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A BIOLOGICAL BASIS FOR APHASIA TREATMENT: MIRROR NEURONS AND OBSERVATION–EXECUTION MATCHING

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ABSTRACT

Aphasia is caused by damage to the human brain, and recovery requires adaptive changes to the structure and function of this organ. Despite this obvious fact, biology plays little role in rehabilitation of persons with aphasia. Although linguistics can be useful in characterizing aphasic behaviour, thus providing a way to assess the effects of therapy, there is little evidence to suggest that linguistic models of impairment can themselves form the basis of effective therapy.

Biological evidence from primates has demonstrated the presence of neurons that have both visual and motor properties, which discharge both when an action is performed and during observation of the same action. We postulate that behavioural stimulation of this system may play an important role in motor learning for speech and thereby aid language recovery after stroke.

IMITATE is a computer-assisted system for aphasia therapy based on action observation and imitation. IMITATE therapy consists of silent observation of audio-visually presented words and phrases spoken aloud by six different speakers, followed by a period during which the participant orally repeats the stimuli. The treatment approach is motivated by the physiology of the brain in an effort to change specific anatomical connections, and the treatment method draws strongly from psychological evidence on learning.

IMITATE is currently being used in a clinical trial, and results will not be known until these data are available in late 2010. At that juncture, it will be possible to evaluate fully the efficacy of IMITATE and to inform theoretically about the mechanism of action and the role of a human mirror system in aphasia treatment.

KEYWORDS: Keyword.

1. Introduction

Stroke is the third leading cause of death in the United States (Hoyert et al. 2001) and Europe (Mackay and Mensah 2004), and is the primary cause of long-term disability in these countries (American Heart Association 2003; Rosamond et al. 2007). The incidence of stroke in less wealthy countries is even higher, and the World Heath Organisation estimates that 15 million people are affected annually by stroke, of whom 5 million die and another 5 million are permanently disabled (Mackay and Mensah 2004). In a recent survey, the prevalence of stroke in the U.S. was about 2.6% (8.1% of people aged over 65 years old) for a total of 5,839,000 persons with a history of stroke (Centers for Disease Control and Prevention, May 18, 2007). Of people with stroke, approximately 80% have motor dysfunction and 33–40% have some impairment in language (Benson and Geschwind 1989; Pedersen et al. 1995).

The resulting calculation reveals the enormity of the situation: More than a million people are living with aphasia in the U.S. alone (NIDCD 1997). The impact of aphasia on the individual patient is enormous, with negative ramifications on the person's participation in social, vocational, and recreational activities. Over the past several decades, public awareness of stroke (Alberts et al. 2000) and successes in the treatment of acute stroke, e.g. intravenous thrombolysis (Hacke et al. 1995; The NINDS rt-PA Stroke Study Group 1995), has been associated with an increase in stroke survivors (Fang and Alderman 2001), and a proportionate increased need for treatment of its major manifestations, including aphasia.

Recovery from aphasia occurs over a period of time ranging from several months to many years (Benson and Geschwind 1989; Goodglass 1993; Kertesz and McCabe 1977; Lecours et al. 1983). Although this recovery is accompanied by changes in brain physiology, basic neurobiology has not yet had significant impact on clinical practice, and rehabilitation measures for persons with aphasia remain rooted in educational rather than biological models (Small 2004b). Although linguistics can play a role in characterizing aphasic behaviour (e.g. Blumstein et al. 1977; Grodzinsky 1986; Tobin 2002), the premise of our work is that biology (i.e., brain repair) must play an integral role in rehabilitation of aphasia, since the cause of the problem is brain injury. There is little evidence to suggest that neuropsychological or linguistic models of impairment can form the basis of rational therapy (Caramazza 1989), since these models have descriptive and not explanatory adequacy (Chomsky 1965). In this article, we outline a therapeutic approach, based on basic principles from neurophysiology, that we believe can play an important role in the treatment of aphasia.

The application of biological observations to rehabilitation in aphasia is severely limited by the obvious but important fact that animal research cannot inform the situation and that we are in the infancy in the study of human neuroscience (Small 2004a; Small 2008). Only very recently has the study of human systems neurobiology led to an even basic understanding of the nature of neural networks that support the basic perceptual functions and higher cortical functions that enable language.

2. Sensory-motor interactions and mirror neurons

Recent biological evidence from nonhuman primates suggests important interactions between brain regions traditionally associated with either language comprehension or production. Regions traditionally considered responsible for motor planning and motor control appear to play a role in perception and comprehension of action (Graziano et al. 2002; Romanski and Goldman-Rakic 2002). Certain neurons with visual and/or auditory and motor properties in these regions discharge both when an action is performed and during perception of another person performing the same action (Gallese et al. 1996; Kohler et al. 2002; Rizzolatti et al. 1996). These neurons are called mirror neurons and have been shown to exist for both manual and oral actions, and for both auditory and visual sensation. Action observation is thought to induce a re-enactment of similar actions stored in human brains (Buccino et al. 2001; Fadiga et al. 1995; Rizzolatti and Craighero 2004), possibly by inducing simulation of the ongoing actions (Gallese 2003). It is likely that action observation leads to organisational changes in the brain (Fadiga et al. 1995) and may participate via the mirror neuron system in learning of motor skills (Buccino et al. 2004b).

