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Rachel Tomazin
Illinois Wesleyan University

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Task Specificity and Functional Outcome: What is best for Post-Stroke Rehabilitation?

Rachel Tomazin and Advisor Abigail Kerr

Illinois Wesleyan University Department of Psychology

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Abstract

Stroke is a debilitating insult to the brain occurring from a blockage in blood supply (ischemic), or a bleed (hemorrhagic) in one hemisphere of the brain. Worldwide, approximately 10 million people are left with moderate to severe disability due to stroke; the most common deficit is upper extremity impairment. Current stroke rehabilitation strategies utilize task specific training of a skill, meaning one practices the specific skill they want to regain. However, it is possible that there are more generalized types of therapy that can be as effective in rehabilitating debilitated skills. The current study utilizes several skilled reaching tasks in mice which show striking parallels to human dexterous movements in order to observe the effects of task-specific versus generalized upper extremity rehabilitation post-stroke. Our findings through statistical and kinematic analysis have implications that task-specific rehabilitative strategies may promote more true recovery than compensation due to the lesser degree of abnormalities in movement post-training as compared to generalized therapy and control groups. Findings also support the validity of a skilled reaching task used in the rodent model; however, further studies and analysis are necessary.

Keywords: skilled reach, mouse model, kinematic analysis, stroke rehabilitation

Task Specificity and Functional Outcome: What is best for Post-Stroke Rehabilitation?

Stroke is a debilitating, sometimes fatal, insult to the brain occurring from a blockage in blood supply (ischemic), or a bleed (hemorrhagic) in one hemisphere of the brain. Nearly 85% of all strokes are ischemic (Center of Disease Control and Prevention, 2016). Worldwide, approximately 15 million people suffer strokes each year: one-third do not survive, one third are left moderately impaired, and the remaining third are left permanently disabled (World Health Report, 2002). In the United States, stroke is the leading cause of long-term disability, with upper limb impairments representing the most common deficit in stroke survivors. Of four million stroke survivors living with impairments in the U.S., 15-30% are permanently disabled (CDCP, 2016). The majority of those affected live with persistent motor impairments that affect their activities of daily living. Impairments range from paralysis, to weakness, spasticity, and rigidity that impairs movement, and loss of movement or sensation on the side of the body contralateral to the hemisphere where the stroke occurred (Alaverdashvili & Whishaw, 2013). Although stroke is a leading cause of disability worldwide and prevalence is increasing, many survivors are left with permanent loss of function despite receiving rehabilitative services (CDC 2016). It is therefore imperative to improve current rehabilitation procedures to efficiently maximize recovery.

With any type of rehabilitation, there is a primary goal to enhance the efficacy of training and improve recovery outcomes. As mentioned above, current rehabilitative strategies following stroke still leave millions debilitated, which demonstrates the need for better rehabilitative strategies. Stroke rehabilitation typically includes emergency care after brain insult followed by behavioral rehabilitation to help relearn skills that were lost due to stroke (CDCP, 2016). Current stroke rehabilitation strategies utilize task specific training of a skill, meaning one practices the specific skill they want to regain. However, it is possible that there are more generalized types of therapy that can be as effective in rehabilitating debilitated skills. In the current study, generalized therapy refers to the ability to transfer learned skilled use to similar skilled tasks.

Impairment, and therefore functional recovery, can be masked by compensation—the reliance on unaffected motor systems— so it is important to note that rehabilitation inducing compensation versus recovery may be different. Because of this, it is important to be critical of the tasks that are used. Repetitive training may result in compensatory action, whereas more task specific forms of movement may be necessary for functional recovery of actions (Alaverdashvili et al., 2013). An important and yet unanswered question concerning recovery of function is whether or not improvement on one skilled motor task will transfer skilled use to other, similar skilled motor movements. That is, is the task chosen for rehabilitative training important in determining what skills will benefit? The current study seeks to answer the question: Is task specific rehab the best means of recovering lost function, or can generalized therapies be just as effective? Further, this study attempts to kinematically understand the distinction between true behavioral recovery and compensation in both specific and generalized rehabilitation regimens.

What is stroke?

The brain requires adequate blood supply to promote optimal function. Oxygen-rich blood is constantly provided through cerebral arteries. In fact, the brain uses 20% of the oxygen an individual breathes, which allows it to function properly and effectively. When there is a blockage or disruption of oxygen to the brain through impeded blood flow, like in the instance of stroke, brain cells die rapidly. In the case of an ischemic stroke, blood clots or plaque within blood vessels restrict or block blood flow, and the restriction of blood flow and oxygen results in cell death. In a hemorrhagic stroke, blood vessels burst and lead to cell death (CDC, 2016). This local blockage or disruption of blood flow results in unilateral (single hemisphere) insult that ultimately impairs motor and/or cognitive functions.

The location of the stroke determines what functions will be affected by the insult. The right and left hemispheres of the brain control contralateral sides of the body; the right hemisphere controls the left side of the body and the left hemisphere controls the right side of the body (AHA/ASA, 2012). The unilateral nature of stroke therefore results in one side of the body being more severely affected than the other, resulting in an impaired body side and an unimpaired (or less impaired) body side. The most common disabilities from stroke are partial (hemiparesis) or complete (hemiplegia) paralysis of one side of the body contralateral to the brain hemisphere in which the stroke occurred (NINDS, 2018).

There are two types of recovery that can occur after stroke: spontaneous recovery and functional recovery. Spontaneous recovery is when a patient naturally regains some function of the affected limb, often within three months of stroke. Functional recovery occurs when patients learn either (1) how to perform lost or affected functions through compensation or an adaptation of a task—writing with the left hand instead of the right (NeuroNow, 2011) or (2) regain lost function through behavioral training. Structurally, spontaneous recovery occurs in the brain in response to stroke via neuroprotective properties. Growth of synapses, dendrites, axonal remodeling and angiogenesis are a few of the structural changes the brain makes in an effort to repair damage after insult (Cassidy & Cramer, 2016). However, even with regenerative properties of the brain, recovery is far from complete and disabilities are still highly prevalent in stroke survivors. With the knowledge of when recovery can be maximized with rehabilitative training—the first three months following stroke—the field now needs to establish what type of rehabilitation must occur to maximize recovery and potentially minimize compensation. In some cases, however, compensation may be the desired outcome, and so rehabilitation should have a primordial focus of regaining lost functions most efficiently. Continued research on training and rehabilitative strategies for efficient stroke recovery is necessary to improve functional outcomes and maximize recovery potential for stroke survivors.

Stroke rehabilitation: Practices and outcomes

Stroke rehabilitation is crucial to stroke survivors' recovery, quality of life, and independence in life after stroke. The type of rehabilitation one participates in depends on what the individual needs to live as independently as possible. Some areas of rehabilitation include self-care skills, mobility skills, communication skills, cognitive skills, and social skills (AHA/ASA, 2012). The rehabilitation and recovery process is complex, occurring through a combination of spontaneous recovery and learning-dependent processes. These processes include restoring functionality of damaged neural tissue through restitution, reorganization of affected neural pathways through substitution, and improvement of disability by using different means through compensation (Langhorne, Bernhardt, & Kwakkel, 2011).

To maximize recovery outcome, rehabilitation should begin as soon as a practitioner deems a stroke survivor medically stable. Early assessment and intervention post-stroke are critical to optimizing rehabilitation and functional recovery (Duncan et al., 2005). Though recovery can occur months or even years after stroke, most motor recovery occurs within the first three months post-stroke, when spontaneous recovery is still possible (Cassidy & Cramer, 2016). However, at-home occupational therapy services administered within one year of stroke have also aided improvement in activities of daily living (Langhorne et al., 2011). The type of rehabilitation necessary depends on the individual's needs and functional goals post-stroke and should be implemented by a multidisciplinary team with the mutual goal to maximize quality of life and functional recovery (Duncan et al., 2005). There is still much debate on exactly what methods are best for rehabilitative care post-stroke due to the many variables involved.

