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Neuromodulation paired with learning dependent practice to enhance post stroke recovery?

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Abstract. Over the past two decades, experimental studies following brain injury have shown that the central nervous system is dynamic and malleable to internal and external inputs. Neuromodulation and/or direct manipulation of motor and sensory experience can modify brain plasticity and functional outcome after experimental lesions. Specifically, pharmacologic modulation has been found to facilitate recovery of various behavioral deficits following occlusive injury. Additionally, the behavioral experience that induces long-term plasticity in motor and sensory maps after injury appears to be limited to those that entail the development of new skills. These data have strong application to human rehabilitation. This review will: (1) overview critical experimental studies that show that pharmacologic manipulation and/or specific behavioral experience may modify the functional organization of the injured brain and (2) review beginning studies which are exploring the application of this knowledge clinically.
Keywords: Stroke, neuromodulation, pharmacotherapy, learning dependence, hemiplegia, aphasia

1. Introduction

Despite tremendous efforts in stroke prevention and acute intervention over the past 20 years, stroke rehabilitation has received relatively little attention. This is changing, in large part, due to the robust evidence from animal and human studies regarding central nervous plasticity and recovery of function which has application to the design of neurological rehabilitation methodologies. It is now recognized that neuromodulation and/or direct manipulation of motor and sensory experience can modify brain plasticity and functional outcome after experimental focal cortical injury.

The focus of our group has been the clinical application of an animal model of recovery using neuromodulation paired with focused behavioral treatment to accelerate rate of recovery of hemiplegia and aphasia subsequent to occlusive stroke. This review will include relevant experimental literature which influenced our protocol development and beginning clinical studies using the noradrenergic agonist, dextroamphetamine [dAMPH] paired with learning dependent experience to enhance post stroke recovery.

2. The use dependent/learning dependent model

In our beginning studies we were influenced by the early work of Merzenich and colleagues [19,23,

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24] who studied functional plasticity of primary somatosensory cortex in adult mammals following alteration of peripheral inputs. In a systematic series of studies, Merzenich et al. [23,24] defined a type of reorganization following median nerve section and digit amputation in the monkey that they described as a dynamic self-organizing process resulting from *use-dependant* alteration of the neo-cortical field. An important aspect of this work is that it has shown that the type of input affects reorganization. More recently, plasticity of motor [26] and somatosensory systems [40] has been studied after cortical experimental lesions in adult monkeys. The term *learning dependent* has been suggested for the activity dependent changes in brain reorganization following motor and sensory injury [26,27]. Nudo and colleagues [26] observed that motor maps are altered by motor skill acquisition and not by repetitive use alone. Topographic plasticity coincided with the acquisition of new motor skills in intact animals or the reacquisition of motor skills in lesioned animals. Studying plasticity of somatosensory cortex Xerri et al. [40] found post lesion representational remodeling influenced by use-driven activity idiosyncratic to each animal. These data imply that the specificity of the behavioral treatment following brain injury with or without pharmacologic modulation critically determines the type of recovery that occurs.

3. Pharmacologic modulation

Neuromodulation as an adjunct to rehabilitation is not a new idea. There are clinical reports dating back almost 70 years that suggest the use of various agents in the treatment of both hemiplegia and aphasia [7,21, 22,33]. More recently, the most studied drugs to facilitate recovery have been those affecting the noradrenergic system. The best studied of these drugs has been dextroamphetamine [d-AMPH] [12].

Feeney and colleagues published the first papers investigating the hypotheses that modulation of brain catecholamines might influence recovery of motor function [2,4,8,10]. A single dose of d-AMPH administered to a rat 24 hours after motor cortex ablation significantly improved the animal's ability to traverse a narrow beam [8]. This acceleration of motor recovery has been replicated in other studies in rats [2] and cats [17]. When administered 10 days following focal injury, cats who received multiple doses of d-AMPH paced over six treatments at four day intervals made greater recovery when compared to animals that received only a single d-AMPH dose [17]. In this study there was a time limit however, as no behavioral improvement was found if drug administration was delayed for 90 days. Positive d-AMPH effects have also been reported for other behavioral deficits including sensory-motor integration [18] and binocular depth perception [9]. It is important to note that d-AMPH facilitated recovery was greater when drug treatment was paired with practice or experience during the drug action period, as compared with drug administration alone [8,9,13,17].