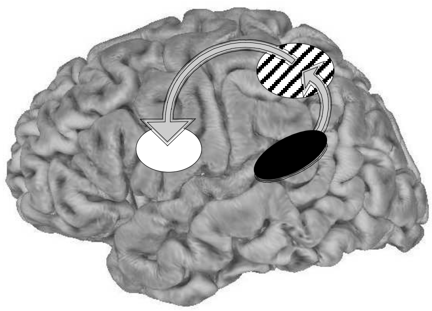

Figure 1. The left hemisphere of a human brain with two of the main connections of the putative mirror neuron system of the human, including the superior temporal sulcus (black), the inferior parietal lobule and intraparietal sulcus (hatched), and the ventral premotor cortex (white). The connection from the parietal lobe (hatched) and the frontal lobe (white) is probably critical for imitation.

Based on these findings, we have been exploring audiovisual imitation as a way to take advantage of putative human observation-execution matching systems to improve language function after stroke. Imitation permits the visual system to provide input into oral speech mechanisms, and the brain appears to have circuits particularly active in imitation (Gallese et al. 1996; Iacoboni et al. 1999; Murata et al. 1997). These circuits may play a special role in motor development (Tomasello et al. 1993), speech (Fadiga et al. 2002; Rizzolatti and Arbib 1999), and language (Rizzolatti and Arbib 1998; Tettamanti et al. 2005).

This system exists both in non-human primates (Gallese et al. 1996) and humans (Iacoboni et al. 1999). The first mirror neurons were discovered in the F5 region of the lateral frontal lobe in macaque monkeys (Gallese et al. 1996). This has a corresponding anatomy at the interface of the ventral premotor and frontal opercular regions in humans (Iacoboni et al. 1999; Rizzolatti et al. 2002). An additional site of mirror neurons is area PF of the inferior parietal lobule of the macaque, and this area corresponds to a region in the inferior parietal lobule and/or intraparietal sulcus of the human. Both of these regions are active during observation and imitation of syllables in humans (Skipper et al. 2007b), and the connection between them seems to be critical to both processes (Mashal et al, in press). Figure 1 shows the (very rough) location of these regions with their main source of visual input.

Imitation has played an important role in many treatments for aphasia (Duffy 1995), with the rationale that visual input complements other sensory information for use in oral speech mechanisms. Research has only recently demonstrated that the brain has circuits particularly active in motor imitation (Gallese et al. 1996; Iacoboni et al. 1999; Murata et al. 1997), including oral motor imitation (Buccino et al. 2001; Buccino et al. 2004a; Rizzolatti and Arbib 1998; Tettamanti et al. 2005). Imitation depends on connections between the inferior parietal lobule and the ventral premotor/inferior frontal homologue of the macaque mirror neuron locus (Buccino et al. 2004b).

The human mirror system appears critical for observation/execution matching in oral motor actions for speech production (Skipper et al. 2006; Skipper et al. 2007a; Skipper et al. 2007b), and thus could be of significant benefit in aphasia therapy after stroke. Furthermore, the role of this system in predicting the consequences of motor activity (Iacoboni et al. 2001; Iacoboni 2003) and contributing to comprehension of sentences describing actions (Beilock et al. 2008; Tettamanti et al. 2005), gives this system major potential for aiding language recovery more generally.

3. Principles of learning

Taking advantage of this biological system to change the relevant parts of the brain requires more than a reasonable physiological rationale. The implementation of the treatment must draw heavily on previous work in both treatment of aphasia and motor speech disorders and on theoretical work in learning. Our approach includes oral repetition of words and sentences in an ecological setting (i.e., with visualisation of the speaker), intensively, with graded incremental changes in stimulus difficulty.

Of all the components of aphasia therapy that have been analysed, intensity of therapy is consistently correlated with increased therapeutic success, apart from the specific details of the therapy program (Basso 1993; Bhogal et al. 2003; Huber et al. 1993; Robey 1998). The ethical mandate for society to provide health care, along with its increasingly high cost, has led to the drive for evidence-based medicine and more cost-effective treatments. In many countries, these two mandates are limiting access to aphasia therapy. We address this problem by building our approach around a computer-based system that can provide intensive aphasia therapy at a low cost. Despite the large number of computer programs and web-based systems for language practice, there is a paucity of theory-driven computational systems for aphasia therapy *per se* (Weinrich 1997), although some good research has been done (Canseco-Gonzalez et al. 1990; Cherney et al. 2008; Crerar et al. 1996; Fitch 1983; Grawemeyer et al. 2000; Katz and Wertz 1997; Naeser et al. 1998; Steele et al. 1989; Weinrich et al. 1997a; Weinrich et al. 1997b; Weinrich et al. 2002).

