Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Special Article - Neurorehabilitation

Maintenance of Hand Motor Recovery Following Action Observation Treatment for Stroke

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Received: May 31, 2017; **Accepted:** June 26, 2017; **Published:** July 06, 2017

Abstract

Background: Current approaches to stroke rehabilitation can be effective at conferring functional gains; and yet these gains are commonly lost once therapy has ended. It is therefore imperative to develop rehabilitative methods that foster the maintenance of functional gains over the long-term. We propose that shifting emphasis away from behavioral compensation and toward remediation could lead to significant advances in maintenance of therapeutic gains. Whereas it has been shown that Action Observation Therapy (AOT) is effective at improving motor functioning following stroke, the present study tests the hypothesis that AOT can improve function and preserve functional gains for at least six months following therapy.

Methods: Structural and resting functional MRI scans and measures of hand motor function were obtained in 21individuals with chronic stroke prior to, immediately following, and six months to one year after a one month course of either AOT or a control therapy (neuro developmental therapy; NDT).

Results: AOT resulted in significant gains in motor function immediately after therapy and six months to one year later. Modest gains were seen following NDT at both time points. Individuals receiving AOT performed significantly better than those receiving NDT on the Nine Hole Peg Test at maintenance. Importantly, maintenance of gains with AOT was related to baseline stability of resting functional connectivity, unlike the NDT group.

Conclusion: This study suggests that AOT, but not a standard physical therapy approach, may remediate neural networks critical for motor function after stroke, and that these gains are maintained over the long term.

Keywords: Mirror neuron system; Stroke rehabilitation; Network stability; Functional connectivity

Introduction

Stroke remains a major source of disability in the United States; with approximately 6.5 million individuals living with long-term impairments [1]. Following initial hospitalization and stabilization; stroke survivors usually undergo rehabilitative physical therapy with an emphasis on recovery of Activities of Daily Living (ADLs). Neuro Developmental Therapy (NDT); for example; is a widely used treatment; and has been shown to be as effective as other therapies [2]. Although functional gains are often seen initially; it is all too common for the stroke survivor to stagnate or even regress following the completion of such therapy [3]. Maintenance of gains following rehabilitative therapy is a crucial but often an unsuccessful component of stroke care. It is therefore imperative to develop rehabilitative therapies that maximize functional gains; returning the individual to self-sufficiency as quickly as possible; while at the same time maintaining these gains over the long term.

Currently; improved function may occur during the course of standard therapy; only to be lost upon completion. Physical therapy for upper extremity weakness generally focuses on training an individual to compensate for weakness by shifting functionality to remaining motor effectors; typically through some degree of trunk rotation/displacement; scapular elevation; shoulder abduction; and/or internal rotation [4]. While this may expedite improvement in ADLs; it has limitations for long-term maintenance. The required motor adaptations confer a risk of developing new; less natural motor patterns that may lead to decreased range of motion; pain; and learned disuse [4]. Furthermore; following such therapy; stroke survivors often have limited access to further therapy; partly due to the high cost of providers [5] and of specialized therapeutic equipment [6].

Most contemporary physical therapy does not address the underlying neurophysiologic changes occurring in the brain following stroke; and thus has only indirect and unfocused effects on development of sustainable neuronal substrates. One effort aimed at remediation is Constraint Induced Motor Therapy (CIMT). In CIMT; the unaffected arm is intermittently restrained to encourage greater use of the affected arm; leading to improvement in function following stroke. However; these gains appear to be compensatory in nature [7] and arm restraint is often perceived as unpleasant for the stroke survivor [8]; thus complicating the potential for long term gains. Indeed; accumulating evidence suggests that CIMT is not superior to standard therapy in providing long term functional gains [9,10]. Electrical stimulation therapies aim to improve motor function by influencing neuronal activity directly [11]. Although some benefits

Citation: Riley JD, Falcon MI, Small SL, Collins K, Chen EE, Buccino G, et al. Maintenance of Hand Motor Recovery Following Action Observation Treatment for Stroke. Austin J Clin Neurol 2017; 4(4): 1114.

Table 1: Subject demographics and stroke characteristics.