Though the duration, intensity, and efficacy of stroke rehabilitation are still strongly debated, it is known that, on average, stroke survivors only regain about 70% of their potential functional recovery after stroke (Krakauer, Carmichael, Corbett, Wittenberg, 2012). At least 40% of stroke survivors show moderate impairments post stroke and 15-30% show severe impairment that require special rehabilitative care (Duncan et al., 2005). With this large percentage of individuals who exhibit deficits, it is necessary to determine the most successful methodology of stroke rehabilitation. In order to better determine functional outcome and best practice for stroke rehab, research requires the animal model to help guide translational and clinical research practices.

Why animal models?

Experimentation with stroke in the animal model is essential to the investigation of efficacy of stroke rehabilitation in humans. Approximately 80% of strokes affect hand use (Lemon, 1997), but only about 40% of those affected experience any recovery from their impairment (Klein, Sacrey, Whishaw, and Dunnett, 2012). Among the many motor deficits that result from stroke, loss of dexterity or skilled use of hands can be the most debilitating for humans (Klein et al., 2012). Fine motor skills like skilled reaching and grasping are movements used by humans daily that can also be modeled in animals under mild food deprivation in rats and mice (Foroud and Whishaw, 2010; Klein et al., 2012; Farr and Whishaw, 2002).

Skilled reaching, a form of prehension, is the act of extending a limb towards a food source, grasping the food, then bringing the food to the mouth for consumption—similar to the act of eating that humans participate in many times a day (Alaverdashvili & Whishaw, 2013;

Klein et al., 2012). Such prehensile movements as the skilled reach are advantageous to study in relation to stroke due to the importance of the behavior in everyday living. These tasks are particularly dependent on neural connections that are typically affected by stroke—i.e., regions of the motor cortex. Comparative studies of skilled reaching across rodent and human models suggest that the general functions of the task are synonymous (Cenci, Whishaw, Schallert, 2002; Sacrey 2009; Whishaw, Pellis, Gorny, 1992; Whishaw et al., 2002). This indicates skilled reaching has high validity and is generalizable to the human model.

Along with recreating similar behavior within the rodent model and humans, we can also reproduce strokes with similar looking deficits. Artificially-simulated producible strokes illustrate behavioral deficits on tests of skilled motor function and sensorimotor asymmetry, similar to the effects of stroke in the humans (Tennant & Jones, 2009). Deficits in skilled reaching, such as digit flexion, grasping, and controlled reaching, are consistent among rodent models post-stroke and correspond to human fine motor deficits often observed following stroke that impacts the motor cortex (Gharbawie, Gonzalez, Whishaw, 2005; Gharbawie, Auer, Whishaw, 2006; Whishaw, Pellis, Gorny, Pellis, 1991). Further, the reproducibility of both neural and behavioral deficits in animal models permit systematic and easily replicated investigations of stroke, rehabilitation, and recovery. There is great generalizability of the rodent model to the human model in observing stroke deficits and recovery, and therefore, the rodent model will be used within this study.

Rehabilitation in rodents

There is much to learn from motor training for stroke rehabilitation in the animal model. When given a stroke that leads to motor deficits similar to post-stroke deficits in humans, rodents display incomplete or delayed recovery of reaching success in a daily-trained skilled reaching task. Rats in previous studies nearly doubled their reaching attempts post-stroke and improved success to near pre-lesion levels in about two to three weeks of post-stroke training; however, in the majority of studies, compensatory actions appear to have accounted for much of the success (Alaverdashvili et al., 2008, 2010, 2013). Rats have shown recovery post-stroke that reach nearly pre-lesion performance similar to human stroke patients who, though they suffered permanent motor deficits, developed compensatory functions to successfully complete a reach (Klein et al., 2012; Johansson, 2002). In the mouse model, reaching was similarly impaired post-stroke with compensation as the purported primary component for increasing success (Farr et al., 2002). Animal models have shown the potential for near-full recovery, but what is the protocol and what role is compensation playing?

Intensity and timing of training are extremely important aspects to assess when creating a rehabilitation protocol. Studies reviewing these aspects of training suggest increased intensity and frequency in the first four weeks, and up to three months, in post-stroke rehabilitation to maximize functional outcome (Krakauer et al., 2012). Intensity can be markedly increased within this time period to show positive results in functional recovery (Birkenmeier, Prager, Lang, 2010). An increase in intensity in the first few weeks, and maintained intensity throughout the first few months, are suggested to be essential to improve functional recovery and rehabilitation outcomes.

It is interesting to note that the current practice in rodent model rehabilitation is to use repeated practice on the impaired task to rehabilitate performance. This is known as task-specific training. It has been shown that task specific training pre- and post-stroke leads to a high level of recovery in rodents (Langhorne et al., 2011; Khallafa, Ameerb, Fayedc, 2017). However, human stroke survivors experience deficits in a variety of skilled tasks and repeated practice on each may be difficult to achieve. Therefore, it is important to address whether task specific training is the best route of rehabilitation, or if generalizable training would just as effective. Generalized training refers to the rehabilitation of a specific skill that can then be transferred for use in similar tasks. If a skilled task is impaired following stroke, does new learning of any motor skill improve the lost function or is focused training of the specific impairment necessary?

Task specificity in humans

Strong evidence supports task-specific training in aiding the natural process of functional recovery, which also supports the idea that recovery is driven by adaptive, compensatory strategies to recover impaired functions (Langhorne et al., 2011). Motor learning approaches advise rehabilitation of a task should be task-specific, tailored to the patient's needs, and repeated enough to ensure learning occurs (Barreca et al., 2003). In a study following these guidelines, successful and long-lasting recovery of function post-stroke was exhibited in participants involved in task specific rehabilitation (Khallafa et al., 2017). Stroke care suggests that most successful rehabilitation occurs when targeted at task-specificity. However, specificity should be understood as an explanation to why there is poor transfer of task improvement to non-targeted tasks—task-specific training does not transfer well to non-specific tasks (Langhorne et al., 2011). Task specificity shows functional improvements, but it is still unknown whether it is the best route for stroke rehabilitation. For example, task-specific training is quite tedious—requiring specific rehabilitative training on each impaired task. The current study explores a more efficient rehabilitation strategy by generalizing similar rehabilitative tasks pre- and post-stroke.

The current study

The current study has two primary aims. First, this study will investigate the concept validity of a specific skilled reaching task, the single pellet reaching task (SPRT). We strive to answer: is the SPRT a valid rehabilitative method that elicits functional recovery in mice? Though this task is commonly used in rats (Miklyaeva & Whishaw, 1996; Allred & Jones, 2004, 2008; Alaverdashvili et al., 2008), there is little experimental evidence of the validity of this task as a rehabilitative strategy in mice. In order to compare results between mice and rats, a common task would be useful. In addition, limitations in the more common skilled reaching tasks used in mice leave room for an alternative option. The SPRT requires an animal to learn and repeat a single task with the primary goal of observing an advance, grasp, withdraw, and release (Foroud and Whishaw 2010). The task, performed in a plexiglass chamber, allows for video recording of movements, allowing for precise analysis of movement (Alaverdashvili et al., 2008, 2010, 2013; Farr and Whishaw, 2002; Foroud and Whishaw, 2006, 2010;). Furthermore, this method allows for behavioral analysis of motivation, learning, kinematic movements, and allows for deviations from baseline due to stroke to be noticeable (Alaverdashvili and Whishaw 2013). A limitation of the SPRT in current literature is that there is not a well-established protocol that explains the in-depth methods of the task. Due to this lack in literature, the current lab has had difficulty utilizing the task effectively to rehabilitate mice. It is important to create a protocol that labs can follow so that, if interested, researchers can move away from tasks like the Pasta Matrix Reaching Task (PMRT; the most common skilled behavior task in mice), which involves limitations including a strength component to breaking the pasta and inability to record activity due to visual obstructions (pasta and the matrix). The SPRT is also a desirable task because it better lends itself to kinematic reach analysis, allowing for a distinction between true recovery of function and compensation in improved task performance. For the current study, the SPRT is the task of interest to investigate task specificity in the mouse model of stroke rehabilitation. Further, a novel kinematic analysis of the task will be proposed.