4. Aphasia classification

The neurobiological data on observation–execution matching in macaque motor systems and human motor systems and speech suggests a potential role for such a mechanism in therapy of aphasia. But aphasia is a broad concept, referring equally to language problems that principally involve input (Goodglass 1993; Heilman and Scholes 1976; Wernicke 1874), output (Broca 1861; Mohr 1976), other stages in linguistic processing (e.g. syntax – Goodglass 1997; Swinney and Zurif 1995), phonology (Milberg et al. 1988), lexical access (Martin et al. 1994)), and/or attention (Tseng et al. 1993) and working memory (Caplan and Waters 1999; Caspari et al. 1998). Although it might be assumed that speech imitation might be particularly relevant to output problems (we do not make the common modular distinction between motor and language systems, since all biological evidence suggests a close interaction between the two), and we have started our therapy trial with patients having a behavioural diagnosis of Broca's aphasia (Kertesz 1982), there are reasons to believe that the approach might have more general relevance. Indeed, a basic finding in the biological research is that the same neuronal systems used to perform hand and mouth actions are also used for understanding these same actions (Gallese et al. 1996; Rizzolatti et al. 1996), including speech (Skipper et al. 2007b; Wilson et al. 2004). Furthermore, these action understanding systems have been shown also to be involved in representing some aspects of meaning (Aziz-Zadeh et al. 2006; Beilock et al. 2008; Gallese 2003). Thus, an imitation-based approach might have broad relevance.

5. Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effect (IMITATE)

We have developed a novel computer-based treatment for aphasia based on action observation and imitation. This treatment approach, called IMITATE, is embodied in a computer program and organisational strategy for its use. A fundamental feature of the system and the basis of its therapeutic program is the set of particular audiovisual stimuli that are used and the order in which they are presented to aphasic people of different levels over time. The computer-assisted treatment program consists of several independent parts, including an interface for aphasic patients, a clinical interface, and an administrative component. We are using IMITATE in a randomised controlled clinical trial aimed both at evaluating its efficacy in aphasia therapy and in understanding its effects on the biology of aphasic patients. Although the clinical trial is currently in progress, and we do not yet have results, we discuss some of trial details at the end of this section.

One of the overarching goals in the development of IMITATE was to create an innovative aphasia treatment supported by theoretical rationales and biological data about the anatomy and physiology of the human brain and its adaptability after injury. The therapy as a whole has been designed to stimulate the human parietal-frontal system for observation-execution matching, thought to be the human analogue of the mirror neuron system. Although mirror neurons per se are known to exist at this time only in the monkey (Gallese et al. 1996), there is ample evidence supporting the presence of a human system that operates like that of the macaque (Buccino et al. 2001). The treatment approach consists of observation of words and phrases presented audiovisually, followed by oral repetition of the stimuli. Treatment is provided at high intensity, all stimuli are ecological, the approach incorporates both stimulus and speaker variability, and stimuli are presented with graded incremental changes in complexity. Table 1 summarises the important general features of the therapeutic approach.

Table 1: IMITATE: Important design features for therapeutic effectiveness.

Visual observation
Oral repetition
Speaker variability
High intensity
Ecological stimuli
Graded incremental learning
Variability in gradation

Given the importance of intensity in therapeutic success, IMITATE is designed to provide intense treatment via the computer. Since the number of hours provided in a week appears to be significantly correlated with greater improvement on language outcome measures (Bhogal et al. 2003), IMITATE requires 90 minutes of daily therapy. Although our clinical trial is testing six weeks of therapy, the computer program itself contains a total of twelve weeks of organised therapy, starting from very simple speech samples (i.e., high visibility single syllables that are words, such as “ma”, “pa”) to phrases containing several words.

In addition to high intensity, a second key therapeutic feature of IMITATE is the exclusive use of ecologically valid stimuli. The therapeutic tasks use only stimuli that are part of normal speech (e.g., words, sentences) and are uttered with normal prosody by a speaker whose face, lips, and mouth are visible. This need for ecological validity is based on the physiology: Those neurons that discharge when an action is performed and during perception of another person performing the same action (i.e., mirror neurons) may work by matching an observed action onto an internal motor representation of that action (Kohler et al. 2002; Rizzolatti et al. 1996). Such neurons are not active on tasks that are not part of the normal motor repertoire of the animal or person tested (Ferrari et al. 2005).

