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**SYMPOSIA—INTRODUCTION**

# The changing view of neurorehabilitation: A new era of optimism

LESLIE J. GONZALEZ ROTHI[1,2] and ANNA M. BARRETT[3,4]

[1]Brain Rehabilitation Research Center and Geriatric Research, Education and Clinical Center, Malcom Randall VA Medical Center, Gainesville, Florida
[2]Department of Neurology, University of Florida, Gainesville, Florida
[3]Kessler Medical Rehabilitation Research and Education Corporation, West Orange, New Jersey
[4]Department of Physical Medicine and Rehabilitation and Basic and Clinical Neurosciences, the University of Medicine and Dentistry, New Jersey Medical School, New Jersey

Stroke is the leading health care problem requiring rehabilitation services today (CDC, 2001; Lee et al., 1996) with the worldwide incidence estimated to be between 300 and 500 per 100,000 people (Sudlow & Warlow, 1997). In most recent years, the rates of mortality are decreasing, resulting in a significant increase in the number of survivors living with the disabilities/handicaps associated with stroke (Thorvaldsen et al., 1997). Not only is stroke a common health problem, but the cognitive disorders that result are common as well (Mayo, 1993; Paolucci et al., 1996).

While the risk of stroke increases with age, stroke is not necessarily a disorder of aging: Approximately 30% of all strokes occur among people younger than 65 years of age (Walker et al., 1981). So it is possible that many of our patients will live for many many years with the effects of these strokes. Of those suffering stroke, 50% are alive more than 5 years after the event (Dombovy et al., 1987). We know that the incidence of *enduring* cognitive deficits is high. For example, 79% with aphasia from stroke have aphasia 12 months post onset. Studies also show that the etiology contributes to the level of recovery in aphasia, complete recovery noted in over 50% of patients with traumatic brain injury but only 21% of patients with stroke (Kertesz & McCabe, 1977).

The estimated direct and indirect cost of stroke in the US for 2006 is $57.9 billion (American Heart Association, 2006). The average cost for an individual stroke survivor is over $140,000, including acute medical care, rehabilitation and follow-up care of lasting deficits, which may account for as much as 30% of total costs (Taylor et al., 1996). The presence of cognitive disorders clearly contributes to the potential loss of productivity and the need for more restrictive living environments. In addition to the large financial impact of stroke, the functional impact of stroke can also be devastating. While dependence in activities of daily living (ADLs) such as grooming and eating are highest just after the onset of stroke and diminishes as recovery occurs, it is estimated that at least 50% of stroke victims remain dependent on others for assistance with some ADLs even after rehabilitation is completed (Dombovy et al., 1987; Jorgensen et al., 1995; Christie, 1982; Herman et al., 1983). The functional effect of stroke on instrumental ADLs, for example shopping, is estimated to be even higher. Gresham et al. (1979) suggest that 90% of stroke survivors are left with one or more disability. Our concern escalates when it is noted that only 47% of long-term survivors (4.9 years or older) have a caregiver living with them!

In cases where caregivers are present, one recent study determined that as many as 55% of caregivers of stroke survivors expressed "significant emotional distress" (Dennis et al., 1998) and another study documented high levels of depression (Han & Haley, 1999). A major contributor to emotional distress in caregivers of stroke patients occurs when the patient has anosognosia (Knapp & Hewison, 1999), yet precious little is available to effectively manage such cognitive deficits. No wonder that cognitive disorders are consistently found to be a reliable predictor of poorer quality of life (Galski et al., 1993; Kalra et al., 1997) and of institutionalization (Lincoln et al., 1989) compared with those who have brain impairments but not cognitive deficits.

Even with this great need for effective methods to manage neurologically-induced cognitive deficits, the value of neurorehabilitation has been viewed with great skepticism

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Correspondence and reprint requests to: Leslie J. Gonzalez Rothi, Malcom Randall VA Medical Center (151A), 1601 SW Archer Road, Gainesville, FL 32608-1197. E-mail: gonzalj@neurology.ufl.edu

for over 100 years. In spite of this, we find a history of repeated attempts to treat cognitive disorders beginning in antiquity and spanning thousands of years. Descriptions of forms of cognitive rehabilitation can be found in the Old Testament of the Bible. During the Age of the Pyramids, Egyptian medicine provided the first attempts to use mechanism-based treatments with smelly potions and charms placed on the bodies of those suffering the ill effects of stroke. The intent was to make the body uninhabitable to demonic possession, the suspected mechanism at that time for suddenly incomprehensible verbal communication. Blood letting was recommended in 400 BC when the thought was that apoplexy resulted from an imbalance of humors. These optimistic attempts continued until the earliest parts of the 20th century when Cajal (1928) first described the nature of the synapse and, as an aside, stated that, once formed, the synaptic connection was "immutable". This concept of immutability of structure laid the foundation for the notion that little could be gained by enriching interventions for cognitive deficits resulting from neurologic disease or injury after puberty. It is thus ironic that the scientific view of neurorehabilitation subsequently came to be nihilistic. We live with this view today, with the consequences being a widespread hesitance to refer patients to cognitive rehabilitation, and certainly a resistance on the part of payers to support these efforts without further evidence of its effectiveness.