The second aim of this study is to explore the role of task specificity in post-stroke rehabilitation training. To that end, mice will be trained and assessed on one skilled reaching task (SPRT) and will receive rehabilitation in either a task specific (using SPRT) or generalized (using PMRT) manner. If task specificity is important, the mice receiving rehabilitation training using the SPRT will show better overall functional recovery through assessments than animals who are trained on the PMRT post-stroke. These findings will bring implications for improving the efficacy of stroke rehabilitation in humans.

Methods

Subjects

In the current study, thirty-two male C57BL/6 mice were trained pre-operatively on the single pellet reaching task (SPRT). Mice were motivated to participate in the skilled reaching task through modified food deprivation. All mice were weighed five days a week to ensure they maintained at least 85% of their free feeding body weight. They were fed between 2.5-4 grams of food daily, depending on their body weight, and were therefore sufficiently food-motivated. Mice were housed in groups of four, unless extenuating situations (aggression or illness) forced the separation of a cage. Each housing unit received standard housing supplies--a small PVC pipe, pieces of a cardboard, nesting material, and the appropriate bedding. The mice experienced a 12:12 light/dark cycle, with feeding, handling and training only occurring during the light cycle (typically between 10am-2pm).

Materials

A Plexiglas chamber (15 cm in length x 8.5cm in width x 15cm in height) with two vertical 1 cm wide slots (2.7 cm apart) on one side and one vertical 1 cm wide slot centered on the other side was utilized for this study (Figure 1). A Plexiglas food platform (8.5 cm in length x 4 cm in width x 1 cm in height) with two indentations (5 mm away from slot) was used for the placement of food pellets utilized throughout the duration of training and assessment of the study (Figure 2). For the SPRT training, 20 mg purified Bioserv mouse food pellets were utilized as the incentive and reward for mice to reach. The Plexiglas chamber with the two vertical slots accessible to the mouse, and the food platform were used as the training apparatus for the SPRT. A stopwatch and data collection sheet developed by the researcher were also utilized during each training session. For an alternative skilled reaching task, the Pasta Matrix Reaching Task (PMRT), the Plexiglas chamber with the single slot available to the mouse was utilized. The PMRT also required the use of a pasta matrix food platform that held vertically placed pasta pieces (3.2cm in length) in place (Figure 3). The PMRT also utilized a handheld counter, a timer, and a data sheet developed by the research lab during each training session.

Video Recording. A Panasonic Full HD 90X zoom camcorder was used for the recording of assessments. Video recordings were taken during each assessment session, occurring the day before surgery, four days post-surgery, and 10 days post-surgery. The first five successful reaches of each animal were analyzed on the pre-operative assessment day. For post-operative and post-training assessment days, the first five reaches were analyzed, whether successful or not, to analyze characteristics of the reach. Video analysis focused on five distinct movements and utilized a three-point rating scale to score each reach as detailed below.

Video Analysis. Adapted from Alaverdashvili et al., (2008) and Whishaw & Pellis (1990) the five movements of focus and analysis were (1) aim, (2) advance, (3) grasp, (4) withdraw, and (5) release. Aim was characterized by lifting the paw off the ground and bringing it to the midline. An advance was when a paw was extended from midline and pronated as extended through the slot (also known as an attempt). A grasp was a movement in which the paw was above the food pellet with digits extended in preparation to grasp pellet; digits flex around pellet to grasp pellet in paw. A withdraw occurs when the limb is pulled back through the slot while the forelimb is supinated and returns to midline. Finally, a release consists of the animal bringing the supinated paw to mouth to eat the retrieved pellet without dropping it and returning limb back to starting position (Figure 4). Each movement was rated on a three-point scale (Alaverdashvili & Whishaw, 2010; Farr & Whishaw, 2002; Gharbawie et al., 2006). If the movement was present and normal it received a 0. If the movement was present but partial or abnormal, it received a 0.5. If the movement was absent it received a 1 on the scoring scale. Attempts to establish inter-rater reliability of video analysis statistically is underway; however, through observation of data, there appears to be very little variability between researchers' scores.

Procedure

Shaping (to determine limb preference). On day 1 mice were placed in the training chamber (one per chamber) for 10 minutes with 10 pellets scattered amongst the chamber floor. On day two mice were placed in the training chamber for 10 minutes with 10 pellets arranged at the front of the chamber near the slot. On days three-five mice were placed in the training chamber for 10 mins with 10 pellets available through the slot on a slanted tray—limb preference observation is begun. Criteria was met for limb preference if in 10 minutes, mice were reaching with a preferred limb 70% of reaches.

Pre-Operative Training. Training consisted of 10 min daily sessions occurring five days a week for five weeks. Each session consisted of 30 trials where mice were expected to reach for a pellet placed in the indentation contralateral to their preferred limb. A successful reach was one in which the mouse extended their limb, grasped the pellet and withdrew in to his mouth for eating. Each mouse was allowed five reaches per trial, with a trial being the presentation of a pellet. A success was recorded if the pellet was retrieved within five reaches without swatting the pellet out of reach or dropping it throughout the attempt. If the pellet was swatted out of reach or dropped in the process of retrieval, the trial was documented as a fail. Success was measured with the equation: success percent = (pellets successfully obtained / number of completed trials) x 100. A success rate of at least 40% needed to be achieved to meet pre-operative training criterion, proceed in the study, and consequently receive a unilateral stroke.

Photothrombotic Stroke. Twenty-four mice met the success criterion and received unilateral photothrombotic stroke (Tennant & Brown, 2013). Mice were anesthetized intraperitoneally (i.p.) with ketamine (100 mg/kg) and xylazine (10 mg/kg). Once anesthetized, mice were placed in a stereotaxic frame and injected with photosensitive dye (Rose bengal; 100 mg/kg, i.p.). A green laser (532 m, 2 mW; Beta Electronics) was illuminated over the exposed skull directly above (5 mm) the brain region responsible for motor movement of the preferred forelimb (0.3 mm anterior to Bregma; 1.5 mm from midline; unilateral exposure contralateral to preferred limb). Once illuminated, the green laser interacted with the photosensitive dye to create a thrombus in the blood vessel. The thrombus caused restricted blood flow to this portion of the brain and resulted in ischemic stroke. Mice were given four days to rest and recover after surgery before assessment of reaching deficits and training began.

Post-Stroke Training. Twenty mice survived photothrombotic stroke and were put into groups for post-operative training. Seven mice were trained on the same task (SPRT group) to observe the effects of task specific training. Seven mice were trained in a different skilled reaching task (PMRT group) to observe the effects of generalized training. Finally, six mice were controls (control group) that were yoked to mice of the other two conditions and only received assessment and no form of training. Groups received post-operative assessment four days after stroke (post-stroke assessment) and again after 10 days of post-operative training (post-training assessment). The SPRT group received training sessions identical to the training procedure that occurred during pre-operative training. The PMRT group were trained on a similar skilled reaching task. PMRT mice were expected to reach contralaterally with their preferred/affected limb for pasta pieces set up in the pasta matrix. Mice were encouraged to extend their limb, grasp the pasta, break the pasta, and withdraw it into the chamber for eating. Sessions were 15 minutes long or 100 reach attempts—whichever occurred first. Success was measured based on the amount of pasta broken. The control group were put into a chamber beside a SPRT or PMRT mouse and was simply fed pellets or pasta pieces while the other mouse was trained.

Perfusions. Once all data were collected, mice were euthanized with a 0.2cc dose of euthasol (sub-cutaneous). Each mouse was then intracardially perfused with approximately 50 mls of phosphate buffer followed by 100 mls of paraformaldehyde. After perfusions were complete, the brain tissue of each animal was removed from the skull and stored in paraformaldehyde at 4° C. Collected tissue was stored for future analysis such as lesion verification; however, no anatomy was conducted for the current study.