Thirdly, IMITATE treatment incorporates the principle of graded, incremental learning through changes in stimuli complexity. As a patient improves and becomes able to imitate successively monosyllabic words, disyllabic words, two to three word phrases, and longer utterances, these are incrementally changed to be more difficult, and the rate is increased, in a process referred to as incremental learning (Sutton and Barto 1998), adaptive training (Merzenich et al. 1996; Tallal et al. 1996), or "shaping" (Taub et al. 1994). Work in neural network computer models also reinforces the notion that gradual, incremental learning has theoretical advantages (Elman 1993). Graded, incremental learning is integrated into the IMITATE therapy as patients advance through increasingly complex treatment levels.

Finally, the IMITATE approach includes variability as a fundamental design feature. Although stimulus complexity increases over the course of treatment, based on the improving skills of the patient, the words and phrases presented are selected randomly from a database with a probabilistic favouring of stimuli near the appropriate level. Thus, early in treatment, a patient will occasionally be presented with a relatively complex word or even a phrase, and later in treatment, a patient will sometimes be asked to imitate a very simple word. We believe that such variability represents the best learning strategy and reconciles the two conflicting sets of data that suggest on one hand that "starting small" improves learning (Elman 1990), and on the other, that complexity is the desirable starting point (Kiran and Thompson 2003). Finally, we have included speaker variability as well, since this is a fundamental component of speech perception (Magnuson and Nusbaum 2007; Wong et al. 2004).

Examples of words and phrases presented at each level of training are shown in Table 2. Note that the inherent randomness in the computer program will lead a participant to see words and phrases from many levels during a single session, but with the preponderance of the stimuli favouring the graded incremental learning approach.

6. A randomised controlled trial

We are currently conducting a randomised clinical trial evaluating the efficacy of the computer-assisted IMITATE treatment approach. In this trial, we aim to recruit as many as twenty subjects in each of two experimental groups. The first group will receive IMITATE therapy as described here, and have a range of behavioural (language and cognitive) and biological (imaging) variables assessed before and after the experimental treatment. The second group will receive identical therapy and evaluations, except that (a) they will not see the moving face of the speaker, i.e., an audiovisual stimulus, but will see a static face and hear the stimuli auditorily; and (b) they will not be presented with the same linguistic entity spoken by a range of different speakers prior to repeating it, but will hear it once by one speaker and then repeat it immediately. (Note that auditory stimuli from all speakers will be used, but these will be randomly presented.).

Table 2: Sample words and phrases across all twelve IMITATE treatment levels.

Treatment Level	Sample Words	Sample Phrases
1	man, pie, moon, bed, meat	N/A
2	pear, matter, buy, mouth, food	N/A
3	mile, peer, voice, pear, outside, four	run over, come in, pull through, plan for
4	church, die, side, deep, pause, beam	point out, give in, stand up, take off
5	pocket, repair, famous, jaw, choose	call in, see you soon, stressed out, hear about
6	greatly, bell, tube, van, machine, blush	find out, one more time, figure out, go for it
7	market, smart, comfort, further, foolish, strain	raise your hand, come off, text message, don't pout
8	former, danger, motor, admire, stranger, shrimp	take care of, wait a second, dressing room, wait a minute
9	thunder, preaching, loose, show, welfare, division	it rained all night, close your eyes, have a safe trip
10	teacher, ceiling, military, committee, literature	I need exact change, fix the heater, the town is very small, it is Memorial Day
11	officer, reaction, medicine, prize, utter	hand me my ID card, a glass of orange juice, please accept my apology, may I leave a message?
12	principle, highway, empire, determine, medicine	directory assistance, he went to the museum, the student produced poor work, could you fill this prescription?

In both experimental groups, participants are required to work with the program at home for three 30-minute sessions per day, six days a week (i.e., 9 hours/week), for a period of six weeks. The first of the 18 sessions is completed with the therapist during the participant's weekly visit. While the dosage of therapy is in itself intensive, the treatment design and mechanism by which stimuli are presented also provide opportunities for massed practice. The levels were designed with the intention that participants could move through six levels during the six-week treatment period. However, a participant could also repeat one or more treatment levels for an additional week if the clinician judged it to be necessary.

Although formal data analysis has yet to be completed, five participants with varying aphasia types and severities have completed the treatment protocol thus far. Each of the five participants learned the mechanics of the program easily after one initial training session with the speech-language pathologist. The program automatically tracks treatment sessions completed throughout the week, and thus we know that four of the participants were fully compliant with the treatment schedule.