Subject	Age	Gender	Handedness	Affected Hemisphere	Affected Hand	Location of stroke	Volume of stroke (mm^3)
1	53	F	Right	Left	D	Cort/subcort	21650.8
2	59	F	Right	Left	D	Subcort	11029.3
3	54	F	Right	Left	D	Subcort	8713.1
4	63	F	Right	Right	ND	Subcort	10964.6
5	41	F	Right	Right	ND	Cort	22495
6	54	F	Right	Left	D	Cort/subcort	49078
7	57	M	Right	Left	D	Cort/subcort	17411
8	57	M	Right	Left	D	Cort/subcort	38703
9	54	F	Right	Left	D	Subcort	27677
10	50	M	Right	Right	ND	Subcort	3570
11	68	M	Right	Left	D	Subcort	1988.3
12	56	F	Right	Left	D	Subcort	6239.7
13	46	M	Right	Left	D	Subcort	325
14	56	F	Left	Right	D	Cort/subcort	60669
15	72	F	Right	Left	D	Cort	39295.3
16	37	M	Right	Left	D	Cort/subcort	83406.2
17	62	M	Right	Left	D	Subcort	22154.8
18	61	M	Right	Left	D	Subcort	978
19	74	M	Right	Left	D	Cort/subcort	63642
20	67	F	Right	Right	ND	Subcort	588
21	74	F	Right	Left	D	Cort/subcort	44892

D= dominant, ND= non-dominant, Cort= cortical, Subcort= subcortical

appear to outlast the stimulation period [12]; the degree to which they are maintained is unclear [13]. Cellular based strategies (e.g., stem cells) offer the potential for true neuronal remediation [14]; but these require further testing before their immediate and long term efficacy will be known. Given the extensive study of emerging therapies such as these; it is striking that their effect on long-term maintenance has not received much attention.

Action Observation Treatment (AOT) is an emerging therapeutic technique that has the potential to address many of these shortcomings [15,16]. At a neuronal network level; AOT aims to the extent possible; to stimulate the brain network involved in observation and imitation of motor actions; and by doing so; to re-establish motor functioning targeting the pre-stroke state via the repair or reorganization of neural circuitry. The rationale for this approach comes from neurophysiological data from macaque [17]; in which neurons in the posterior parietal lobe and inferior premotor cortex process perceived motor actions. This “mirror neuron system” is increasingly understood to play a role in action observation and imitation in humans [18,19]. We hypothesize that using AOT to harness this motor circuit for stroke rehabilitation represents a promising remediative approach; and has particular promise for both immediate therapeutic benefits and maintenance of these gains over the long term. Indeed; previous studies have supported the effectiveness of AOT in functional recovery following stroke [20-22]. In this work; we seek to expand upon these findings; comparing AOT to a widely used rehabilitative treatment; furthermore; we include multiple neuroimaging techniques in order to gain insight into the mechanism underlying functional gains associated with AOT.

Resting State Functional Connectivity (rsFC) provides insight into the baseline coupling between brain regions; and thus the organization of neural networks of an individual [23]. Previous studies have provided evidence that rsFC relates to both underlying neural activity as well as the structural connectivity of the brain [24]. To date; rsFC has been predominantly quantified using an average measure over the course of a scan; but such connectivity is in fact not stable; but rather tends to vary over time [25]. One way to characterize such dynamic rsFC is by assessing the stability and variance of interactions between regions over time. For example; Shen and colleagues [26] found that homotopic functional connectivity; facilitated by direct anatomical connections; was more stable over time when compared to other types of connections. Furthermore; the degree of variability of brain signal has been shown to be related to cognitive functioning in both healthy [27] and damaged [28] brains. Investigating the stability and variance of functional connectivity can therefore provide critical insight into the mechanisms underlying changes in the brain.

Objective

We hypothesize training motor observation and imitation in ecological patient-specific tasks via AOT will depend on the stability of brain networks in order to perform motor tasks following ischemic stroke. We further expect a direct effect of this approach on the long term; with an extended maintenance phase following therapy.

Materials and Methods

Twenty-one volunteers (age 57.9 ± 9.7 years; mean ± standard deviation) with chronic stroke were recruited for this study. Individuals were screened using the mini-mental state exam (MMSE) [29]; the short version of the Token Test [30]; the Edinburgh handedness inventory [31] and Hamilton depression inventory [32]. Inclusion criteria included age ≥ 18 years; single stroke by clinical history; lesion in the middle cerebral artery distribution; stroke onset ≥ 6 months earlier; moderate to severe hand impairment (50 ≥ Fugl-Meyer Score ≥ 20); normal state of consciousness; normal corrected visual and auditory acuity; language comprehension (short Token test ≥ 26); and upper extremity protective responses. Exclusion criteria included history of significant central neurological illness other than stroke; history of significant arm injury with residual functional impairment; history of spinal cord injury; cognitive impairment (Mini Mental Status Exam < 23); untreated depression (Center for Epidemiologic Studies Depression scale ≥ 16; visual neglect; significant carotid stenosis; metallic implants; pregnancy; and severe spasticity in affected arm (Ashworth Scale ≥ 3). Patient demographics are in Table 1. All participants provided informed consent prior to inclusion in the study; and all procedures were approved by the Institutional Review Boards of the University of Chicago and the University of California; Irvine.