Results

Quantitative data (percent success and quantified kinematic analysis) was statistically analyzed with SPSS software. A repeated measures ANOVA was conducted to analyze within and between subject differences of percent success. As depicted in Figure 5, there was a main effect of assessment day (pre-op, post-op, post-training; $F_{(2,30)} = 19.638$, $p < 0.001$), which was expected and confirms neurological changes (i.e., the effect of the stroke) occurred between each assessment day. However, there was no main effect of group ($F_{(2,15)} = 0.353$, $p = 0.708$) and no interaction between assessment day and group ($F(4,30) = 0.64$, $p = 0.639$). Planned comparisons were conducted to analyze differences in conditions (SPRT, PMRT, Control) per assessment day and a univariate ANOVA was completed for each assessment day. There was no statistical differences between groups at pre-operative ($F_{(2,\ 15)}=.046$, $p =.955$), post-operative ($F_{(2,\ 15)}=.159$, $p =.854$), or post-training ($F_{(2,\ 15)}=1.594$, $p=.236$) assessment. Means and SEMs are reported in Table 1.

Kinematic analysis was conducted through the observation and analysis of assessment day video recordings (pre-operative, post-operative, post-training). Researchers scored five components of a reach (aim, advance, grasp, withdraw, and release) quantified on a three-point rating scale (normal (0), abnormal (0.5), or absent (1)). Between and within subject differences were analyzed through a repeated measures ANOVA to assess main effect by assessment day, group, and interactions between group and assessment day for each component of the reach (Table 2).

For the aim component of the skilled reach, a repeated measures ANOVA showed no statistically significant differences between groups and no significant interactions between group and day (Table 2). However, there was a main effect by assessment day, where abnormalities in a skilled reach showed statistically significant increases pre- and post-stroke. The graph shows a very low amount of abnormality in the aim component of the reach compared to other components (Figure 6-10), which may mean the movement is not affected very much by stroke (Figure 6).

For the advance component of the skilled reach, a repeated measures ANOVA showed a main effect by assessment day, but no statistically significant differences between groups and no significant interaction between group and day (Table 2). There is an observed variability in abnormality of the advance between groups across assessment days, especially in the control group at post training assessment (Figure 7). Interestingly, the controls did not differ in abnormality of the advance pre-and post-stroke, but there is a notable increase in abnormality of movement post-training. Lesion verification may permit a better understanding of these behavioral changes.

In the grasp component of the skilled reach, a repeated measures ANOVA revealed main effects by assessment day (significant) and group (approaching significance), and a significant interaction between assessment day and group (Table 2). For the control and generalized group (PMRT), there was a markedly apparent increase in abnormality post-op and post-training (Figure 8). Interestingly, although not statistically significant, an observable pattern has emerged depicting that the task-specific group (SPRT) was consistently demonstrating the smallest degree of abnormality in movement compared to their counterparts (Figure 6-10). In the grasp movement, they were the only group to decrease abnormality post-training while the other groups increased. In other components of the reach, the task-specific group similarly either decreased or remained stagnant in degree of abnormality.

In the withdraw component of the skilled reach, a repeated measures ANOVA showed a main effect by assessment day, but no other significant differences or interactions (Table 2). There was a significant increase in abnormality by all groups, pre-op to post-op, but then abnormality remained stagnant (PMRT, Control) or decreased (SPRT) post-training (Figure 9). This reveals a component of the skilled reach that is significantly affected by stroke.

In the fifth and final component of the skilled reach, release, a repeated measures ANOVA revealed a main effect of assessment day and an interaction between day and group that was approaching significance (Table 2). There was a notable increase of abnormality from pre-op to post-op indicating another movement that is significantly affected by stroke (Figure 10). The same pattern can be observed in which the task-specific (SPRT) group's abnormality decreases post-training while the other groups increase in abnormality. This leads to implications about task specificity as a rehabilitative strategy and its potentially decreased usage of compensation compared to generalized rehabilitation.

Discussion

Quantitative and kinematic data collection allowed for in depth analysis of the validity of the SPRT as a skilled reaching task as well as comparing effects of task specific versus generalized rehabilitative strategies on post-stroke recovery. Ultimately, data looking at percent success showed no statistical differences between groups and were thus inconclusive; overall measure of success revealed no significant differences between groups. However, many variables were at play, which may have contributed to the lack of statistical significance. Additionally, kinematic analysis allowed for a better understanding of compensation versus true recovery in functional outcome with post-stroke rehabilitation, assuming abnormality of a skilled reach can be denoted as compensation. We report abnormality and compensation as synonymous within this discussion because success could still be achieved through these types of movements, but the movements were observably different after insult to the motor cortex—different mechanisms were being utilized to achieve the same goal (Farr & Whishaw, 2002). We believe increased abnormality may be evidence of compensation because increased abnormalities from post-op to post-training in the PMRT group lead to increased (though slight) functional outcome. This suggests that behavioral outcome success with great abnormality in the reach may be an indication of compensation.

Our video recordings, analyzed through repeated measures ANOVAs, revealed several main effects and interactions between groups and assessment days (Table 2, Figure 6-10), which lead to implications about compensation's role in stroke rehabilitation based on the strategy used—task-specific or generalized training. Ultimately, the current study suggests that a primary difference between task specific and generalized rehabilitative training may be less about functional outcome and more to the degree of abnormalities in behaviors that develop to achieve task completion. By utilizing similar mechanisms pre- and post-stroke in the task specific group, these mice showed less abnormality of function than the generalized rehabilitation group. The generalized group showed greater abnormalities in upper limb function and thus likely utilized more compensation to complete the same tasks.

As mentioned, kinematic analysis allowed for the observation and analysis of compensation through general abnormalities in components of a skilled reach. There was a consistent main effect for assessment days across each movement of the reach (aim, advance, grasp, withdraw, release) as could be predicted since a stroke was induced to impair preferred limb reaching (Table 2). More interestingly, there was an interaction between group and assessment day as well as a slight main effect of group for the grasp movement of the reach

(Figure 7). Additionally, the grasp showed the greatest difference between groups, with the task-specific group showing the least abnormality of movement compared with the other two groups, which may indicate that the grasp component of a skilled reach requires less compensation when the skill is rehabilitated in the same fashion pre- and post-stroke. Previous analysis on mice performing the SPRT showed most compensation/abnormality of movement during pronation (advance) and supination (withdraw/release) of reach, but little has been reported on how stroke and rehabilitation impacts the dexterous movements required of a grasp (Farr & Whishaw 2002). Further data collection and analysis are necessary to better understand these processes.

Another pattern revealed by kinematic analysis was the observable reliance on compensation through abnormal movements between groups post-stroke and post-training. In the task-specific group, compensation either remained stagnant or decreased with training; this assumedly indicates that task-specific rehabilitation allowed for functional recovery of the specific task and therefore a decreased need for compensation. On the contrary, the generalized therapy and control groups either increased or plateaued with their compensatory movements. This may be due to the ineffectiveness of generalized therapy (the ability to transfer skilled use among similar tasks) in functional recovery, or it may indicate that the strokes were progressive after primary insult and resulted in increased neural tissue damage leading to worse recovery of function. If this is the case, task-specific rehabilitation may be protective against progressive dysfunction of stroke since success levels were similar among groups regardless of degree of measured abnormality (i.e., compensation). In this case, we would expect to see larger lesions in the generalized and control groups. However, these results are unlikely as training effects on lesion size are rarely cited in literature; lesion sizes typically look similar between trained and untrained animals post-stroke (Allred & Jones, 2004; 2008; Allred et al., 2005; Kerr et al., 2013; 2016). To answer these questions, lesion verification and a replication of the study are necessary.