7. Summary and conclusions

IMITATE is an innovative computer-assisted treatment for aphasia based on action observation and imitation. Our goal was to create a novel treatment for aphasia supported by a theoretical rationale from neuroanatomy and neurophysiology. The central hypothesis is that a systematic activation of the observation–execution matching "mirror neuron" system of the premotor and parietal cortices can be used to produce functional changes in speech and language in patients with ischemic stroke. Speech production is heavily represented in these regions, and there is significant reason to believe that the phylogenesis of speech (i.e., its evolution from the non-verbal mouth movements of apes) depended on observation-execution matching, that its ontogenesis (i.e., development of speech in children) also depends on imitation, and that good recovery from aphasia might also benefit from the use of this system.

In addition to its physiological rationales, IMITATE incorporates features of language treatment that are based on current knowledge in clinical, behavioural, and neural sciences: The therapy is provided at a high intensity, incorporates ecological stimuli, includes both stimulus and speaker variability, and presents graded incremental changes in stimulus complexity. In conclusion, IMITATE is a therapeutic approach, based on basic principles from neurophysiology, that we believe can play an important role in aphasia treatment and recovery. We postulate that functional outcome of patients with language dysfunction can be influenced by tasks involving observation–execution matching and that degree of recovery will depend on changes to the ventral premotor cortex, the dorsal premotor cortex, and the pars opercularis ipsilateral to a cerebral infarction. Results from the clinical trial will provide valuable information regarding treatment efficacy and the potential impact of biologically based aphasia interventions on brain physiology.

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REFERENCES

Alberts, M. J., G. Hademenos, R.E. Latchaw, A. Jagoda, J.R. Marler, M.R. Mayberg, R.D. Starke, H.W. Todd, K.M. Viste, M. Girgus, T. Shephard, M. Emr, P. Shwayder and M.D. Walker. 2000. "Recommendations for the establishment of primary stroke centers. Brain Attack Coalition". *Journal of the American Medical Association* 283. 3102–3109.

American Heart Association. 2003. *Heart and stroke statistical update*. Dallas, TX: American Heart Association.

Aziz-Zadeh, L., S.M. Wilson, G. Rizzolatti and M. Iacoboni. 2006. "Congruent embodied representations for visually presented actions and linguistic phrases describing actions". *Current Biology* 16. 1818–1823.

Basso, A. 1993. "Therapy for aphasia in Italy". In: Holland, A.L. and M.M. Forbes (eds.), *Aphasia treatment: World perspectives*. San Diego, CA: Singular Publishing Group. 1–24.

Beilock, S.L., I.M. Lyons, A. Mattarella-Micke, H.C. Nusbaum and S.L. Small. 2008. "Sports experience changes the neural processing of action language". *Proceedings of the National Academy of Sciences of the United States of America* 105. 13269–13273.

Benson, D.F., and N. Geschwind. 1989. "The aphasias and related disturbances". In: Joynt, R. (ed.), *Clinical neurology*. Philadelphia: J.B. Lippincott Company. 1–28.

Bhogal, S.K., R. Teasell and M. Speechley. 2003. "Intensity of aphasia therapy, impact on recovery". *Stroke* 34. 987–993.

Blumstein, S.E., E. Baker and H. Goodglass. 1977. "Phonological factors in auditory comprehension in aphasia". *Neuropsychologia* 15. 19–30.

Broca, P.P. 1861. "Nouvelle observation d'aphémie produite par une lesion de la partie postérieure des deuxième et troisième circonvolutions frontales". *Bulletin de la Société anatomique de Paris* 6. 398–407.

Buccino, G., F. Binkofski, G.R. Fink, L. Fadiga, L. Fogassi, V. Gallese, R.J. Seitz, K. Zilles, G. Rizzolatti and H.J. Freund. 2001. "Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study". *European Journal of Neuroscience* 13. 400–404.

Buccino, G., F. Lui, N. Canessa, I. Patteri, G. Lagravinese, F. Benuzzi, C.A. Porro and G. Rizzolatti. 2004a. "Neural circuits involved in the recognition of actions performed by *nonconspecifics*: An FMRI study". *Journal of Cognitive Neuroscience* 16. 114–126.

Buccino, G., S. Vogt, A. Ritzl, G.R. Fink, K. Zilles, H.J. Freund and G. Rizzolatti. 2004b. "Neural circuits underlying imitation learning of hand actions: An event-related FMRI study". *Neuron* 42. 323–334.

Canseco-Gonzalez, E., L.P. Shapiro, E.B. Zurif and E. Baker. 1990. "Predicate-argument structure as a link between linguistic and nonlinguistic representations". *Brain and Language* 39. 391–404.

Caplan, D., and G. S. Waters. 1999. "Verbal working memory and sentence comprehensio". *Behavioural and Brain Sciences* 22. 77–94. (Discussion 95–126.)

Caramazza, A. 1989. "Cognitive neuropsychology and rehabilitation: An unfulfilled promise?" In: Seron, X. and G. Deloche (eds.), *Cognitive approaches in neuropsychological intervention*. Hillsdale, NJ: Lawrence Erlbaum Associates. 383–398.

