroimage, pii*, S1053-8119(17)30682-1.

Pantoni, L., Bianchi, C., Beneke, M., Inzitari, D., Wallin, A., & Erkinjuntti, T. (2000). The Scandinavian Multi-Infarct Dementia Trial: A double-blind, placebo-controlled trial on nimodipine in multi-infarct dementia. *Journal of Neurological Sciences, 175*(2), 116–123.

Pantoni, L., del Ser, T., Soglian, A. G., Amigoni, S., Spadari, G., Binelli, D., & Inzitari, D. (2005). Efficacy and safety of nimodipine in subcortical vascular dementia: A randomized placebo-controlled trial. *Stroke, 36*(3), 619–624.

Paolucci, S., Bureca, I., Multari, M., Nocentini, U., & Matano, A. (2010). An open-label pilot study of the use of rivastigmine to promote functional recovery in patients with unilateral spatial neglect due to first ischemic stroke. *Functional Neurology, 25*(4), 195–200.

Parsons, C. G., Stöffler, A., & Danysz, W. (2007). Memantine: A NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system-too little activation is bad, too much is even worse. *Neuropharmacology, 53*(6), 699–723.

Pendlebury, S. T., & Rothwell, P. M. (2009). Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: A systematic review and metaanalysis. *Lancet Neurology, 8*(11), 1006–1018.

Perng, C. H., Chang, Y. C., & Tzang, R. F. (2018). The treatment of cognitive dysfunction in dementia: A multiple treatments meta-analysis. *Psychopharmacology, 235*(5), 1571–1580.

Peters, O., Lorenz, D., Fesche, A., Schmidtke, K., Hüll, M., Perneczky, R., & Heuser, I. (2012). A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. *The Journal of Nutrition, Health & Aging, 16*(6), 544–548.

Piai, V., Meyer, L., Dronkers, N. F., & Knight, R. T. (2017). Neuroplasticity of language in left-hemisphere stroke: Evidence linking subsecond electrophysiology and structural connections. *Human Brain Mapping, 38*(6), 3151–3161.

Price, J. F., Stewart, M. C., Deary, I. J., Murray, G. D., Sandercock, P., Butcher, I., & Fowkes, F. G. (2008). AAA Trialists. Low dose aspirin and cognitive function in middle aged to elderly adults: Randomized controlled trial. *BMJ, 1*, 337.

Raymer, A. M. (2003). Treatment of adynamia in aphasia. *Frontiers in Bioscience, 8*, 845–851.

Raymer, A. M., Bandy, D., Adair, J. C., Schwartz, R. L., Williamson, D. J., Gonzalez Rothi, L. J., & Heilman, K. M. (2001). Effects of bromocriptine in a patient with crossed nonfluent aphasia: A case report. *Archives of Physical Medicine and Rehabilitation, 82*(1), 139–144.

Riepe, M. W., Adler, G., Ibach, B., Weinkauf, B., Tracik, F., & Gunay, I. (2007). Domain-specific improvement of cognition on memantine in patients with Alzheimer's disease treated with rivastigmine. *Dementia and Geriatric Cognitive Disorders, 23*(5), 301–306.

Rist, P. M., Chalmers, J., Arima, H., Anderson, C., Macmahon, S., Woodward, M., & Christophe Tzourio (2013). Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. *Stroke, 44*, 1790–1795.

Riveros, R., Chabriat, H., Flores, R., Alvarez, G., & Slachevsky, A. (2011). Effects of donepezil on behavioral manifestations of thalamic infarction: A single-case observation. *Frontiers in Neurology, 24*(2), 16.

Rogawski, M. A., & Wenk, G. L. (2003). The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. *CNS Drug Reviews, 9*(3), 275–308.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., & Turner, M. B. (2012). Heart disease and stroke statistics – 2012 Update: A report from the American Heart Association. *Circulation, 125*(1), 2–220.

Román, G. C., & Kalaria, R. N. (2006). Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. *Neurobioly of Aging, 27*(12), 1769–1785.

Román, G. C., Salloway, S., Black, S. E., Royall, D. R., Decarli, C., Weiner, M. W., & Posner, H. (2010). Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: Differential effects by hippocampal size. *Stroke, 41*, 1213–1221.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., & Perenin, M. T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 395*, 166–169.

Sabe, L., Leiguarda, R., & Starkstein, S. (1992). An open-label trial of bromocriptine in nonfluent aphasia. *Neurology, 42*, 1637–1638.

Sabe, L., Salvarezza, F., Cuerva, A. G., Leiguarda, R., & Starkstein, S. (1995). A randomized, double-blind, placebo controlled study of bromocriptine in nonfluent aphasia. *Neurology, 45*, 2272–2274.

Salter, K., Teasell, R., Bhogal, S., Zettler, L., & Foley, N. (2012). Aphasia. In *The evidence-based review of stroke rehabilitation (EBRSR) reviews current practices in stroke rehabilitation*. London: Routledge. Retrieved fromwww.ebrsr.com

Schlaug, G., Marchina, S., & Norton, A. (2009). Evidence for plasticity in white matter tracts of chronic aphasic patients undergoing intense intonation-based speech therapy. *Annals of the New York Academy of Sciences, 1169*, 385–394.

