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Amphetamine and other pharmacological agents in human and animal studies of recovery from stroke

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ABSTRACT

Neuromodulation with pharmacological agents, including drugs of abuse such as amphetamine, when paired with behavioral experience, has been shown to positively modify outcomes in animal models of stroke. A number of clinical studies have tested the efficacy of a variety of drugs to enhance recovery of language deficit post-stroke. The purpose of this paper is to: (1) present pertinent animal studies supporting the use of dextro-amphetamine sulfate (AMPH) to enhance recovery after experimental lesions with emphasis on the importance of learning dependent activity for lasting recovery; (2) briefly review neuropharmacological explorations in the treatment of aphasia; (3) present a pilot study in aphasia exploring a drug combination of AMPH and donepezil hydrochloride paired with behavioral treatment to facilitate recovery; and (4) conclude with comments regarding the role of adjunctive pharmacotherapy in the rehabilitation of aphasia, particularly AMPH.

1. Introduction

Neuromodulation with pharmacological agents, including drugs of abuse such as dextroamphetamine sulfate (AMPH), when paired with behavioral experience has been shown to modify outcomes after experimental lesions in animals (Barbay et al., 2006; Bütefisch et al., 2002; Feeney et al., 1982; Hovda and Feeney, 1984; Stroemer et al., 1998). A number of clinical studies have tested the efficacy of a variety of drugs to enhance recovery from post stroke deficits including aphasia (Ashtary et al., 2006; Berthier et al., 2006; Kessler et al., 2000; Pashek, 2006; Sabe et al., 1995; Szelies et al., 2001; Tanaka et al., 2001; Walker-Batson et al., 2004). Evidence regarding critical periods of plasticity post-injury, theories of learning and the enhancing effects of certain drugs has application to biologically based approaches for human rehabilitation. The purpose of this paper is to: (1) present pertinent animal studies supporting the use of AMPH to facilitate recovery following experimental lesions with emphasis on the importance of learning dependent activity to for lasting recovery; (2) briefly review clinical studies employing a range of pharmacologic agents to facilitate recovery of post-stroke aphasia; (3) present a pilot study exploring a drug combination of AMPH and donepezil hydrochloride paired with language treatment to facilitate recovery of aphasia; and (4) conclude with comments regarding the role of adjunctive pharmacotherapy in the rehabilitation of aphasia, particularly AMPH.

2. Evidence from the basic science laboratory

There is an impressive literature in animal models of stroke exploring pharmacological agents to facilitate recovery after injury. Much of this literature has focused on the noradrenergic and dopaminergic systems. A number of experiments have investigated the hypothesis that modulation of brain catecholamines might influence recovery of motor function. One of the primary agents explored was AMPH (Boyeson and Feeney, 1993; Feeney et al., 1982; Hovda and Feeney, 1984;). An important finding from these studies was that recovery was greater when targeted behavioral experience was paired with the drug intoxication phase and not drug administration alone. AMPH facilitated recovery has also been reported for binocular depth perception (Feeney and Hovda, 1985) and sensory motor integration (Hurwitz et al., 1991) with limits to the AMPH effect in terms of lesion location (Boyeson and Feeney, 1993) and time post-injury (Hovda and Feeney, 1984). Recently other groups have reported positive findings in post-lesioned animals after AMPH administration (Atkins and Jones, 2005; Barbay et al., 2006; Bütefisch et al., 2002; Papadopoulos et al., 2009; Stroemer et al., 1998). Previous research studied the relationship between behavioral recovery and expression of proteins involved in neurite growth and synaptogenesis (Stroemer et al., 1998). AMPH and placebo treated rats were exposed to beam walking as a motor activity. AMPH treated rats had accelerated recovery compared to the placebo treated rats at two time periods: at the early assessment period, which

Abbreviations: AMPH, dextro-amphetamine sulfate; PICA, Porch Index of Communicative Ability; WAB-R, Western Aphasia Battery-R; MCA, middle cerebral artery; ST, speech therapy; OLCT, open label clinical trial.