Caspari, I., S.R. Parkinson, L.L. LaPointe and R.C. Katz. 1998. "Working memory and aphasia". *Brain and Cognition* 37. 205–223.

Centers for Disease Control and Prevention. May 18, 2007. "Prevalence of Stroke – United States, 2005". In: *Morbidity and Mortality* Weekly Report. Government Printing Office. 469–474.

Cherney, L.R., A.S. Halper, A.L. Holland and R. Cole. 2008. "Computerised script training for aphasia: Preliminary results". *American Journal Speech Language-Pathology* 17. 19–34.

Chomsky, N. 1965. *Aspects of the theory of syntax*. Cambridge, MA: MIT Press.

Crerar, M.A., A.W. Ellis and E.C. Dean. 1996. "Remediation of sentence processing deficits in aphasia using a computer-based microworld". *Brain and Language* 52. 229–275.

Duffy, J.R. 1995. *Motor speech disorders: Substrates, differential diagnosis, and management*. Philadelphia, PA: Mosby.

Elman, J.L. 1990. "Finding structure in time". *Cognitive Science* 14. 179–211.

Elman, J.L. 1993. "Learning and development in neural networks: The importance of starting small". *Cognition* 48. 71–99.

Fadiga, L., L. Fogassi, G. Pavesi and G. Rizzolatti. 1995. "Motor facilitation during action observation: A magnetic stimulation study". *Journal of Neurophysiology* 73. 2608–2611.

Fadiga, L., L. Craighero, G. Buccino and G. Rizzolatti. 2002. "Speech listening specifically modulates the excitability of tongue muscles: A TMS study". *European Journal of Neuroscience* 15. 399–402.

Fang, J. and M.H. Alderman. 2001. "Trend of stroke hospitalisation, United States, 1988–1997". *Stroke* 32. 2221–2226.

Ferrari, P.F., S. Rozzi and L. Fogassi. 2005. "Mirror neurons responding to observation of actions made with tools in monkey ventral premotor cortex". *Journal of Cognitive Neuroscience* 17. 212–226.

Fitch, J.L. 1983. "Telecomputer treatment for aphasia". *Journal of Speech and Hearing Disorders* 48. 335–336.

Gallese, V., L. Fadiga, L. Fogassi and G. Rizzolatti. 1996. "Action recognition in the premotor cortex". *Brain* 119(2) 593–609.

Gallese, V. 2003. "A neuroscientific grasp of concepts: from control to representation". *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 358. 1231–1240.

Goodglass, H. 1993. *Understanding aphasia*. San Diego, CA: Academic Press.

Goodglass, H. 1997. "Agrammatism in aphasiology". *Clinical Neuroscience* 4. 51–56.

Grawemeyer, B., R. Cox and C. Lum. 2000. "AUDIX: A knowledge-based system for speech-therapeutic auditory discrimination exercises". *Studies in Health Technology and Informatics* 77. 568–572.

Graziano, M.S., C.S. Taylor, T. Moore and D.F. Cooke. 2002. "The cortical control of movement revisited". *Neuron* 36. 349–362.

Grodzinsky, Y. 1986. "Language deficits and theory of syntax". *Brain and Language* 27. 135–159.

Hacke, W., M. Kaste, C. Fieschi, D. Toni, E. Lesaffre, R. von Kummer, G. Boysen, E. Bluhmki, G. Hoxter and M. H. Mahagne. 1995. "Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS)". *Journal of the American Medical Association* 274. 1017–1025.

Heilman, K.M., and R.J. Scholes. 1976. "The nature of comprehension errors in Broca's, conduction, and Wernicke's aphasics". *Cortex* 12. 258–265.

Hoyert, D.L., E. Arias, B.L. Smith, S.L. Murphy and K.D. Kochanek. 2001. "Deaths: Final data for 1999". *National Vital Statistics Report* 49. 1–117.

Huber, W., L. Springer and K. Willmes. 1993. "Approaches to aphasia therapy in Aachen". In: Holland, A.L. and M.M. Forbes (eds.), *Aphasia treatment: World perspectives*. San Diego, CA: Singular Publishing Group. 55–86.

Iacoboni, M., R.P. Woods, M. Brass, H. Bekkering, J.C. Mazziotta and G. Rizzolatti. 1999. "Cortical mechanisms of human imitation". *Science* 286. 2526–2528.

Iacoboni, M., L.M. Koski, M. Brass, H. Bekkering, R.P. Woods, M.C. Dubeau, J.C. Mazziotta and G. Rizzolatti. 2001. "Reafferent copies of imitated actions in the right superior temporal cortex". *Proceedings of the National Academy of Sciences of the United States of America* 98. 13995–13999.