Randomization

Participants were assigned to treatment groups using blocked randomization; stratified primarily by baseline severity of hand motor dysfunction; and secondarily by age and education. The first half of participants was randomly assigned to AOT or NDT. Subsequent participants were assigned to one or the other group based on a match in severity of weakness (determined by time on the nine hole peg test; NHPT); and then by age and education.

Therapeutic Interventions

Both treatment groups received 1 hours - 1.5 hours of therapy per day for four weeks (week days). Individuals with weakness in the dominant hand performed unimanual motor tasks; whereas those with weakness in the non-dominant hand performed bimanual tasks.

Action Observation Treatment: AOT was performed as previously described [20]. First; a specific; goal-oriented ecological action was presented on a television screen for three minutes; and the patient was instructed to observe the action with the intention of imitating it. The actions involved fine-skilled manipulation of everyday objects. The patient subsequently executed the observed movements for three minutes. Subsequent videos showed similar actions with additional motor elements of increasing difficulty present (e.g., first reaching to grab a telephone; then reaching to grab it and holding it next to the ear). Following the completion of several such incremental stages of motor imitation; the entire sequence was repeated from the beginning. By showing increasingly complex actions; imitation difficulty progressively increased throughout the month of therapy.

Control (NDT) Intervention: Individuals assigned to the control therapy received standard NDT administered by a licensed Physical Therapist who was both an APTA certified Neurological Clinical Specialist and certified in NDT (KC). As with AOT; NDT involved performance of similar skilled motor tasks and gradual incremental training. These sessions incorporated tasks commonly used in NDT (40-50 minutes) as well as tasks used in the AOT treatment arm (20-30 minutes). NDT was provided to each participant based on individual arm ability; and therapy progressed as needed. In the NDT therapy; the therapist demonstrated each task to the participant; who then practiced it for 3 minutes. Unlike in the AOT arm; which incorporated no verbal feedback; patients in the NDT arm received verbal feedback on the quality of whole arm and hand movements; and strategies to compensate for errors. In NDT; the focus of therapy was on the quality of movements rather than the goal. Similarities and differences between AOT and NDT are listed in Table 2.

Table 2: Similarities and differences between AOT and NDT.

	Action Observation Therapy	Neuro developmental Therapy
Similarity	Goal Oriented Movements	Goal Oriented Movements
	Incremental	Incremental
	Intense training	Intense training
	Uni/Bimanual	Uni/Bimanual
Difference	No feedback	Feedback
	Visual	Verbal
	Whole Movements	Fractionated Movements
	Re-establishing movements	Re-learning movements
	Fine-skilled hand movements	Gross arm-hand movement

Outcome measures

Performance measures were collected at three time points: (1) pre-treatment; (2) post-treatment; and (3) six months to one year post-treatment. The primary outcome measure was the difference in score on the Functional Ability Scale of the Wolf Motor Function Test (WMFT) [33]; developed specifically to assess motor function of the upper limb after stroke. Secondary measures included brain network physiology assessed by functional MRI (fMRI) and additional behavioral measures; including the Nine hole peg test [34]; and the Fugl-Meyer upper arm test [35]. Assessments were performed by a licensed physical therapist blinded to treatment group.

Imaging

Image Acquisition: We collected high-resolution T1-weighted MPRAGE scans (3T Philips; SENSE head coil) with FOV= 250 x 250; resolution = 1 mm x 1 mm x 0.6 mm; SENSE reduction factor= 1.5; TR/TE= 7.4/3.4 ms; and whole brain BOLD fMRI images (resting state) using gradient echo single-shot echo-planar imaging (EPI); with FOV= 230 mm x 230 mm; Flip angle 70 degrees; TR= 2 sec; TE= 20 ms; participants are instructed to relax; but avoid falling asleep.

Functional Image Pre-processing: Data processing and analysis were performed blind to treatment group. Resting fMRI preprocessing was performed using the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk) as follows: (1) Removal of the first five scans; (2) slice timing correction; (3) motion correction; (4) brain extraction; (5) registration to the anatomical volume; (6) removal of voxel-wise temporal mean; and (7) removal of nuisance variables including six motion parameters; global white matter and CSF signals; and temporal band pass filtering at 0.01 Hz - 0.1 Hz (2^{nd} order butter worth).