In conjunction, kinematic and percent success data allowed for a more thorough understanding of task-specific versus generalized rehabilitation. Through kinematic analysis of video recorded reaches, the task-specific group showed less compensation (based on less abnormalities of a reach compared to pre-stroke levels) than the generalized and control groups overall (Figure 6-10). This may indicate that task-specific rehabilitation supports true recovery processes more so than compensation. It is possible the task-specific animals relearned the components of the task and were utilizing the same/similar mechanisms they utilized pre-stoke, therefore requiring less compensation when attempting the task post-stroke/post-training. However, less compensation did not necessarily correlate with higher percent success in the skilled reaching task—the task specific group did not have a significant difference from the other groups in terms of percent success (Figure 5). So, even if less compensation is occurring, the impaired mouse is not any more or less successful than mice that are utilizing compensation. That is not to say this is never true—less compensation may yield better functional recovery over time—but in the current study, there were no observable differences between conditions that did/did not use compensatory movements. However, defining the differences between recovery and compensation (even with kinematic analysis) comes with its own complications and requires more extensive research; misinterpretation occurs often within the recovery/compensation debate (Levin, Kleim, & Wolf, 2009). In studies interested in understanding the effects of true recovery versus compensation, comparing task-specific versus generalized rehabilitation may yield more interesting implications about the two and their effects on functional recovery overall.

Limitations & Future Directions:

There were several limitations to be accounted for within this study that may contribute to or better explain the inconclusive percent success results. To begin, the SPRT is more commonly used in the rat model as opposed to the mouse model; few researchers utilize mice for this skilled reaching task (Farr & Whishaw, 2002). That being said, the student researcher conducting the study had to adjust protocol measures to account for the current subjects—mice—and adapt the task and parameters accordingly. The video analysis utilized in this study is similarly a novel task in mice (Farr & Whishaw, 2002) adapted by the student researcher. The procedures are supported by literature utilizing rats (Miklyaeva & Whishaw, 1996; Allred & Jones, 2004, 2008; Alaverdashvili et al., 2008, 2010), but SPRT and video analysis are ultimately novel tasks in the mouse model.

Due to the time constraints of academic semesters and the extent of resources necessary for this study, lesion verification has not yet been completed. This anatomical analysis will lend the experiment validity by confirming the location and size of ischemic damage and thus ensuring that our conclusions are based on accurate information regarding injury. This analysis is also important in the case that the stroke was progressive and may explain why some mice continued to get slightly worse between post-operative and post-training assessment days. Lesion verification is set to be completed next semester to verify this study’s results.

Again, due to the traditional set up of an academic semester, training periods (pre- and post-operative) were not sufficiently long enough for the mice to fully learn and then relearn the task. In previous literature, researchers have trained animals until they reached a predetermined criterion rather than allowing a set number of days for training. This criterion is often at least 50% success before stroke is induced (Alaverdashvili et al., 2008, 2010, 2013). By training until criterion is met instead of training for a specific amount of days, this allows the animals to fully learn the task and allow for more comparable rehabilitation to human rehabilitation. It is predicted with elongated training periods, pre-operative levels of success can be achieved post-operatively with task-specific rehabilitation (Langhorne et al., 2011; Khallafa, Ameerb, Fayedc, 2017). We used a generous criterion of 40% success in the current study to accommodate the time constraints that we faced. By increasing amount of training, it is also possible that more of a deviation between the training groups and the control would emerge when observing percent success, leading to statistically significant differences. Since it has been seen in previous literature that rehabilitative strategies lead to better functional outcome, it is fair to assume the same would occur in this case (Alaverdashvili 2008, 2010, 2013). Additionally, this enhancement of the study may allow a better understanding of the effectiveness of generalized rehabilitation versus task-specific rehabilitation.

Our findings regarding the comparison between compensation and true recovery based on the rehabilitative task used raises the question: if both lead to functional recovery, why does it matter how functional outcome is achieved? This study raises further questions regarding if true recovery is more beneficial or generalizable than compensation. Does task specific training activate different neural connections (true recovery) than generalized therapy (compensation)? If so, which is more effective, or does it really matter if there is a mutual regaining of tasks in either rehabilitative model? These questions are easily transferrable to the human model and so, we hope they can be addressed through research to further the betterment of post-stroke rehabilitation in humans.

Overall, this study tested the validity of the SPRT and also compared task-specific versus generalized rehabilitative strategies. Though some data was inconclusive, this study advanced the mouse model by utilizing the SPRT, video analysis, and better understanding the mechanisms behind task-specific rehabilitation. Our results suggest that task specificity leads to less use of compensation and therefore may promote true recovery processes more so than generalized rehabilitation. However, less compensation did not necessarily correlate with better functional recovery, therefore suggesting that generalized rehabilitation may be as effective in function recovery as task-specific rehabilitation if training periods were prolonged. This also suggests that if success rates are similar between tasks (using compensation or not), it may not matter how the success is achieved as long as functional outcome is enhanced. In a replication study with longer training periods, larger groups, and completed lesion verification, SPRT in the mouse model can gain validity and more could be understood about different rehabilitative strategies. Further research on task specific versus generalized rehabilitative strategies can lead literature to further progress in the direction of bettering post-stroke rehabilitation and functional recovery in humans.

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Table 1

Percent Success Means and SEMs

Assessment Day	Group	*M*	*SEM*
Pre-Op	SPRT	56.667	± 0.077
	PMRT	57.143	± 0.047
	Control	54.660	± 0.072
Post-Op	SPRT	31.117	± 0.088
	PMRT	24.771	± 0.260
	Control	30.680	± 0.102
Post-Training	SPRT	41.117	± 0.072
	PMRT	30.486	± 0.078
	Control	25.340	± 0.043

A univariate ANOVA revealed no statistically significant differences between groups by assessment day.

Table 2

Statistical Analysis of Kinematic Video Analysis

	Main Effects		
Behavior	Assessment Day *F*(2,15)	Group *F*(2,15)	Interaction *F*(4,30)
Aim	*F* = 7.245 **	*F* = 0.909	*F* = 1.564
Advance	*F* = 13.118 ***	*F* = 1.655	*F* = 1.570
Grasp	*F* = 81.454 ***	*F* = 3.469 +	*F* = 3.272 *
Withdraw	*F* = 453.873 ***	*F* = 1.711	*F* =1.805
Release	*F* = 262.617 ***	*F* = 1.947	*F* = 2.338 +

*** $p<0.001$** $p<0.005$ *$p<0.05$ +$p<0.1$

A repeated measures ANOVA was run for each component of a reach to analyze main effects by assessment day and group, and interactions between assessment day and group.

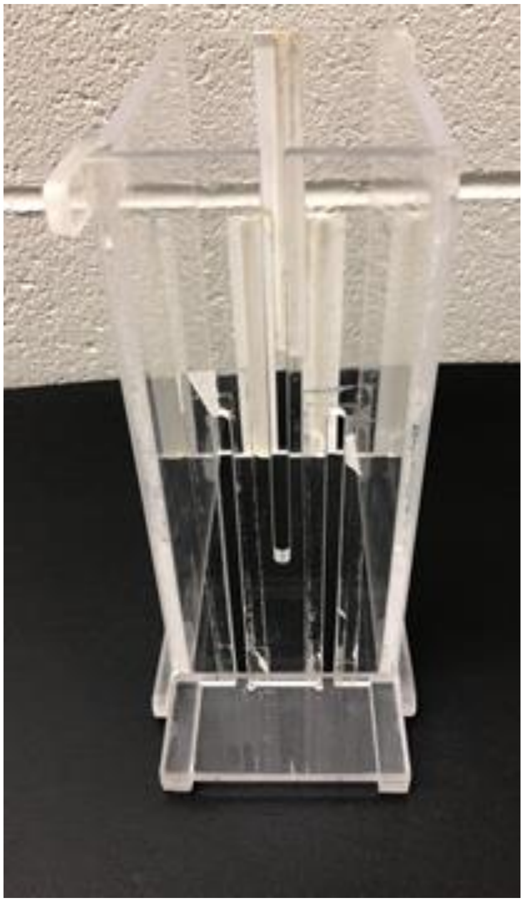

Figure 1. Reaching chamber. Mice were individually placed in the Plexiglas chamber for shaping, pre- and post-operative training, and assessment.