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the authors have suggested could be due to resolution of diaschisis and at a later period, which was suggested to contribute to neuronal remodeling. Papadopoulos et al. (2009) studied how differing levels of motor treatment paired with short term AMPH administration enhanced forelimb function in rats. Results showed that short term pairing of AMPH with specifically focused activity induces long-term improvement. The anatomical data suggested that cortico-efferent plasticity of axonal sprouting contributes to improved motor recovery. These authors emphasize that sufficiently focused physical activity (dosing) is needed to realize the therapeutic benefits of AMPH recovery. This implies that the amount and specificity of rehabilitation paired with neuromodulation are of utmost importance.

The type of behavioral treatment needed to facilitate neuroplasticity and lasting recovery has been well studied in the laboratory with implications for translation to human rehabilitation. Post-lesion plasticity of sensory and motor systems has been studied in adult monkeys. The term learning dependent (Plautz et al., 1995) has been suggested to describe the type of treatment required for changes in cortical plasticity to occur following motor and sensory injury. Nudo et al. (1997) observed that motor maps are altered by motor skill acquisition and not by repetitive use alone. Topographic plasticity paralleled the reacquisition of motor skills in lesioned animals and the acquisition of new motor skills in intact animals. Plasticity of the somatosensory cortex was studied by Xerri et al. (1998) who found that post-lesion remodeling was influenced by activity that was idiosyncratic to each animal. This research suggests that the specificity of the behavioral treatment following brain injury with or without pharmacologic modulation critically determines the type of recovery that occurs.

3. Clinical explorations of neuropharmacological agents in the treatment of aphasia

Research reports exploring various neuropharmacological agents as an adjunct in the treatment of aphasia date back over 80 years. As would be expected, there is considerable variability in study design and outcome measures employed over this period. Differences include time post-stroke of study initiation, drug administered alone or paired with behavioral treatment, timing of the behavioral treatment (e.g. during the peak period of drug action), intensity and dosing of the behavioral treatment, and measures assessing lasting behavioral effects at follow-up.

Table 1 provides an overview of the diversity of the drugs that have been explored to facilitate recovery of aphasia. The search strategy used key phrases on search engines along with PudMED and PsychInfo. Older publications not identified on search engines were part of personal libraries or specifically requested. As seen in Table 1 the greatest percentage of studies have been open label or cross over design with small numbers and few double blind comparisons. Drugs showing moderately positive effects include Piracetam, acetylcholinesterase inhibitors, and dextroamphetamine sulfate.

4. Combined AMPH/donepezil in the treatment of aphasia: a pilot study

Influenced by previous explorations of cholinesterase inhibitors (Berthier et al., 2006; Tanaka et al., 1997; Tanaka et al., 2001; Pashek, 2006), the asymmetry of acetylcholine in the left temporal lobe (Amaducci et al., 1981), coupled with our experience (Unwin and Walker-Batson, 2000; Walker-Batson et al., 2004) and that of others (Benson, 1970) administering AMPH to facilitate recovery from aphasia, we were curious if a drug combination might have more impact than a single drug alone. The purpose of this Phase I pilot study was two-fold: to investigate the safety of the drug combination of AMPH and donepezil sulfate and to determine if this combined drug regimen when paired with 36 h of language treatment showed clinically significant effects which were maintained at follow-up long after drug treatment ceased.

4.1. Methods and procedures

4.1.1. Subjects

Eight consecutively entered patients with aphasia due to a single left middle cerebral artery (MCA) occlusive infarction participated in the study. Written informed consent was obtained from all subjects before the study was initiated. The research protocol was approved by the Institutional Review Boards for Human Subjects at the participating centers. Participants were recruited from medical centers in a metropolitan area and entered in a consecutive manner. Over a two-year period the medical charts of approximately 320 patients were screened. The primary reasons for exclusion were history of a previous stroke or aphasia either too mild or too severe to meet our inclusion criteria.

All patients were native English speakers. Diagnosis was based on radiological and neurological examination. Either CT or MRI confirmed the presence of a single infarction at entry. The National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989) was administered to provide a baseline score of the degree of neurological involvement. Exclusion criteria specified that none of the subjects have a terminal medical condition such as AIDS or cancer, other coincident neurological disease, history of psychiatric illness, extensive alcohol or drug abuse, unstable cardiac dysrhythmia, hypertension not controlled by medication (<160/100 mm HG) or untreated hyperthyroidism. Participation was limited to persons not older than 80 years and not receiving alpha-adrenergic antagonists or agonists, major or minor tranquilizers. The Porch Index of Communicative Ability-PICA (Overall Score) (Porch, 1982) and the Western Aphasia Battery—WAB-R (Aphasia Quotient) (Kertesz, 2006) were the dependent measures and were obtained within three days of study initiation. The presence of aphasia was defined as a score of 15 to 70 on the Overall Score on the PICA. The primary outcome measure was the PICA Overall Score at the one week off drug assessment. Patients were closely monitored during the six week treatment period and follow-up in an attempt to eliminate any confounding medications that might have a deleterious effect on recovery.