In reflecting upon a nihilistic view of neurologic recovery, we wonder why it was so influential in the face of our own potential to learn across our life spans. For example, we learned the alphabet as 6 year olds, we learned geometry as 14 year olds, we may have learned techniques of natural childbirth as 20 year olds, we learned informed research participant consent rules as adult researchers, and we most certainly will learn retirement payment options as 65+ year olds. If we lay down new information within neural networks containing millions of connections, and if new connections are not possible after puberty, how could we learn new information after the age of 14? Yet we do. Thus, since we learn across our entire life spans, Cajal's statement that the synapse is immutable once formed and not changeable by experience *must* be incorrect.

What is the basis for the notions that the adult central nervous system (CNS) might be naturally dynamic and that experience has the potential to change structure and, in turn, function? Fundamental work in this regard began emerging in the final decades of the 20th century. Juraska (1990), for example, reported a meta-analysis of 9 studies that showed that differences in developing rat occipital cortex occur as the result of differences in visual environmental experience. That experience could induce such changes in a mature CNS was also provided by investigators such as Jenkins et al. (1990) who showed evidence of experience-dependent changes in normal hand somatosensory cortex in adult owl monkeys as did Kilgard & Merzenich (1998) in auditory cortex in rats. Finally, the potential for neuroplasticity in the context of relearning in an injured mature CNS is reported in investigations such as that of Pons et al. (1988) who showed cortical remapping of secondary somatosensory cortex post infarction of primary somatosensory cortex in adult macaques.

How can we take advantage of our apparent innate ability to learn new things well into late adulthood and, in particular, how can that new learning be optimized, especially in the context of re-learning associated with chronic injury to the adult CNS? This question constitutes a research frontier for neuropsychology and for neurorehabilitation in general. We find ourselves now at the start of the 21st century with a new optimism about the potential of neurorehabilitation and a new mission to discover the principles by which experience can be optimized to reap its greatest potential to change the nervous system and, in particular in the context of neural injury, to encourage new connections in support of cognition and cognitive processes newly relearned through rehabilitation. The papers in this issue are attempts to do just that: To begin to examine new approaches to optimize what can be reaped by behavioral interventions guided by principles of experience-dependent neuroplasticity that focus on:

- Schedule of dosing reported by Maher and colleagues.
- Recruitment of added modalities in the cases of Raymer and colleagues and of Beeson and Egnor.
- Temporally limited advantages to processing provided by contextual priming in the report of Martin et al.
- Potential influences on task-dependent changes (or lack thereof) in brain activation in conjunction with behavioral changes (or lack thereof) in the context of treatment in the case of the exploratory study of Cherney and Small.

Cognitive rehabilitation research, still in its infancy with much yet to be achieved, is lagging well behind other forms of rehabilitation research. This lag may indeed be due in part to the pessimism that has dominated the field for a century, but it may also be due to factors that impede scientific progress in rehabilitation: It is widely understood that science and clinical treatment are ideally closely entwined, with basic discovery continuously inspiring and informing the development of treatments. Unfortunately, even if only the development of treatments alone were under consideration, we think that there is a lack of appreciation by scientists, clinicians, funding agencies, and book and journal reviewers for the value of all phases of clinical trial development. It is common to hear that randomized clinical trials (RCT) are the "gold standard," but this view may seriously undermine a necessary process of evolution (Iggo, 1995). In one perspective (Rodriguez & Rothi, 2006), an overwhelming emphasis on Phase III studies de-values the early stages of clinical research, that is, Phase I and Phase II studies, that are essential to develop and ready experimental treatments for RCTs. A prejudice against early stage research, ironically, is likely to serve as a barrier to innovation and to thus result in the lag of decades between discov-

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ery and application found in medicine today (Balas et al., 2004). As stated by Bradley & Field (1995), while "*evidenced-based care has the potential to rescue us from sinking in a sea of papers . . . proponents of the movement threaten to swamp us in a tidal wave of enthusiasm. . . . Categorizing interventions by evidence makes an implicit value judgment. It is a short step from 'without substantial evidence' to 'without substantial value'*". Class 1 level of clinical evidence rating (Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, 1994) is important and needed, but, to reach a stage at which RCTs contribute valuable information, we must develop treatments through the rigorous scientific steps needed: hypothesis-generating pilot studies, well-run case studies, case series, or analysis of existing data to derive new treatment approaches, and studies examining treatment approaches for proof of concept, feasibility and safety (Phase I); for efficacy (Phase II); and only then for effectiveness (Phase III) (Robey & Schultz, 1998). Finally, Cicerone et al. (2005) challenge that "*research should move beyond the simple question of whether cognitive rehabilitation is effective, and examine the therapy factors and patient characteristics that optimize the clinical outcomes of cognitive rehabilitation*."

Our point is that good research for clinical treatment does not exclusively involve a randomized clinical trial or meta-analysis supporting effectiveness. With research such as that demonstrated in this collection of papers, treatment research also involves extending the treatment to true individual patient application with observational, case-based, or exploratory studies to document how the treatment might be refined and targeted to those patients most likely to benefit. Such studies should be theoretically-based, and we suggest that the research presented in this collection of papers offers examples of the honing process needed to proceed through the entire continuum of treatment development.

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