The first human study of the use of d-AMPH in recovery of deficits following occlusive stroke was reported by Benson [1] for treatment of aphasia. Published in abstract form only, this placebo-controlled study compared early (2–3 months) and late (>6 months) treatment post stroke with five subjects in each group. Patients were given two daily doses of d-AMPH (10 mg and 5 mg) for two months. Patients received intensive speech and language therapy five days per week during the study period. A facilitative effect of amphetamine was found in the early but not late treated patients (D. Frank Benson, personal communication).

More recent clinical studies exploring administration of various noradrenergic agonists have focused on motor recovery. Small studies have explored amphetamines [6,16,29,34,36] methylphenidate [15] and L-DOPA with mixed results [31]. This may be due in part to differences in experimental design, related to type of treatment during the drug action period and/or to time interval between stroke onset and initiation of drug administration. While Crisostomo et al. [6] and Walker-Batson et al. [36] found facilitative effects following d-AMPH administration; Reding et al. [29] and Sonde et al. [34] did not. The failure of the Reding group [29] to find effects was attributed to the time post onset of study initiation (after day 30) and not timing the physical therapy during the peak period of drug action. Sonde et al. [34] used a different isomer of amphetamine in some of their patients and their behavioral intervention appeared to be disability not impairment level treatment.

Our protocol was modeled from the cat study of Hovda and Feeney [17] in which multiple spaced doses were used. In a small pilot study of motor recovery comparing drug/placebo conditions, 10 hemiplegic patients were entered between day 16 and day 30 post stroke and followed over 12 months. Hemisphere of injury was: 4 left/1 right in the AMPH group and 4 right/1 left in the placebo group. Radiological profiles included a wide range of neurological deficits including large striatal infarction, MCA cortical and sub-

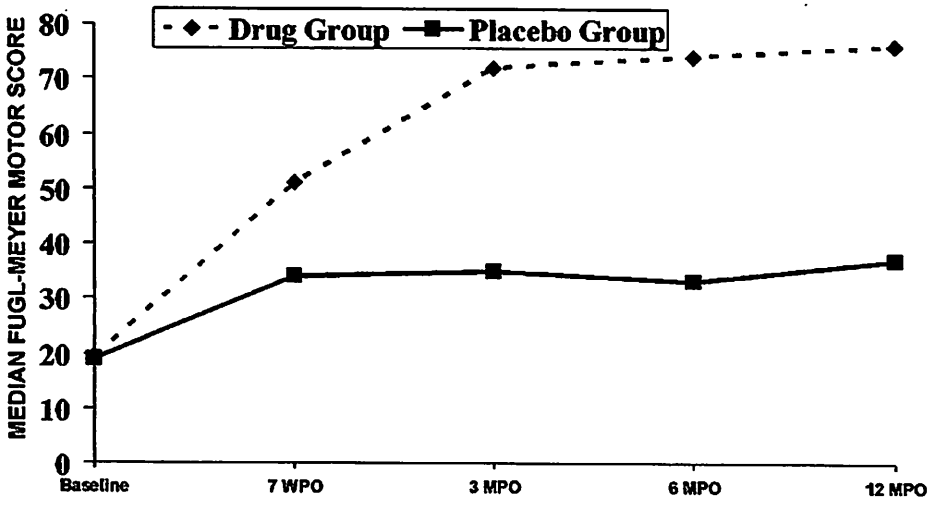

Fig. 1. Line graph shows median Fugl-Meyer Motor Scale scores at baseline, during the 10 sessions, when the drug had been discontinued for 1 week and 3, 6, and 12 months after onset. (modified from Walker-Batson, et al. [35]).

cortical and subcortical only. The Fugl-Meyer Motor Scale [11] was the primary dependent measure of motor recovery. Documentation of all medications was kept on all subjects after the stroke to establish that at no time during the 12-month period did any subject receive any confounding drugs. Complicating drugs included α-adrenergic antagonists or agonists as well as other agents such as neuroleptics, benzodiazepines, and antidepressants shown to affect behavioral recovery in laboratory animals [5] and motor recovery in humans [14]. Administration of a 10 mg dose of d-AMPH was scheduled every fourth day for 10 sessions paired with physical therapy and timed so the initiation of the physical therapy was during the peak period of drug action. Intense impairment focused interventions addressing both upper and lower extremity recovery were performed during each session. Component parts of varied synergies were executed by the patient. Joints, where there was a void of active motion, were ranged passively while the patient was encouraged to "try and help me move" or "think about it moving." The patient was positioned during treatment to use gravity to enhance the weakest motions. Total synergistic patterns were practiced in context of functional activities. The daily activities were designed so the patient would be successful 60% of the time he attempted the task. The number of repetitions of each activity was based on the patient's subjective comments of fatigue as well as the total degradation of the movement. The therapist recorded the number of repetitions, the position of the patient and the type of muscle contraction or movement each day. Figure 1 shows the result of the pilot study of 10 patients.