4.1.2. Procedures

This was an open label study designed to evaluate the effects of combining AMPH and donepezil to enhance recovery from aphasia. All participants received a 1.5 hour language therapy session four days per week, Monday through Thursday (36 hours total) for six weeks. On Monday and Thursday only, an oral dose of 10 mg of AMPH was administered 30 min prior to the treatment session for a total of 12 doses of AMPH over the six week study period. Every day, the participant took 5 mg of donepezil. Therapeutic protocols for each participant were individually designed using cognitive linguistic approaches which targeted the most complex language behaviors (Thompson et al., 2003; Raymer and Rothia, 2008; Kiran and Thompson, 2003) that could be elicited by the therapist. Blood pressure was checked each treatment day before AMPH administration and at the end of the 1.5 hour treatment session. A log of any negative side effects was kept by each subject or significant other and monitored bi-weekly.

4.2. Data preparation

The Porch Index of Communicative Ability—PICA (Overall Score) (Porch, 1982) and the Western Aphasia Battery—WAB-R (Aphasia Quotient) (Kertesz, 2006) were the dependent measures. The PICA Overall score at the one week off treatment (gain scores from Time 1 to Time 3) was considered the primary outcome measure. We chose to administer two standard aphasia batteries used in research settings both for reliability and to compare our data to other published studies. PICA Overall and Verbal scores were obtained at baseline, mid-

Table 1
Summary of studies exploring various drugs to facilitate recovery from aphasia.