Structural Analysis: To permit the use of standardized brain anatomical atlases despite the presence of large brain lesions; we use dour virtual brain transplantation (VBT) approach [36,37]. VBT transplants the anatomical data from the non-lesioned hemisphere to the lesioned hemisphere; makes a number of corrections for ipsilesional volume loss and contralesional shifting; and provides anatomical landmarks for standard alignment and inflation algorithms developed for healthy individuals. We then used the Free Surfer software [38] to parcellate the brain (2005 Destrieuxatlas). Using SUMA [39]; we imported the 2D surface representations back into the 3D volume in AFNI.

Functional imaging measures: Functional connectivity at rest: Network stability. Stability of resting functional connectivity was determined using a sliding window approach; in which the resting fMRI time series from each brain region were first divided into windows with a length of 28 seconds and an overlap (i.e., lag) of 2 seconds across windows. For each window of time series; pairwise Pearson correlation coefficients between each pair of brain regions were then determined. These correlation coefficients were then cross-correlated with themselves to find normalized autocorrelation coefficients. These values were averaged across all lags to produce the temporal stability of each pairwise functional connection. In order to compare between groups and test for relationships with measures of motor function; the mean and standard deviation of the temporal stability measures for all regions was determined for each subject [26,40].

Statistics

Measures were compared between the two stroke groups at all time points using a Wilcoxon rank sum test. Pre-therapy behavioral measures were compared between the two stroke groups using a Mann-Whitney test. Behavioral measures obtained post-therapy and at maintenance were compared to pre-therapy measures using a Wilcoxon signed-rank test. Comparisons between resting state fMRI stability measures and changes in motor function measures from baseline to immediately post-therapy and at the maintenance stage were done using linear regression.

Results

Demographics

The AOT group (N = 11; age 55.4 ± 7.4; 9 female) and the NDT group (N = 10; age 60.6 ± 11.9; 4 female) did not differ in any age or other demographic factor (Table 2); but did differ in gender (AOT 81% female versus NDT 40% female).

Motor function outcomes

Pre-therapy: The two groups were not significantly different with respect to functional ability prior to therapy for all measures (all $p > 0.05$).

1. AOT group: When examining the within-group change in motor function as a result of therapy (e.g., pre-therapy to post-therapy); individuals receiving AOT showed a significant level of improvement in the WMFT ($p = 0.003$). At the maintenance phase; improvements persisted for the WMFT ($p = 0.003$).

Secondary analyses: There was a significant improvement in the nine-hole peg test ($p = 0.004$) at the maintenance stage.

2. NDT group: Individuals receiving NDT showed modest differences in the WMFT from pre-therapy to post-therapy ($p = 0.01$) and from pre-therapy to maintenance ($p = 0.03$); these differences; however; do not survive correction for multiple comparisons.

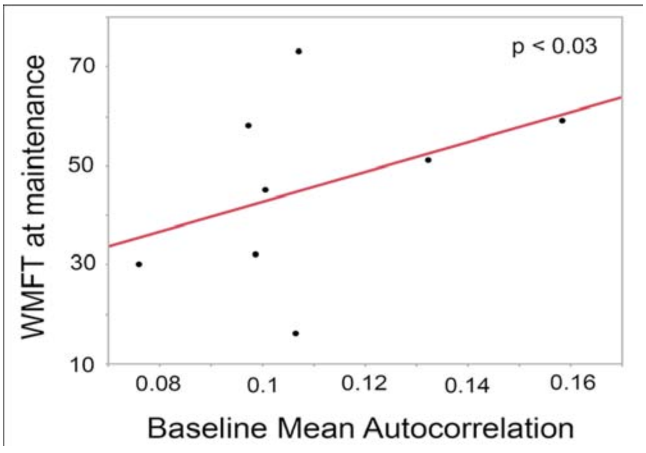

Figure 1: Scatter plot showing the significant correlation between baseline resting state fMRI mean autocorrelation values and motor functioning in individuals receiving AOT. In this group, but not NDT, there was a significant correlation between baseline mean autocorrelation values and the Wolf Motor Function Test (WMFT) at the maintenance stage ($p < 0.03$).

Secondary analyses: Differences were seen from pre-therapy to post-therapy in FM ($p = 0.02$); and pre-therapy to post-therapy in FM ($p = 0.02$) and MAL-AOU ($p = 0.02$); again; these differences do not survive correction for multiple comparisons.