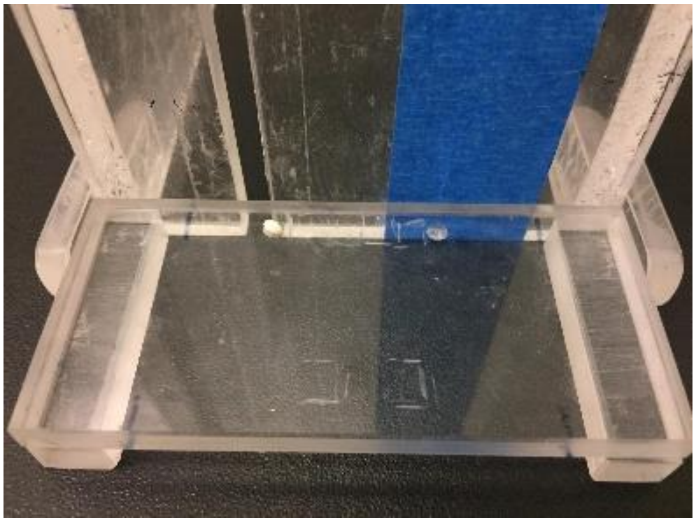

Figure 2. Food platform. Platform was used for all SPRT training and assessment.

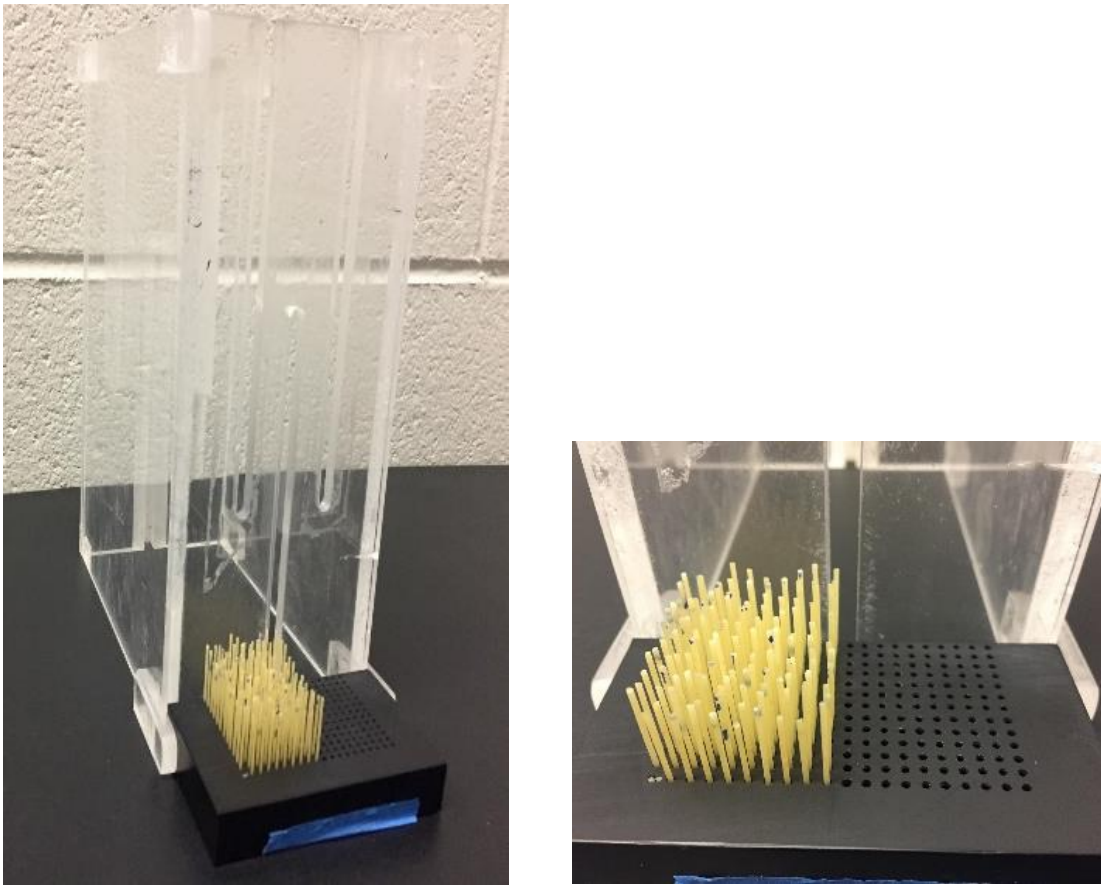

Figure 3. Pasta matrix. Mice in the generalized training group were individually placed in the Plexiglas chamber for post-operative training of the Pasta Matrix Reaching Task.

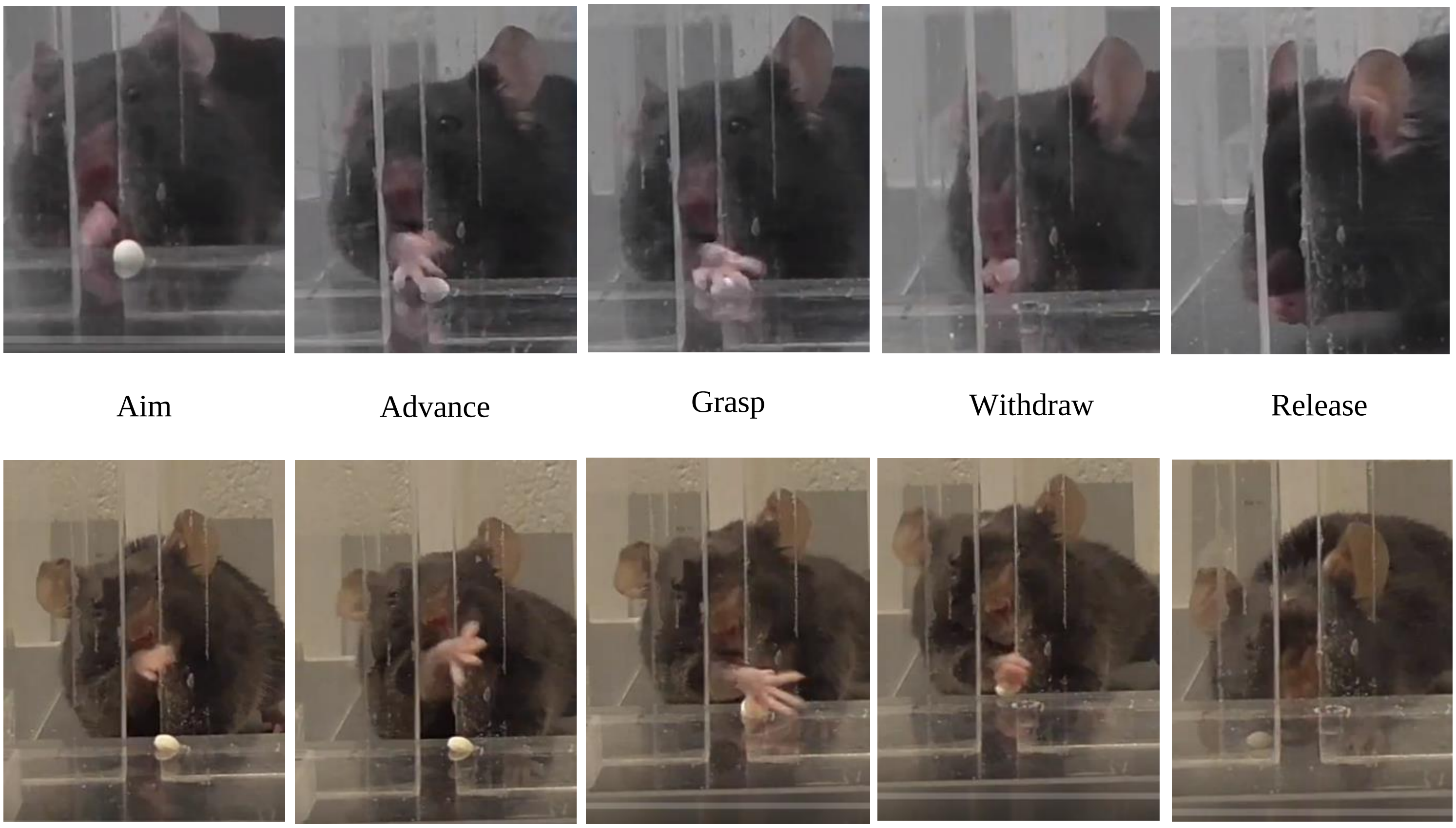

Figure 4. Kinematic analysis. Each movement of a skilled reach was video recorded and scored on a 3-point scale. The top row were normal movements recorded during pre-op assessments, and the bottom row were abnormal movements recorded during post-op assessment.