Authors	Participants	Time post-onset	Design	Drug/dosing regimen	Associated treatment	Outcome measures
Bromocriptine						
Albert et al. (1988)	1	3.5 years	OLCT	Bromocriptine; up to 30 mg/d for 6 weeks	ST	Improved verbal fluency and naming, decreased paraphasias
Gupta and Micoch (1992)	2	18 months and 10 years	OLCT	Bromocriptine; 30 mg/d for 16 months	No	Improved verbal fluency, naming and mean length of utterance
Sabe et al. (1992)	7	1–3 years	OLCT	Bromocriptine; 60 mg/d for 12 weeks	No	Improved verbal fluency, decrease pauses in 3 patients. No improvements in patients with severe aphasia
Gupta et al. (1995)	20	1–17 years	Double-blind, crossover with placebo	Bromocriptine; up to 15 mg/d for 8 weeks with 4-week washout	No	No treatment effects on language
Sabe et al. (1995)	7	1–7 years	Double-blind, crossover with placebo	Bromocriptine; up to 60 mg/d for 6 weeks with 3-week washout	No	No treatment effects on language
Bragoni et al. (2000)	5	1–4 years	Double-blind, crossover with placebo	Bromocriptine; 30 mg/d for 8 weeks with ST, then 8 weeks without ST	ST	Drug + ST: improved reading comprehension & verbal fluency. Drug alone: improved reading comprehension & verbal fluency but not as significant as drug + ST.
Gold et al. (2000)	4	9 months to 6.5 years	OLCT	Bromocriptine; 15 mg/d for 8 weeks	No	Improved naming
Reed et al. (2004)	6	Not reported	Double-blind, crossover with placebo	Bromocriptine; 22.5 mg/d for 7 weeks	No	Improved mean length of utterance
Piracetam						
Enderby et al. (1994)	66	Day 35 to Day 63	Random, double-blind, with placebo	Piracetam; 4.8 g/d for 12 weeks	ST	No treatment effects on language
Huber et al. (1997)	50	Day 28 to 3 years	Random, double-blind, with placebo	Piracetam; 4.8 g/d for 6 weeks	Some ST	Some language improvement but did not reach significance
Orgogozo (1999)	373	Day 0	Random, double-blind, with placebo	Piracetam; 4.8 g/d for 12 weeks	Some ST, no details	Some language improvement compared to placebo but did not reach significance
Kessler et al. (2000)	24	Day 14	Random, double-blind, with placebo	Piracetam; 4.8 g/d for 6 weeks	ST	Some improved language compared to placebo
Szelies et al. (2001)	19 30	Day 14	Random, double-blind, crossover with placebo	Piracetam; 4.8 g/d for 6 weeks	ST	Some improved language compared to placebo
Amphetamine:						
Benson (1970)	10	2–6 months	Random, double-blind, with placebo	Dexamphetamine	Not reported	Improved verbal language and some non-verbal for early post-onset group (2–3 months). No effect on 6 months post-onset group
Darley et al (1977)	28	After 3 weeks	Random, double-blind, crossover with placebo	Methylphenidate	Not reported	No treatment effects on language
Walker-Batson (1992)	6	Day 16 to Day 30	OLCT	Dexamphetamine 10 mg 2×/week for 5 weeks	ST	Improved language
Walker-Batson et al. (2001)	21	Day 16 to Day 45	Random, double-blind, with placebo	Dexamphetamine 10 mg 2×/week for 5 weeks	ST	Significantly improved language compared to placebo
Cholenergic:						
Tanaka et al. (1997)	4	6–8 weeks	Random, blind	Bifemelane; 300 mg/d for 4 weeks	ST	Improved language comprehension and naming
Tanaka et al. (2001)	8	Not known	Random, double-blind, crossover with placebo	Aniracetam	Not clear	Improved language
Berthier et al. (2006)	11	Over 1 year	OLCT	Donepezil; 5 mg/d for 4 weeks, then 10 mg/d for 12 weeks. Washout 4 weeks	ST	Improved language after 4 weeks and 16 weeks. Gains reduce after wash out
Pashek (2006)	5	6 months	OLCT	Donepezil; 5 mg/d for 6 weeks. Washout 3 weeks		Improved language and articulation
Serotoninergic:						
Tanaka et al. (2004)	10	Not clear	Random, double-blind, crossover	Fluvoxamine for 4 weeks then 4 week washout	Not clear	Improved language and mood for mild-moderate patients
GABA-ergic:						
Cohen et al. (2004)	1	3 years	Case report	Zolpidem 10 mg	Not reported	Improved verbal fluency, repetition
IMAO:						
Laska et al. (2005)	90	Day 0 to Day 21	Random, double-blind, crossover with placebo	Moclobemide 600 mg/d for 6 months	Not reported	No treatment effects on language
Meprobromate:						
Bergman and Green (1951)	27		OLCT	Meprobamate	Not reported	No objective improvement
West and Stockel (1965)	29		Double-blind, crossover with placebo	Meprobamate	Not reported	Difficulty interpreting due to participation in varying number of cycles

OLCT (open label clinical trial); ST (speech therapy).

treatment (3 weeks), post-treatment (7 weeks), and at follow-up (4.5 months later). We defined a 15 percentile point gain on the PICA Overall Score (Wertz et al., 1986) and a 10 point gain on the WAB-R Aphasia Quotient as a significant clinical difference. All assessments were videotaped. Two experienced testing administrators independently scored 100% of the assessments and reached 100% agreement on a point-by-point basis on both dependent measures.

Statistical Package for Social Sciences (SPSS) Version 21.0 was used to analyze the data. Demographic and assessment information were analyzed with descriptive statistics (e.g., ranges, means, and standard deviations). Due to the small sample size, paired sample t tests were conducted to test for change between the time points. Due to the number of paired comparisons (12), the significance level of .05 was adjusted using a Bonferroni correction, thus the significance level was .0042. Gains between baseline (T1) and one-week off all treatment (T3) and gains between baseline (T1) and a four-week follow-up (T4) were the primary comparisons of interest.

4.3. Results

Eight subjects (5 men/3 women) with single left non-hemorrhagic MCA distribution infarction completed the study with a range of severity, aphasia types and co-occurring neurological deficits (Table 2). Four subjects had moderate to severe co-occurring apraxia of speech. Entry into the study ranged from one to five months, with a mean day post-stroke of 79 for study initiation. The age range of the subjects was from 21 to 74 with mean age of 53. The mean NIH Stroke Scale (Brott et al., 1989) score at entry was 10.4. There were no negative side effects reported over the six-week study period. Within-session monitoring of heart rate and blood pressure revealed no significant fluctuations due to drug administration at levels set for the study (<160/100 mm Hg).