Iacoboni, M. 2003. "Neural circuitry of imitation: The human homologues of monkey STS, PF, and F5". Paper presented at the Human Brain Mapping conference, New York.

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

Kertesz, A., and P. McCabe. 1977. "Recovery patterns and prognosis in aphasia". *Brain* 100. 1–18.

Kertesz, A. 1982. *The Western Aphasia Battery*. New York: Grune and Stratton.

Kiran, S. and C.K. Thompson. 2003. "The role of semantic complexity in treatment of naming deficits: Training semantic categories in fluent aphasia by controlling exemplar typicality". *Journal of Speech, Language and Hearing Research* 46. 608–622.

Kohler, E., C. Keysers, M.A. Umilta, L. Fogassi, V. Gallese and G. Rizzolatti. 2002. "Hearing sounds, understanding actions: Action representation in mirror neurons". Science 297. 846–848.

Lecours, A.R., F. Lhermitte and B. Bryans. 1983. *Aphasiology*. London: Baillière Tindall.

Mackay, J. and G.A. Mensah. 2004. *The atlas of heart disease and stroke*. Geneva: World Health Organisation.

Magnuson, J.S., and H.C. Nusbaum. 2007. "Acoustic differences, listener expectations, and the perceptual accommodation of talker variability". *Journal of Experimental Psychology*: *Human Perception and Performance* 33. 391–409.

Martin, N., G.S. Dell, E.M. Saffran and M.F. Schwartz. 1994. "Origins of paraphasias in deep dysphasia: Testing the consequences of a decay impairment to an interactive spreading activation model of lexical retrieval". *Brain and Language* 47. 609–660.

Mashal, N., A. Solodkin, E.E. Chen and S.L. Small. In press. "A mirror neuron system for human speech demonstrated through a network model of observation and imitation". *Brain and Language*.

Merzenich, M.M., W.M. Jenkins, P. Johnston, C. Schreiner, S.L. Miller and P. Tallal. 1996. "Temporal processing deficits of language-learning impaired children ameliorated by training". *Science* 271. 77–81.

Milberg, W., S. Blumstein and B. Dworetzky. 1988. "Phonological processing and lexical access in aphasia". *Brain and Language* 34. 279–293.

Mohr, J.P. 1976. "Broca's area and Broca's aphasia". In: Whitaker, H. and H. Whitaker (eds.), *Studies in neurolinguistics*. New York: Academic Press. 201–233.

Murata, A., L. Fadiga, L. Fogassi, V. Gallese, V. Raos and G. Rizzolatti. 1997. "Object representation in the ventral premotor cortex (area F5) of the monkey". *Journal of Neurophysiology* 78. 2226–2230.

Naeser, M.A., E.H. Baker, C.L. Palumbo, M. Nicholas, M.P. Alexander, R. Samaraweera, M.N. Prete, S.M. Hodge and T. Weissman. 1998. "Lesion site patterns in severe, nonverbal aphasia to predict outcome with a computer-assisted treatment program". *Archives of Neurology* 55. 1438–1448.

NIDCD. 1997. *Aphasia*. National Institute of Deafness and Other Communication Disorders.

Pedersen, P.M., H.S. Jorgensen, H. Nakayama, H.O. Raaschou and T.S. Olsen. 1995. "Aphasia in acute stroke: Incidence, determinants, and recovery". *Annals of Neurology* 38. 659–666.

Rizzolatti, G., L. Fadiga, V. Gallese and L. Fogassi. 1996. "Premotor cortex and the recognition of motor actions". *Brain Research. Cognitive Brain Research* 3. 131–141.

Rizzolatti, G. and M.A. Arbib. 1998. "Language within our grasp". *Trends in Neurosciences* 21. 188–194.

Rizzolatti, G. and M.A. Arbib. 1999. "From grasping to speech: Imitation might provide a missing link: Reply". *Trends in Neurosciences* 22. 152.

Rizzolatti, G., L. Fogassi and V. Gallese. 2002. "Motor and cognitive functions of the ventral premotor cortex". *Current Opinion in Neurobiology* 12. 149–154.

Rizzolatti, G. and L. Craighero. 2004. "The mirror-neuron system". *Annual Review of Neuroscience* 27. 169–192.

Robey, R.R. 1998. "A meta-analysis of clinical outcomes in the treatment of aphasia". *Journal of Speech, Language, and Hearing Research* 41. 172–187.

Romanski, L.M. and P.S. Goldman-Rakic. 2002. "An auditory domain in primate prefrontal cortex". *Nature Neuroscience* 5. 15–16.

Rosamond, W., K. Flegal, G. Friday, K. Furie, A. Go, K. Greenlund, N. Haase, M. Ho, V. Howard, B. Kissela, S. Kittner, D. Lloyd-Jones, M. McDermott, J. Meigs, C. Moy, G. Nichol, C.J. O'Donnell, V. Roger, J. Rumsfeld, P. Sorlie, J. Steinberger, T. Thom, S. Wasserthiel-Smoller and Y. Hong. 2007. "Heart disease and stroke statistics – 2007 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee". *Circulation* 115. e69–171.