There were no baseline differences on the Fugl-Meyer Motor Scale between the two groups (median F-M baseline d-AMPH-19.5/ placebo-19.0). Differences between the two groups began to emerge by session 2 and continued 1 week after drug administration and at 12 months after onset. Gain scores between baseline and 1 week after AMPH/placebo sessions and baseline and 12 months after onset were computed for each patient in each of the two groups. A two-tailed Mann-Whitney test was used to compare the differences in the two time periods. The tests revealed a significant ($P = 0.047$) difference between the groups at both time periods. In this study we purposely spaced the d-AMPH dosing to in an attempt to prevent tolerance effects. It is not known if this is important. Also we were cautious regarding a protracted period of drug administration. Since d-AMPH is a potent releaser of neurotransmitters, we were concerned that continuous administration might have diminishing therapeutic effects by depleting the stores of the neurotransmitter system (in particular, norepinephrine) that needs to be stimulated to influence recovery rate. The fact that the differences between d-AMPH and placebo patients was maintained long after drug administration ceased at 12 months was encouraging; however the results of this initial study are limited because of the small sample size.

We employed the same 5-week 10 paced doses as in the hemiplegia study to explore the use of d-AMPH in recovery from aphasia in a double-blind study of 25 patients [38]. The only modification was a 3rd/4th day dosing regimen instead of the previous every 4th

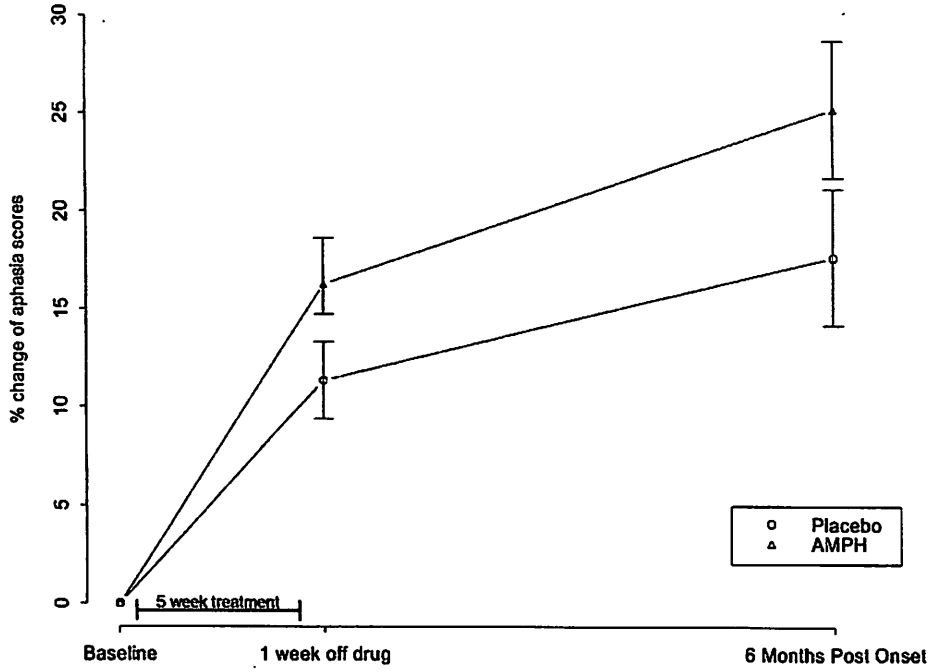

Fig. 2. ± SEM percentile change in overall PICA scores at the 1-week-off-drug assessment and the 6-month (after stroke) follow-up for the dextroamphetamine and placebo groups. (modified from Walker-Batson et al. [37].

day. Patients in this study were entered up to day 42 post stroke. For the aphasia sessions the level of treatment was initially determined by the patient's performance on the Porch Index of Communication Ability (PICA) [28] and thereafter on the previous session's data. The speech language protocol was based on a hierarchy of tasks collated from the published intervention literature. Use of the protocol was individualized as needed to treat a patient's specific disabilities striving for a balance between establishing an infrastructure for communication and stimulating the most complex language behaviors possible.