Table 3 shows the mean PICA Overall and Language Scores and the WAB-R Aphasia and Language Quotients across the four testing periods—baseline, mid-treatment, one week off treatments, and follow-up at 4.5 months. Mean gains from baseline to one week off drugs and follow-up for all four measures were greater than the clinically significant gains that were predetermined (15 points for PICA and 10 points for WAB). Of note is the mid-treatment PICA Overall 14 point mean gain at the three week assessment period after 18 h of language therapy. Independent sample t tests with Bonferroni correction revealed statistically significant gains from baseline to each time point for all four measures, all < .001.

Table 3
Summary data across the treatment period of showing the Porch Index of Communication Ability Overall and Verbal scores and the Western Aphasia Battery-R showing Aphasia Quotient and Language Quotient.

Measure	Baseline	Mid-3 wks		1-wk off		Follow-up	
PICA OA	41.63	55.63	(+14.00)*	63.25	(+21.62)*	67.38	(+25.75)*
PICA Verbal	35.13	49.13	(+14.00)*	54.50	(+19.37)*	60.75	(+25.62)*
WAB AQ	52.33	65.35	(+13.02)*	72.58	(+20.25)*	75.55	(+23.22)*
WAB LQ	54.89	66.59	(+11.70)*	71.43	(+16.54)*	79.26	(+24.37)*

Note: *indicates significant gain from baseline measure based on independent samples t test with Bonferroni correction, $p < .0042$.
PICA OA baseline – mid-3 wks, $t(7) = 9.56$, $p = .00003$, Cohen's $d = 1.001$; baseline – 1-wk off, $t(7) = 8.51$, $p = .00006$, Cohen's $d = 1.485$; baseline – follow-up, $t(7) = 9.81$ $p = .00002$, Cohen's $d = 1.673$.
PICA Verbal baseline – mid-3 wks, $t(7) = 5.91$, $p = .001$, Cohen's $d = .834$; baseline – 1-wk off, $t(7) = 5.93$, $p = .001$, Cohen's $d = 1.081$; baseline – follow-up, $t(7) = 6.96$ $p = .00002$, Cohen's $d = 1.472$.
WAB AQ baseline – mid-3 wks, $t(7) = 5.89$, $p = .001$, Cohen's $d = .540$; baseline – 1-wk off, $t(7) = 5.46$, $p = .001$, Cohen's $d = .882$; baseline – follow-up, $t(7) = 5.95$ $p = .001$, Cohen's $d = 1.037$.
WAB LQ baseline – mid-3 wks, $t(7) = 6.85$, $p = .00002$, Cohen's $d = .562$; baseline – 1-wk off, $t(7) = 5.35$, $p = .001$, Cohen's $d = .827$; baseline – follow-up, $t(6) = 5.35$ $p = .002$, Cohen's $d = 1.56$.

4.4. Discussion

The purpose of this study was to explore the safety of combining of a cholinesterase inhibitor, donepezil, with AMPH to enhance recovery from aphasia. The drug combination was subjectively well tolerated by all subjects. There were no adverse effects on heart rate and blood pressure beyond the safety limits defined in the study. This study was explorative and designed to determine safety and effectiveness of the 36 hour language treatment protocol.

The PICA Overall 21.63 point mean gain one week after the study concluded compares very favorably to another aphasia treatment study initiated at the same time period post-stroke which also used the PICA Overall score as the primary outcome measure (Wertz et al., 1986). Wertz et al. (1986) reported an 18.2 point PICA Overall gain after 12 weeks of treatment during which participants received from 96 to 120 h of language therapy without adjunctive drug modulation. For the WAB-R Aphasia Quotient, a 10 point gain was defined before study initiation to be a notable clinical gain; thus the mean Aphasia Quotient gain of 20.25 one week after the study ended is considerably

Table 2
Subject aphasia type/sex/age, neurological/radiological information.