Schneider, L. S., DeKosky, S. T., Farlow, M. R., Tariot, P. N., Hoerr, R., & Kieser, M. A. (2005). randomized, double-blind, placebo-controlled trial of two doses of Ginkgo biloba extract in dementia of the Alzheimer's type. *Current Alzheimer Research, 2*(5), 541–551.

Selden, N. R., Gitelman, D. R., Salamon-Murayama, N., Parrish, T. B., & Mesulam, M. M. (1998). Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain, 121*(12), 2249–2257.

Seniów, J., Litwin, M., Litwin, T., Leśniak, M., & Członkowska, A. (2009). New approach to the rehabilitation of post-stroke focal cognitive syndrome: Effect of levodopa combined with speech and language therapy on functional recovery from aphasia. *Journal of the Neurological Sciences, 283*(1–2), 214–218.

Small, S. L., Buccino, G., & Solodkin, A. (2013). Brain repair after stroke – A novel neurological model. *Nature Reviews Neurology, 9*(12), 698–707.

Small, S. L., & Llano, D. A. (2009). Biological approaches to aphasia treatment. *Current Neurology and Neuroscience Reports, 9*(6), 443–450.

Spanish Group of Nicardipine Study in Vascular Dementia (1999). An experimental, randomized, double-blind, placebo-controlled clinical trial to investigate the effect of nicardipine on cognitive function in patients with vascular dementia. *Revista de Neurología, 15*, 28–845.

Spiegel, D. R., & Alexander, G. A. (2011). Case of nonfluent aphasia treated successfully with speech therapy and adjunctive mixed amphetamine salts. *The Journal of Neuropsychiatry and Clinical Neurosciences, 23*(1), E24.

Starkstein, S. E., Fedoroff, J. P., Price, T. R., Leiguarda, R., & Robinson, R. G. (1992). Anosognosia in patients with cerebrovascular lesions. A study of causative factors. *Stroke, 23*(10), 1446–1453.

Starkstein, S. E., Jorge, R. E., & Robinson, R. G. (2010). The frequency, clinical correlates, and mechanism of anosognosia after stroke. *Canadian Journal of Psychiatry, 55*(6), 355–361.

Stone, S. P., Halligan, P. W., & Greenwood, R. J. (1993). The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age and Ageing, 22*(1), 46–52.

Szelies, B., Mielke, R., Kessler, J., & Heiss, W. D. (2011). Restitution of alpha-topography by piracetam in post-stroke aphasia. *International Journal of Clinical Pharmacology and Therapeutics, 39*(4), 152–157.

Tanaka, Y., Miyazaki, M., & Albert, M. L. (1997). Effects of increased cholinergic activity on naming in aphasia. Lancet (London, England), 350(9071), 116–117. https://doi.org/10.1016/S0140-6736(05)61820-X.

Tanaka, Y., & Bachman, D. L. (2007). Pharmacotherapy of aphasia. In L. S. Connor & L. K. Obler (Eds.), *Neurobehavior of language and cognition studies of normal aging and brain damage* (pp. 159–162). Berlin: SpringerLink.

Tariot, P. N., Farlow, M. R., Grossberg, G. T., Graham, S. M., McDonald, S., & Gergel, I. (2004). Memantine treatment in patients with moderate to severe Alzheimer disease already receiving

donepezil: A randomized controlled trial. *Journal of the American Medical Association, 291*, 317–324.

Teasell, R., Foley, N., Salter, K., Bhogal, S., Jutai, J., & Speechley, M. (2012). *Evidence-based review of stroke rehabilitation. Executive summary* (15th ed.). London: Routledge. Retrieved from www.ebrsr.com

Toba, M. N., Rabuffetti, M., Duret, C., Pradat-Diehl, P., Gainotti, G., & Bartolomeo, P. (2018). Component deficits of visual neglect: "Magnetic" attraction of attention vs. impaired spatial working memory. *Neuropsychologia, 109*, 52–62.

Tocco, M., Bayles, K., Lopez, O. L., Hofbauer, R. K., Pejović, V., Miller, M. L., & Saxton J. (2014). Effects of memantine treatment on language abilities and functional communication: A review of data. *Aphasiology, 28*(2), 236–257.

Towfighi, A., & Saver, J. L. (2011). Stroke declines from third to fourth leading cause of death in the United States: Historical perspective and challenges ahead. *Stroke, 42*, 2351–2355.

Tsz-Ming, C., & Kaufer, D. J. (2001). Effects of donepezil on aphasia, agnosia, and apraxia in patients with cerebrovascular lesions. *The Journal of Neuropsychiatry and Clinical Neurosciences, 13*, 140.

Vallar, R., & Ronchi, R. (2009). Somatoparaphrenia: A body delusion. A review of the neuropsychological literature. *Experimental Brain Research, 192*(3), 533–551.

Van Der Meulen, I., Van De Sandt-Koenderman, M. W., Heijenbrok, M. H., Visch-Brink, E., & Ribbers, G. M. (2016). Melodic intonation therapy in chronic aphasia: Evidence from a pilot randomized controlled trial. *Frontiers of Human Neuroscience, 10*, 533.