Scores on the Porch Index of Communication Ability [28] at 1-week off drug and at the 6 months follow-up were used to determine effects. There were no differences on the baseline PICA Overall score between the two groups. By 1-week off drug 10 of 12 or 83% of the AMPH subjects had surpassed the 15 percentile points that we had defined as clinically significant change (Fisher-exact test $p = 0.0092$). In the placebo group 2 of 9 (22%) had achieved the predetermined 15 percentile clinically significant change. These differences were maintained at the 6-month post onset follow-up: the mean gain in PICA Overall scores was 25.18 in the AMPH group and 17.687 for the placebo group with a difference between the groups of 7.51 ($p = 0.0482$). Figure 2 shows differences in gain scores between the two groups at 1-week off drug and at the 6-month assessment in the PICA Overall scores. In this study we did not find a relationship between response and the amount or site of tissue loss on anatomic images.

We have pursued other modifications of this protocol in small subsets of patients [37,39]. In an open label study in a small group of patients we have explored this protocol in chronic aphasia (>12 months post stroke) and found no effects [36]. In a second unpublished motor recovery study (Walker-Batson, Smith, Curtis & Unwin, unpublished) we studied patients more than 30 days post stroke in a drug-placebo blinded comparison and did not find differences between d-AMPH treated and placebo treated patients on the Fugl-Meyer Motor Scale. The only differences we could find between these patients and our initial pilot study [36] was in the day of study initiation-day 31, as compared to day 22 in the earlier study. We have also explored an open label protocol of increased dosing of d-AMPH to facilitate aphasia (5 days per week for 8 weeks paired with 60 hours of behavioral treatment) [39]. In this small study of 3 patients who were less than 45 days post stroke the recovery curve was no steeper than previous subjects whom we have considered responders on the 5-week 10 spaced dose schedule.

In a series of 44 patients on the protocol described above we found no differences in median systolic and

diastolic blood pressure measures when comparing d-AMPH and placebo-treated subjects before and within each drug session and no reported negative side effects [35]. At no time during the 12 months course of the study was there documentation of any negative event that could be attributed to amphetamine administration suggesting that in stroke patients with well-controlled hypertension (our exclusion requires 160/100 mm before every session), the side effects of low-dose amphetamine administration are negligible and support many previous reports which suggest that toxicity with doses <15 mg are rare.

4. Critical timing window/physiological limits

The critical timing window after brain injury for initiation of learning dependent practice or pharmacologic modulation is not known. Recent motor recovery studies in animals without pharmacologic treatment suggest that very early intensive treatment (<7days post stroke) may be detrimental increasing both the deficit and the size of the lesion (20,30 and see Shallert et al. this volume). How this extends to humans is not known. It may be that there are different time windows for hemiplegia versus aphasia . How response to neurmodulation is influenced by amount and site of tissue loss is also not clear. We [38] and others [31] did not find a relationship between response to noreadrengeric agonists and amount or site of tissue loss on anatomic images in small numbers of patients.

5. Conclusion

Animal studies of recovery of function after stroke provide a beginning science base, which has application for rehabilitation practice. Neuromodulation with noradrenergic agonists paired with behavioral experience shows promise in animals. It should be noted however, that this model does not extend to all behaviors [32] or sites of brain damage [3,25]. A large number of studies suggest that the type of input following injury may affect brain reorganization. This implies that treatment approaches can be either adaptive or maladaptive depending on what is presented. In animals, specific learning dependent activity practiced over relatively long periods of time is required for brain reorganization paralleling behavioral changes [26,40]. This strongly suggests that rehabilitation should focus on impairment level treatment of specific targeted behaviors. It may be that compensatory activities at critical time periods have costs in terms of recovery of function.

Our clinical experience and that of others [6,31] are encouraging regarding use of certain agents to accelerate recovery. However, there are numerous questions still to be answered before rehabilitation pharmacology becomes a standard of care. These include: How far post stroke can a drug be administered and have an effect What is the dosage and the number of drug administrations needed to provide optimum recovery? What is the amount of learning dependent experience or retraining that must be paired with the pharmacologic intervention for optimal recovery Will a combined drug approach be more effective than a single drug alone In the future, hopefully, consideration of physiologic events surrounding brain injury, manipulation of various neurotransmitter systems and a fuller understanding of mechanisms of learning will be combined to form brain based approach to treatment and ultimate optimum recovery of stroke.