Subject (S) aphasia type	Sex age	Neurological deficits	Radiologic information
S1 Global	M/67	NIHSS-14 R Hemiplegia, A, L AOS—profound	Large left MCA occlusion involving frontal, temporal, parietal regions as well as the periventricular white matter
S2 Wernicke	F/72	NIHSS-7 R VF	Large infarction of the inferior branch of the left MCA in the temporal lobe
S3 Broca	F/41	NIHSS-10 R Hemiplegia, A AOS—severe	Left MCA occlusion involving frontal as well as deep white matter in the basal ganglia region.
S4 Anomic	M/60	NIHSS-10 R Hemiplegia, A, L Dysarthria	Complete occlusion of MCA at its origin
S5 Broca	M/55	NIHSS-17 R Hemiplegia, A, L AOS—severe	Large infarction of left MCA and ACA
S6 Anomic	F/21	NIHSS-9 R Hemiplegia, A, L	Large left MCA infarction with extension to the caudate nucleus, basal ganglia, and the anterior limb of the internal capsule
S7 Mixed	M/63	NIHSS-4 R Hemiplegia A	Left MCA and anterior watershed infarction
S8 Broca	M/44	NIHSS-10 R Hemiplegia A, L AOS—severe	Large left MCA infarction with mass effect, including involvement of basal ganglia

MCA, middle cerebral artery; NIHSS, NIH Stroke Scale; AOS, apraxia of speech; A, arm; L, leg; VF, visual field.

greater than the projected 10 point gain predetermined to be clinically meaningful (A. Kertesz, 2012, personal communication).

It cannot be determined from this study if the language gains were due to the 36 h of impairment level language treatment alone or the drug combination or both. The fact that the subjects in the current study maintained their gains after the treatment period ended could be attributed to an effect of learning from the language treatment, AMPH facilitation of verbal learning, an undefined effect of the donepezil or all three. A limitation of the study was that we did not assess mood which could play a role in the results as stimulants are known to enhance mood. Although we did not find complaints with the low dose donepezil (5 mg) that we administered, higher doses may cause more side effects in some individuals. The participants of this study do not represent all aphasia patients as they were carefully screened with a number of exclusion criteria. Further explorations under double blind-placebo conditions with both drugs alone and in combination are warranted in a Phase II trial.

5. The future for neuropharmacology in the treatment of aphasia and summary

Taking the salient points from the experimental and clinical literature on pharmacological therapy paired with our experience with AMPH as an adjunct to post-stroke deficits we conclude:

(1) Low dose spaced dosing of AMPH is not deleterious in patients with well controlled hypertension, absent cardiac dysrhythmias. A mild increase in blood pressure was found in a small number of placebo treated subjects but not beyond our study limits (Unwin and Walker-Batson, 2000). This mild increase might be attributed to the intensity of the language training during therapy sessions.

(2) There is no consensus on the number of adjunctive doses of AMPH necessary for an optimal level of recovery or if spaced dosing is necessary to prevent tolerance effects. We found in a small number of aphasia patients that increased doses of AMPH (40) paired with behavioral treatment (60 h) did not always show greater effects and may not be required (Walker-Batson, 1999). It may be that since AMPH is a potent releaser of several neurotransmitters continuous administration may deplete the stores of the systems needed to be stimulated and possibly may have a diminishing return on therapeutic efficacy.

(3) The timing of drug (AMPH) and behavioral experience is very important. We timed behavioral treatment within 30–45 min after oral ingestion of AMPH to parallel the peak intoxication period. In healthy controls, Soetens et al. (1995) reported that one hour post-intake of oral AMPH is the peak period for enhancing verbal mediation.

(4) The time window post-stroke to initiate adjunctive pharmacological therapy is important. Evidence increasingly shows that the first 90 days post-stroke is the optimum time for neuroplastic changes (Zeller and Krakauer, 2013). In the past many rehabilitation studies were not initiated until 12 months post-onset to allow for spontaneous recovery. It appears that waiting 12 months post-infarct misses a critical window for restorative rehabilitation.

Currently, few patients receive the intensity (number of treatment hours) needed for a good recovery from aphasia. Studying the relationship between aphasia recovery and the intensity of aphasia therapy, Bhogal et al. (2003) found a good recovery (defined as +15.3 pts. PICA Overall Score) required approximately 100 h of treatment. Our experience suggests that adjunctive neuromodulation with certain drugs, when applied during critical periods of plasticity, may accelerate the recovery curve enhancing the effects of the treatment that is provided. In time, drugs with more specific action than AMPH may be developed for use in rehabilitation pharmacology. Until then, carefully designed Phase II trials must be undertaken leading to Phase III trials. As stated in Goldstein, 2009 Phase III trials of AMPH have yet to be done, that is still the case in 2015.

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