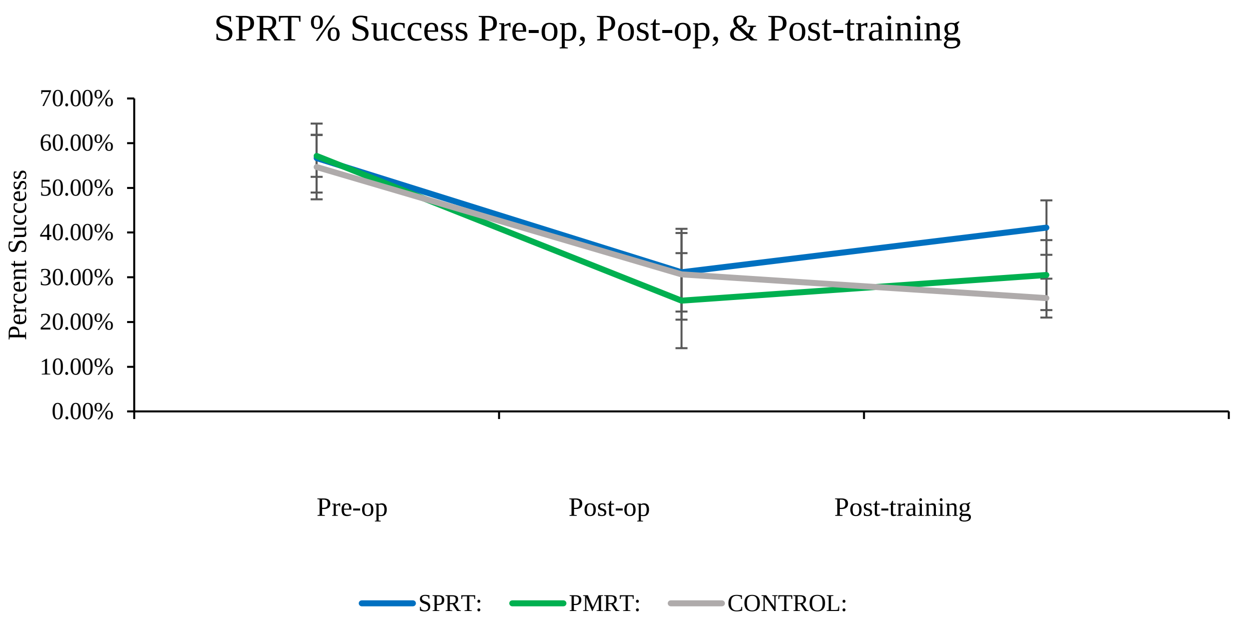

Figure 5. Percent success. Percent Success was measured for each group at three different assessment points (Pre-op, Post-op, Post-training).

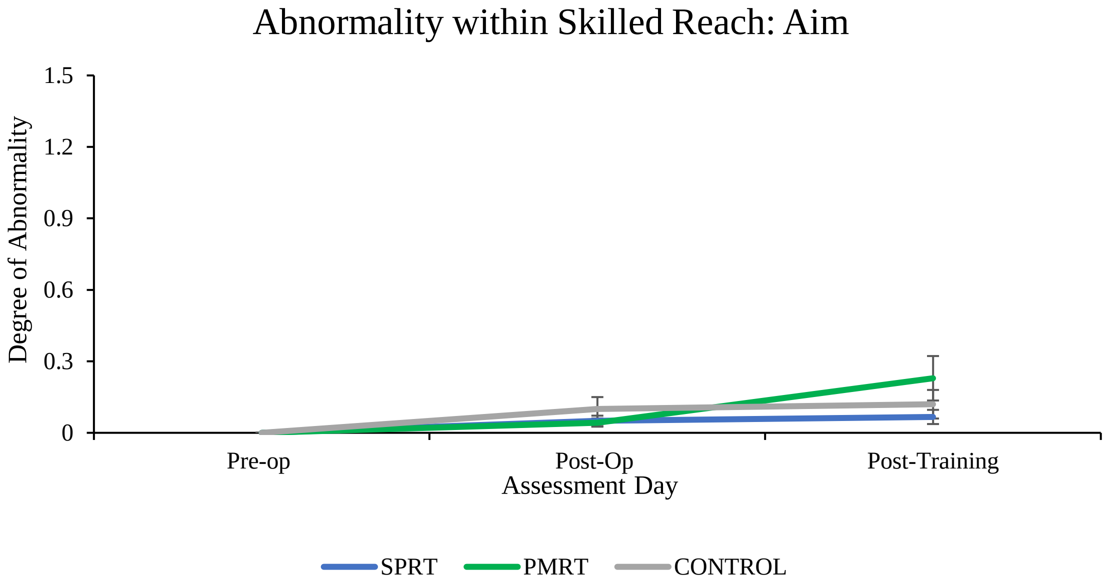

Figure 6. Kinematic analysis of aim. A repeated measures ANOVA revealed a main effect of assessment day, but no other significant differences.

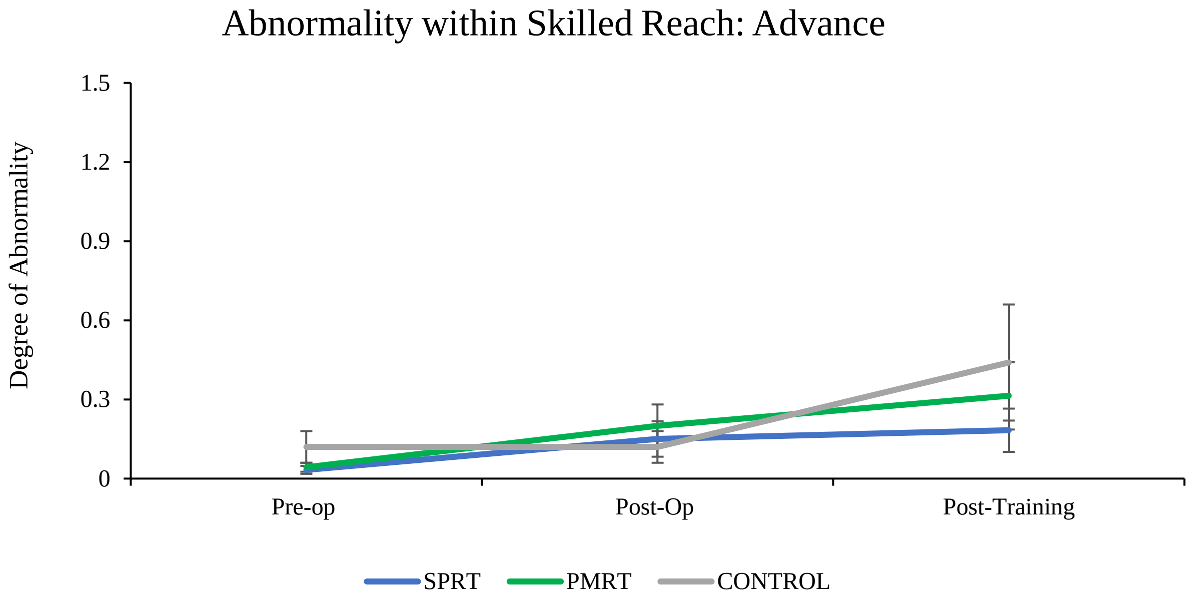

Figure 7. Kinematic analysis of advance. A repeated measures ANOVA revealed variability in abnormality between groups, but no significant differences aside from assessment day.