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References

[1] D.F. Benson, Presentation 10, in: *Behavioral Change in Cerebrovascular Disease*, A.J. Benton, ed., Harper and Row, New York, 1970, p. 77.

[2] M.G. Boyeson and D.M. Feeney, Intraventricular norepinephrine facilitates motor recovery following sensorimotor cortex injury, *Pharmacol. Biochem. Behav.* 35 (1990), 487–501.

[3] M.G. Boyeson and D.M. Feeney, Adverse effects of catecholaminergic drugs following unilateral cerebellar ablations, *Restor. Neurol. Neurosci.* 3 (1991), 227–233.

[4] M.G. Boyeson, K.A. Krobert, P.J. Scherer and C.M. Grade, Reinstatement of motor deficits in brain injured animals: The role of norepinephrine, *Restor. Neurol. Neurosci.* 5 (1993), 283–290.

[5] M.G. Boyeson and R.L. Harmon, Effects of trazadone and desipramine on motor recovery in brain injuryed rats, *Am J Phys Med Rehabil.* 72 (1993), 276–293.

[6] E.A. Chrisostomo, P.W. Duncan, M.A. Propst, D.B. Dawson and J.N. Davis, Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients, *Ann. Neurol.* 23 (1988), 94–97.

[7] F.L. Darley, R.L Keith and S. Sasanuma, The effects of alerting and tranquilizing drugs upon the performance of aphasia patients, in: *Clinical Aphasiology: Conference Proceedings*, R.H. Brookshire, ed., BRK Publishers, Minnesota, 1977.

