

## VIEWPOINT

# The Future of Stroke Treatment

## Bringing Evaluation of Behavior Back to Stroke Neurology

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**Acute stroke interventions** and stroke rehabilitation are aimed at salvaging or restoring brain function. How do we know if we have accomplished this goal? We examine the patient. One neurological historian asserted, "Most of the modern neurological examination evolved in a short time span, between 1850 and 1914..."<sup>1(p3)</sup> This quote is telling; it implies that the examination itself has not changed much since about 1914. For generations of medical students, residents, and other trainees in neuroscience, the neurological examination has achieved almost sacred, untouchable status, while at the same time becoming less important, as diagnostic technologies have become more sophisticated. Indeed, many of the examination's components have become almost empty ritual. Ask a resident what modern neuroscience has revealed about the mechanisms of, for example, increased tone, neglect, apraxia, and alexia, and how this new knowledge relates to the components of the neurological examination, or how the examination might be updated, and you will likely be met with a blank stare. Ironically, even as cognitive neuroscience has advanced, the interest of neurologists in behavior in the broadest sense, and its underlying physiological characteristics and anatomy, has waned. Thus, current stroke neurologists have largely failed to emphasize the evaluation of the effects of our interventions on brain function.

What are the reasons for this loss of interest in behavior? We can only offer some conjectures. First, imaging and other technologies have conveyed the notion that careful examination is less pressing. Second, in an era of evidence-based medicine and large clinical trials, simple outcome measures and scales are favored. We live in the age of the biomarker—"any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease."<sup>2</sup> It is not our intention to criticize the use of biomarkers, but we would argue that an unintended consequence of biomarkers has been to draw attention away from behavior and focus it instead on substances extracted from the body. Third, behavior is unique to the brain; livers and kidneys, for example, do not behave; their function is ascertained through measurements of their physiological characteristics and metabolism, using laboratory tests and scans. From this standpoint, neurology is simply following the norm set by the rest of medicine.

It is essential that we use findings and concepts from cognitive neuroscience to update the behavioral examination and outcome measures. New technologies should be used to enhance behavioral assessments, not just substitute for them. To our knowledge, most studies of acute

stroke treatment to date have used the modified Rankin Scale, Barthel Index, and/or National Institutes of Health Stroke Scale (NIHSS). These scales measure changes in basic physical functions, such as self-care, toileting, walking, or holding up the arm. The implicit assumption is that less easily assessed aspects of behavior will correlate with these scales and thus not be examined. Depending on how cognitive outcome is measured, 24% to 65% of strokes have detrimental cognitive effects. While some cognitive functions recover after stroke, at least 10% of first-ever strokes result in new and progressive cognitive decline.<sup>3</sup> The variables that determine recovery vs decline have yet to be identified. In most cases, it is primarily cognitive impairments that prevent individuals from returning to work or independent living after a stroke. Yet, to our knowledge, none of the major trials of acute stroke intervention and few trials of rehabilitation have measured the effects of the intervention on cognitive function. The few small studies that have evaluated the effects of acute intervention on cognitive function have demonstrated that even very simple bedside testing of behavior documents the effects of intervention better than the traditional scales currently being used. For example, scores on line cancellation, a simple test of hemispatial neglect, correlated better with change in volume of hypoperfused tissue (ie, tissue that was reperfused) than did change in the NIHSS for patients with right hemispheric stroke.<sup>4</sup> This result reflects that there is a mismatch between what acute stroke interventions often restore when they are successful—the function of cortex—and what we typically measure as outcomes. The NIHSS and other stroke scales are poor at measuring right hemisphere cortical function.

Robotic therapy and constraint-induced movement therapy (CIMT), which have both been tested with large randomized clinical trials, are 2 novel rehabilitative interventions for chronic arm paresis after stroke. The VA ROBOTICS<sup>5</sup> study showed a small reduction in impairment, assessed with the Fugl-Meyer scale, compared with usual care. The EXCITE study showed a significant effect on function, assessed with the Wolf Motor Function Test.<sup>6</sup> Of interest here is that positive results were obtained for 2 different kinds of outcome: impairment for robotics vs function for CIMT. What is one to make of this? As there was no a priori mechanistic hypothesis about the expected fine-grained behavioral effect of either of the interventions, nor a task introduced to assess it, our understanding of what these interventions actually did is limited. For example, a functional improvement, as was seen in VA ROBOTICS, could have occurred through either compensation or true re-

duction in impairment. This problem has and can be mitigated by quantitative analysis of movement kinematics using various forms of motion capture.<sup>7</sup> This is just one way that we can move to the neurological examination 2.0.

We conclude that more careful attention to the behavior being treated and of the methods used to assess the behavior are critical to future trials of stroke treatment; sophistication cannot be just at the front end at the level of the interventions (eg, neuroprotection, stem cells, brain stimulation) but also at the outcome end. Current measures do not go much beyond ordinal scales that fail to measure the functions of much of the brain—functions that determine whether patients will resume social roles, vocations, and avocations that are meaningful to them. Fine-grained behavioral tasks are particularly critical to longitudinal studies, in which it is important

to have the sensitivity to detect real but possibly small ongoing changes. Current and future interventions must be able to target specific brain areas (eg, transcranial magnetic stimulation); trials using these techniques will require behavioral assessments that are, at the very least, unique for each region of the brain that is stimulated. The renowned stroke neurologist C. Miller Fisher stated that we learn neurology stroke by stroke. We need to return to a fine-grained understanding of how brain anatomy and physiological characteristics map onto component behaviors. The fact that more information has become available for the effective treatment of stroke does not mean that we should simplify our assessments in proportion. Instead, new treatments must be tested with an augmented and enhanced form of the neurological examination based on new knowledge and new technology.

#### ARTICLE INFORMATION

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