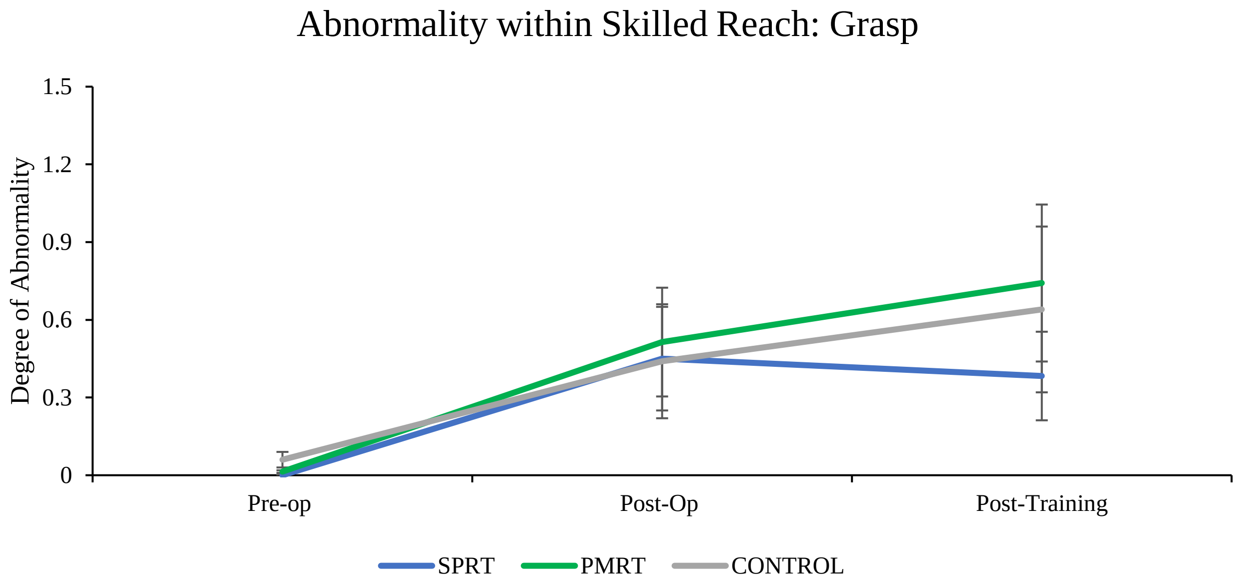

Figure 8. Kinematic analysis of grasp. A repeated measures ANOVA revealed main effects of assessment day and group and an interaction between assessment day and group.

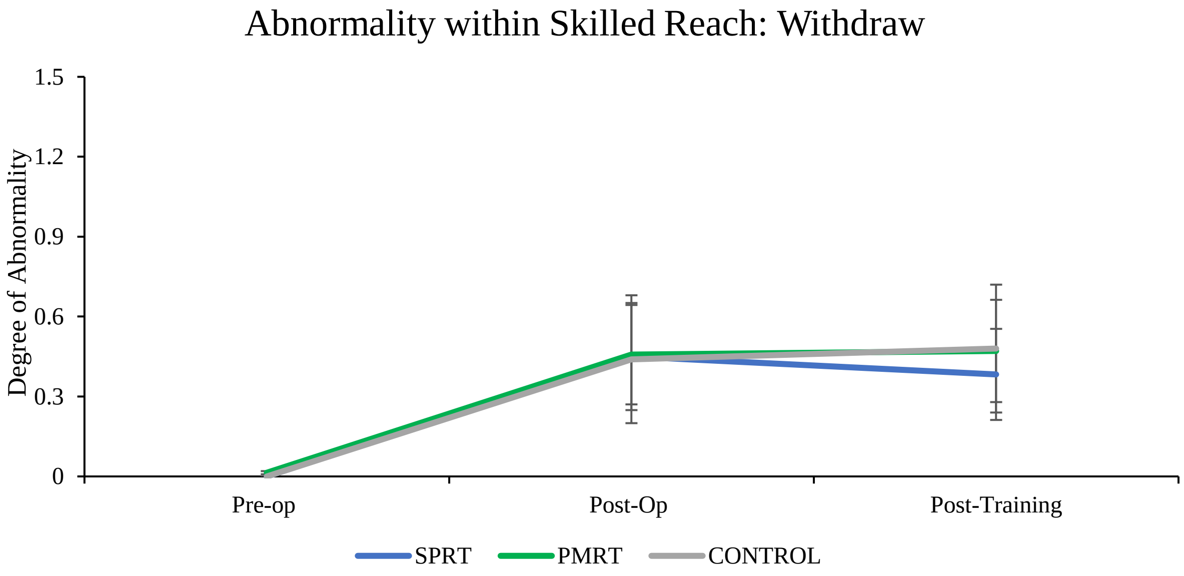

Figure 9. Kinematic analysis of withdraw. A repeated measures ANOVA revealed a main effect by day, but no other significant differences.

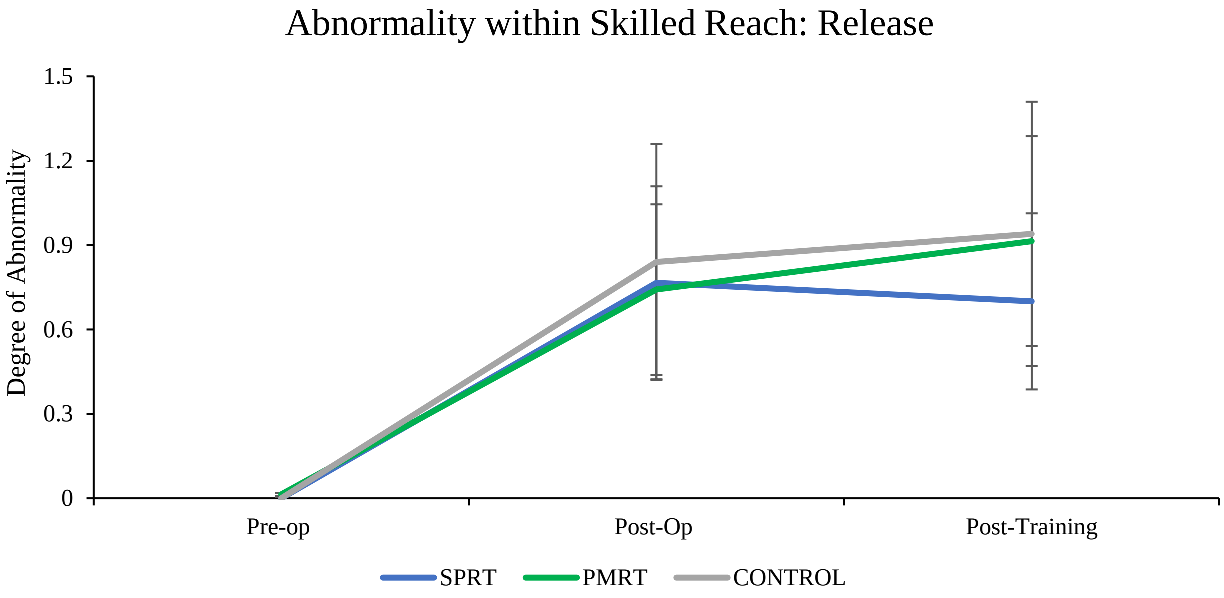

Figure 10. Kinematic analysis of release. A repeated measures ANOVA revealed a main effect by assessment day and an interaction approaching significance between group and day.