[8] D.M. Feeney, A. Gonzales and W. Law, Amphetamine, haloperidol and experience interact to affect rate of recovery after motor cortex injury, *Science* **217** (1982), 855–857.
[9] D.M. Feeney and D.A. Hovda, Reinstatement of binocular depth perception by amphetamine and visual experience after visual cortex ablation, *Brain Res* **342** (1985), 352–356.
[10] D.M.Feeney and R.L. Sutton, Pharmacotherapy for recovery of function after brain injury, *CRC Crit Rev Neurobiol* **3** (1987), 135–197.
[11] A. Fugl-Meyer, L. Jaako, I., Leyman, S. Olsson and S. Steglind, The post stroke hemiplegic patient: a method of evaluation of physical performance, *Scand J Rehabit Med* **7** (1975), 13–31.
[12] D. Gladstone and S. Black, Enhancing recovery after stroke with noradrenergic Pharmacotherapy: A new frontier, *Canad. J. Neurol. Sci.* **27** (2000), 97–105.
[13] L. Goldstein and J. Davis, Post-lesion practice and amphetamine-facilitated recovery of beam-walking in the rat, *Restor. Neurol. Neurosci.* **1** (1990), 311–314.
[14] L.B. Goldstein, D.B. char, J.C. Morgenlander and J.N. Davis, The influence of drugs on the recovery of sensorimotor function after stroke, *J Neurol Rehab* **4** (1990), 137–144.
[15] C. Grade, B. Redford, J. Chrostowski, L. Toussant and B. Blackwell, Methylphenidate in early post stroke recovery: A double-blind, placebo controlled study, *Arch. Phys. Med. Rehab.* **79** (1999), 1047–1050.
[16] J. Greener and R. Whurr, Pharmacological treatment for aphasia following stroke (Cochrane Review), in: *The Cochrane Library, Issue 3*, 2003, Oxford: Update Software.
[17] D.A. Hovda and D.M. Feeney, Amphetamine and experience promotes recovery of locomotor function after unilateral frontal cortex injury in the cat, *Brain Res* **298** (1984), 358–361.
[18] B.D. Hurwitz, W.D. Dietrich, P.M. McCabe, O. Alonson and B.D. Watson, Amphetamine promotes recovery from sensorymotor integration deficits after thrombotic infarction of the primary somatosensory rat cortex, *Stroke* **22** (1991), 648–654.
[19] W.M. Jenkins, M.M. Merzenich, M.T. Ochs, T. Allard and E. Guic-Roberts, Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation, *J. Neurophysiol.* **63** (1990), 82–104.
[20] D.A. Kozlowski, D.C. James and T. Schallert, Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions, *J. Neurophysiol.* **16** (1996), 4776–4786.
[21] L. Linn, Sodium amytal in the treatment of aphasia, Archives Neurol. *And Psychiatry* **58** (1947), 357–358.
[22] A.R. Luria, V.L. Naydin, L.S. Tretkova and E.N. Vinarskaya, Restoration of higher cortical functions following local brain damage, in: *Handbook of Clinical Neurology 3*, P.J. Vinken and G.W. Bruyn, eds, North-Holland Press, Amsterdam, 1969.
[23] M.M. Merzenich, J.H. Kaas and J. Wall, Topographic reorganization of somatosensory cortical areas 3B and 1 in adult monkeys following restricted deafferentation, *Neuroscience* **8** (1983), 33–55.
[24] M.M. Merzenich, R.J. Nelson and J.P. Stryker, Somatosensoy cortical map changes following digit amputation in adult monkeys, *J. Comp. Neurol.* **224** (1984), 591–605.
[25] M.R. Mintz and R. Toner, Exposure to amphetamine after substantia nigra lesion interferes with the process of behavioral recovery, *Pharmacol. Biochem. Behav.* **25** (1986), 1307–1311.
[26] R.J. Nudo, E.J. Plautz and G.W. Milliken, Adaptive plasticity in primate motor cortex as a consequent of behavioral experience and neuronal injury, *Seminars in Neuroscience* **9** (1997), 13–23.
[27] E.J. Plautz, G.W. Milliken and R.J. Nudo, Differential effects of skill acquisition and motor use on the reorganization of motor representations in area 4 of adult squirrel monkeys, *Soc. for Neuroscience Abstracts* **21** (1995), 1902.
[28] B. Porch, *The Porch Index of Communicative Abilities*, Consulting Psychologists Press, Palo Alto, 1982.
[29] M. Reding, Antidepressant effects on recovery, in: *Restorative Neurology: Advances in Pharmacotherapy for Recovery after Stroke*, L. Goldstein, ed., Futura Publishing Company, Inc., New York, 1998.
[30] S. Risedale, J. Zeng and B.B. Johansson, Early training may exacerbate brain damage after focal brain ischemia in the rat, *J. Cerebral Blood Flow & Metabolism* **19** (1999), 997–1003.
[31] K. Scheidtmann, W. Fries, F. Muller and E. Koenig, Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: A prospective, randomized, double-blind study, *Lancet* **358** (2001), 787–790.
[32] T.D. Schmanke, R.A. Avery and T.M. Barth, The effects of amphetamine on reovery of function after cortical damage in the rat depends on the behavioral requirement of the task, *J. Neurotrauma* **13** (1996), 293–307.
[33] F. Sciclounoff, L'acetylcholine dans le traitement de l'ictus hemiplegique, *La Press Medical* **56** (1934), 1140–1141.
[34] L.M. Sonde, C.G. Nordstrom, J. Lokk and M. Viitanen, A double-blind placebo controlled study of the effects of amphetamine and physiotherapy after stroke, *Cerebrovascular Dis* **12** (2001), 253–257.
[35] D.H. Unwin and D. Walker-Batson, Negligible side effects of amphetamine administration in stroke rehabilitation, *Stroke* **31** (2000), 1788–1789.
[36] D.Walker-Batson, P. Smith, S. Curtis, H. Unwin and R.G. Greenlee, Amphetamine paired with physical therapy accelerates recovery from stroke: Further evidence, *Stroke* **26** (1995), 2254–2259.
[37] D. Walker-Batson, Pharmacologic Experimentation for Motor and Cognitive Dysfunction: Clinical Trials to Promote Recovery, in: *Proceedings of the 2nd World Congress in Neurological Rehabilitation*, Canada, 1999, pp. 332–339.
[38] D. Walker-Batson, S. Curtis, R. Natarajan, J. Ford, N. Dronkers, E. Salmeron, J. Lai and D.H. Unwin, A double-blind placebo controlled study of the use of amphetamine in the treatment of aphasia, *Stroke* **32** (2001), 2093–2098.
[39] D. Walker-Batson, Z. Yetkin, S. Curtis, R. Natarajan and H. Unwin, fMRI brain activation and language assessment of amphetamine treatment for aphasia, *Neurorehabilitation and neural repair* **15** (2001), 4.
[40] C. Xerri, M. Merzenich, B.E. Peterson and W. Jenkins, Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys, *J of Neurophysiology* **79** (1998), 2119–2148.