Skipper, J.I., H.C. Nusbaum and S.L. Small. 2006. "Lending a helping hand to hearing: A motor theory of speech perception". In: Arbib, M.A. (ed.), *Action to language via the mirror neuron system*. Cambridge: Cambridge University Press. 250–286.

Skipper, J.I., S. Goldin-Meadow, H.C. Nusbaum and S.L. Small. 2007a. "Speech-associated gestures, Broca's area, and the human mirror system". *Brain and Language* 101. 260–277.

Skipper, J.I., V. van Wassenhove, H.C. Nusbaum and S.L. Small. 2007b. "Hearing lips and seeing voices: How cortical areas supporting speech production mediate audiovisual speech perception". *Cerebral Cortex* 17. 2387–2399.

Small, S.L. 2004a. "Therapeutics in cognitive and behavioural neurology". *Annals of Neurology* 56. 5–7.

Small, S.L. 2004b. "A biological model of aphasia rehabilitation: Pharmacological perspectives". *Aphasiology* 18. 473–492.

Small, S.L. 2008. "The neuroscience of language". *Brain and Language* 106. 1–3.

Steele, R., M. Weinrich, R.T. Wertz, M.K. Kleczewska and G.S. Carlson. 1989. "Computer-based visual communication in aphasia". *Neuropsychologia* 27. 409–426.

Sutton, R.S. and A.G. Barto. 1998. "*Reinforcement learning: An introduction*. Cambridge, MA: MIT Press.

Swinney, D. and E. Zurif. 1995. "Syntactic processing in aphasia". *Brain and Language* 50. 225–239.

Tallal, P., S.L. Miller, G. Bedi, G. Byma, X. Wang, S.S. Nagarajan, C. Schreiner, W.M. Jenkins and M.M. Merzenich. 1996. "Language comprehension in language-learning impaired children improved with acoustically modified speech". *Science* 271. 81–84.

Taub, E., J.E. Crago, L.D. Burgio, T.E. Groomes, E.W. Cook, 3rd, S.C. DeLuca and N.E. Miller. 1994. "An operant approach to rehabilitation medicine: Overcoming learned nonuse by shaping". *Journal of the Experimental Analysis of Behaviour* 61. 281–293.

Tettamanti, M., G. Buccino, M.C. Saccuman, V. Gallese, M. Danna, P. Scifo, F. Fazio, G. Rizzolatti, S.F. Cappa and D. Perani. 2005. "Listening to action-related sentences activates fronto-parietal motor circuits". *Journal of Cognitive Neuroscience* 17. 273–281.

The NINDS rt-PA Stroke Study Group. 1995. "Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group". *New England Journal of Medicine* 333. 1581–1587.

Tobin, Y. 2002. "Phonology as human behavior". In: Fava, E. (ed.), *Clinical linguistics: Theory and applications in speech pathology and therapy*. Philadelphia: John Benjamins. 3–22.

Tomasello, M., S. Savage-Rumbaugh and A.C. Kruger. 1993. "Imitative learning of actions on objects by children, chimpanzees, and enculturated chimpanzees". *Child Development* 64. 1688–1705.

Tseng, C.-H., M.R. McNeil and P. Milenkovic. 1993. "An investigation of attention allocation deficits in aphasia". *Brain and Language* 45. 276–296.

Weinrich, M. 1997. "Computer rehabilitation in aphasia". *Clinical Neuroscience* 4. 103–107.

Weinrich, M., J.R. Shelton, D.M. Cox and D. McCall. 1997a. "Remediating production of tense morphology improves verb retrieval in chronic aphasia". *Brain and Language* 58. 23–45.

Weinrich, M., J.R. Shelton, D. McCall and D. M. Cox. 1997b. "Generalisation from single sentence to multisentence production in severely aphasic patients". *Brain and Language* 58. 327–352.

Weinrich, M., D. McCall, K.I. Boser and T. Virata. 2002. "Narrative and procedural discourse production by severely aphasic patients". *Neurorehabilitation and Neural Repair* 16. 249–274.

Wernicke, C. 1874. *Der aphasische Symptomenkomplex*. Breslau: Cohn & Weigert.

Wilson, S.M., A.P. Saygin, M.I. Sereno and M. Iacoboni. 2004. "Listening to speech activates motor areas involved in speech production". *Nature Neuroscience* 7. 701–702.

Wong, P.C., H.C. Nusbaum and S.L. Small. 2004. "Neural bases of talker normalisation". *Journal of Cognitive Neuroscience* 16. 1173–1184.

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