Van Peppen, R. P., Kwakkel, G., Wood-Dauphinee, S., Hendriks, H. J., Van der Wees, P. J., & Dekker, J. (2004). The impact of physical therapy on functional outcomes after stroke: What's the evidence? *Clinical Rehabilitation, 18*(8), 833–862.

Vossel, S., Kukolja, J., Thimm, M., Thiel, C. M., & Fink, G. R. (2010). The effect of nicotine on visuospatial attention in chronic spatial neglect depends upon lesion location. *Journal of Psychopharmacology, 24*(9), 1357–1365.

Wali, B., Ishrat, T., Won, S., Stein, D. G., & Sayeed, I. (2014). Progesterone in experimental permanent stroke: A dose-response and therapeutic time-window study. *Brain, 137*(Pt 2), 486–502.

Walker-Batson, D., Curtis, S., Natarajan, R., Fords, J., Dronkers, N., Salmeron, E., & Unwin, H. D. (2001). A double-blind, placebo-controlled study of the use of amphetamine in the treatment of aphasia. *Stroke, 32*(9), 2093–2098.

Walker-Batson, D., Mehta, J., Smith, P., & Johnson, M. (2016). Amphetamine and other pharmacological agents in human and animal studies of recovery from stroke. *Progress in Neuropsychopharmacology and Biological Psychiatry, 64*, 225–230.

Walker-Batson, D., Unwin, H., Curtis, S., Allen, E., Wood, M., Smith, P., & Greenlee, R. G. (1992). Use of amphetamine in the treatment of aphasia. *Restorative Neurology and Neuroscience, 4*(1), 47–50.

Wan, C. Y., Zheng, X., Marchina, S., Norton, A., & Schlaug, G. (2014). Intensive therapy induces contralateral white matter changes in chronic stroke patients with Broca's aphasia. *Brain and Language, 136*, 1–7.

Whiting, E., Chenery, H. J., Chalk, J., & Copland, D. A. (2007). Dexamphetamine boosts naming treatment effects in chronic aphasia. *Journal of the International Neuropsychological Society, 13*(6), 972–979.

Wilcock, G., Mobius, H. J., & Stoffler, A. (2002). A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *International Clinical Psychopharmacology, 17*(6), 297–305.

Wilkinson, D., Doody, R., Helme, R., Taubman, K., Mintzer, J., Kertesz, A., & Pratt, R. D. (2003). Donepezil in vascular dementia: A randomized, placebo-controlled study. *Neurology, 61*, 479–486.

Wirsich, J., Rey, M., Guye, M., Bénar, C., Lanteaume, L., Ridley, B., & Ranjeva, J-P. (2018). Brain networks are independently modulated by donepezil, sleep, and sleep deprivation. *Brain Topography, 31*(3), 380–391.

Woodhead, Z. V., Crinion, J., Teki, S., Penny, W., Price, C. J., & Leff, A. P. (2017). Auditory training changes temporal lobe connectivity in 'Wernicke's aphasia': A randomised trial. *Journal of Neurology, Neurosurgery and Psychiatry, 88*(7), 586–594.

Xu, Z. Q., Liang, X. M., Juan-Wu, J. W., Zhang, Y. F., Zhu, C. X., & Jiang, X. J. (2012). Treatment with huperzine A improves cognition in vascular dementia patients. *Cell Biochemistry and Biophysics, 62*(1), 55–58.

Yancheva, S., Ihl, R., Nikolova, R., Panayotov, P., Schlaefke, S., & Hoerr, R. (2008). Ginkgo biloba extract EGb 761®, donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: A randomised, double-blind, exploratory trial. *Journal of Aging and Health, 13*, 183–190.

Yoon, S. Y., Kim, J. K., An, Y. S., & Kim, Y. W. (2015). Effect of donepezil on Wernicke aphasia after bilateral middle cerebral artery infarction: Subtraction analysis of brain F-18 fluorodeoxyglucose positron emission tomographic images. *Clinical Neuropharmacology, 38*(4), 147–150.

Yousuf, S., Atif, F., Sayeed, I., Tang, H., & Stein, D. G. (2014). Progesterone in transient ischemic stroke: A dose–response study. *Psychopharmacology, 231*(17), 3313–3323.

Zhang, R. L., Zhang, Z. G., & Chopp, M. (2008). Ischemic stroke and neurogenesis in the subventricular zone. *Neuropharmacology, 55*(3), 345–352.

Zhang, J., Wei, R., Chen, Z., & Luo, B. (2016). Piracetam for Aphasia in Post-stroke Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *CNS drugs, 30*(7), 575–587. https://doi.org/10.1007/s40263-016-0348-1.

Zhou, Q., & Sheng, M. (2013). NMDA receptors in nervous system diseases. *Neuropharmacology, 74*, 69–75.

Zilles, K., & Amunts, K. (2009). Receptor mapping: Architecture of the human cerebral cortex. *Current Opinion in Neurology, 22*(4), 331–339.