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Review

A behavioral method for identifying recovery and compensation: Hand use in a preclinical stroke model using the single pellet reaching task

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ABSTRACT

One objective of preclinical animal models of stroke is to distinguish behavioral compensation from behavioral recovery. In compensation, a new behavior is substituted for a lost behavior, whereas in recovery, the original behavior is restored. Distinguishing between these processes is important because: (1) compensation can be mistaken for recovery, (2) compensatory strategies can disrupt performance, (3) the behavioral methods, therapy, and neural changes associated with enhancing compensation can be different from those associated with recovery, (4) under different conditions both compensation and recovery can be desirable outcomes. The review describes a behavioral method for assessing hand use in reaching (skilled reaching or reach-to-eat) by the rat, a behavior analogous to single handed prehension in humans. The method consists of seven separate assessments obtained with end point, movement notation, and biometric measures. The method highlights the importance of using multiple measures to identify behavioral change during acute, early, and chronic poststroke periods. Distinguishing between compensation and recovery refines the interpretation of preclinical behavioral findings and expands opportunities for developing therapies for stroke.

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1. Compensation and recovery

Animal models of human neurological conditions can have many objectives amongst which identifying a deficit, developing a restorative procedure, and bringing the procedure to clinical trials are prominent. For many behavioral studies of stroke using rodents these objectives have not been achieved. Indeed, many reports in which it is suggested that recovery has been obtained have used models that inadequately generalize to the human condition, reflect inadequate analysis, or publication biases (Landis et al., 2012; Sena et al., 2010; van der Worp et al., 2010).

At the core of the problem in interpreting behavioral findings following stroke is that there are two behavioral outcomes related to spontaneous and therapeutic improvement: compensation and recovery (Finger, 1978; Finger and Stein, 1982; Levin et al., 2009; Krakauer et al., 2012). A compensatory behavior is one in which a new behavior is substituted, in whole or in part, to replace a lost behavior. In recovery, a portion, or all, of the original behavior is restored. To distinguish compensation from recovery requires a behavioral analysis that is sensitive to the mixture of outcomes that are possible following stroke.

In translating preclinical findings to clinical outcomes it is underappreciated that compensation and recovery are different (Cramer et al., 2007; Finger, 1978; Finger and Stein, 1982; Levin et al., 2009; Krakauer et al., 2012) and compensatory movements may be mistaken for recovery. Compensation is likely to rely on neural structures that have been relatively unaffected by injury. Thus, compensation may mask the capacity of impaired, but surviving, neural tissue to mediate recovery. The methods for inducing compensation may be different from those used to induce recovery. For example, repetition training may enhance compensation whereas more targeted therapy of specific forms of movement may be necessary for obtaining recovery. Finally, compensatory behavior may lead to behavioral strategies that are actually disruptive, as is noted above.

Distinguishing between compensation and recovery is not only a matter of identifying whether a movement is similar or different, but also requires determining the cause of the behavior. For example, a subject may fail to perform for many reasons other than compromised movement. There may be impairments in memory, motivation, and attention. Thus, behavioral methods that distinguish between compensation and recovery are aided by identifying the causes of behavioral change.

Distinguishing between compensation and recovery is also important in the clinical treatment of human stroke (Levin et al., 2009; Krakauer et al., 2012). Even when compensatory movements are adaptive, they may contribute to problems such as pain and reduced range of joint motion (Levin et al., 2009). The use and reinforcement of compensatory movements may interfere with the attainment of normal motor patterns and limit genuine recovery. Compensatory strategies may also have a detrimental psychosocial impact. Self-perception related to aberrant movement contributes to depression and, ultimately, avoidance of the compensatory strategy (Saxena et al., 2008). Thus, clinical improvement requires functional measures that distinguish between recovery and compensation.

This paper presents an overview of a behavioral method using the rat that can assess the extent to which poststroke behavior represents compensation vs recovery. The behavioral assessment uses a single task, the single pellet reaching task (Whishaw and Pellis, 1990). The task requires that an animal use a single hand to reach for and grasp a single food item, which it subsequently brings to the mouth for eating. The task assesses a rodent behavior that is very similar to an everyday behavior used by nonhuman primates and humans; picking up a food item and placing it in the mouth for eating. This generalizability enhances the expectation that principles derived from preclinical assessment of the behavior are clinically applicable.

The core of the behavioral method rests on findings that the complexity of the reach-to-eat act can be described using multiple measures, each of which gives a different perspective of the behavior. Thus, seven different behavioral assessments derived from end point measures of success, movement notation-derived behavioral descriptions, and biometric measures are described. The results obtained from these analyses on the rat are discussed with respect to their relevance to the processes of compensation and recovery in nonhuman primates and humans.

2. Skilled reaching in rodents

Hand movements consist of prehensile and non-prehensile movements (Napier, 1956). Prehensile movements use a hand to place an object in the mouth, to manipulate an object, or to use an object as a tool. Non-prehensile hand movements involve no grasping. Hand activities of gesturing during speech or in sign language or the movements involved in depressing keys on a keyboard are examples of non-prehensile hand movements. Both prehensile and non-prehensile movements are affected by stroke. The advantage of using prehensile movements to study the effects of stroke relate to the importance of the behavior to everyday well-being, the behavior's dependence on neural structures that are frequently affected by stroke, and the rigour with which the behavior can be subject to experimental analysis.

Skilled reaching, the conventional term for the reach-to-eat act, is a form of prehension in which a hand is used to grasp a food item and place it into the mouth for eating. Skilled reaching is an every day activity for humans and is amongst the earliest movements displayed in early human development (Foroud and Whishaw, 2010; Piaget, 1952). Eighty percent of strokes affect hand use (Lemon, 1997), but only 40% of people who have suffered upper limb impairment due to stroke display some recovery. The remaining 60% have persistent motor abnormalities that significantly affect their daily activity. The most enduring hand deficits are paralysis, loss of movement and sensation, weakness of the hand and arm, and spasticity, a form of rigidity that impairs movement. Symptoms are usually more severe contralateral to the damaged brain tissue, but can be bilateral. Among those people who experienced post-stroke improvement in hand use, improvement likely resulted from some degree of true recovery as well as the use of compensatory strategies.

Skilled reaching is displayed by laboratory rodents, including rats and mice. Subjects can be trained to reach for small pieces of food that they grasp in a hand and bring to the mouth for eating. Rodent skilled reaching is impaired by experimentally induced stroke and can show various degrees of improvement both spontaneously and as a result of therapy. Thus, rodent skilled reaching is used to investigate therapies for functional improvement including physical rehabilitation, constrained-induced therapy, robot-assisted therapy, stimulants and other small molecule treatment, growth factors, cell-based therapies, and electrical and magnetic brain stimulation. As will be described, in all of these forms of investigation it is important to determine whether any beneficial effects of the therapy are due to compensation or recovery.

3. Skilled reaching in rodent stroke models

Stroke, or cerebral vascular accident, is a loss or alteration of bodily function due to insufficient supply of blood to the brain (American Stroke Association, 2011). There are three main types of stroke. Ischemic stroke is caused by an artery blockage and accounts

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