3. AOT compared to NDT: When comparing individuals receiving AOT to those receiving NDT therapy immediately following therapy; there were no significant differences between groups for the WMFT.

Secondary analyses: At the maintenance stage; individuals receiving AOT performed significantly better on the nine-hole peg test compared to those in the NDT group ($p < 0.009$).

Brain imaging

Relation between stability of functional connectivity and behavioral measures: To examine the ability of baseline network stability to predict response to rehabilitative treatment after stroke; we tested for correlations between pre-therapy rsFC stability and motor function immediately following treatment and at the maintenance stage. There was no significant relationship between mean or standard deviation of rsFC autocorrelation values and motor function immediately post-therapy; both for individuals receiving AOT and those receiving NDT.

However, at the maintenance stage; individuals receiving AOT had a significant positive correlation between the mean autocorrelation values and the WMFT ($p < 0.03$) (Figure 1); no significant correlation between these measures was found for individuals receiving NDT.

We next examined the standard deviation values of the autocorrelations in order to assess the impact of variance of rsFC stability and motor functioning. For those receiving NDT; the standard deviation of pre-therapy rsFC autocorrelations was positively correlated with WMFT ($p < 0.03$) (Figure 2). For those receiving AOT; pre-therapy correlations were also found between rsFC variance measures and motor function. Specifically, the standard

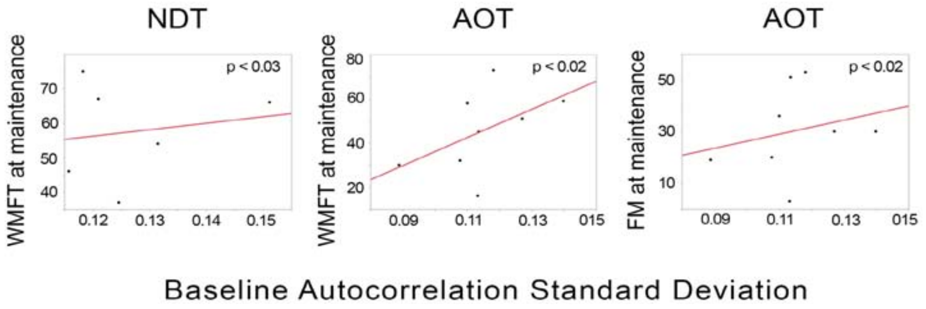

Figure 2: Scatter plots showing the significant correlations between the baseline resting state fMRI standard deviation of autocorrelation values and motor functioning at the maintenance stage. Individuals receiving NDT had a significant correlation between standard deviation values and Wolf Motor Function Test (WMFT) ($p < 0.03$). Individuals receiving AOT had a significant correlation between standard deviation values and WMFT ($p < 0.02$) and Fugl-Meyer (FM) scores ($p < 0.02$).

deviation of autocorrelation values was positively correlated with WMFT ($p < 0.02$). Secondary analyses found a positive correlation of the pre-therapy standard deviation of rsFC autocorrelations with Fugl-Meyer ($p < 0.02$) at the maintenance stage for those receiving AOT.

Notably, there was no significant difference of stability of functional connectivity between individuals receiving AOT and those receiving NDT; this was true prior to therapy (mean: AOT= 0.1155 ± 0.0088 (mean ± standard error); NDT= 0.1299 ± 0.0098; standard deviation: AOT= 0.1182 ± 0.0047; NDT= 0.1291 ± 0.0053); immediately post-therapy (mean: AOT= 0.1366 ± 0.0083; NDT= 0.1307 ± 0.0088; standard deviation: AOT= 0.1299 ± 0.0042; NDT= 0.1293 ± 0.0044); and at maintenance (mean: AOT= 0.1132 ± 0.0079; NDT= 0.1192 ± 0.0085; standard deviation: AOT= 0.1185 ± 0.0078; NDT= 0.1217 ± 0.0051). Furthermore, there were no significant differences in stability metrics with respect to change from baseline; both for change at post-therapy (mean: AOT= 0.0191 ± 0.009 (mean ± standard error); NDT= 0.0007 ± 0.01; standard deviation: AOT= 0.0109 ± 0.005; NDT= 0.0002 ± 0.005) and at maintenance (mean: AOT= 0.001 ± 0.009; NDT= -0.008 ± 0.095; standard deviation: AOT= 0.0018 ± 0.005; NDT= -0.004 ± 0.006).

Discussion

The present study shows that: 1) AOT confers functional gains in chronic stroke; both immediately following therapy and over the long term; and 2) baseline (post-stroke) stability of functional connectivity correlates with long-term response to AOT but not NDT.

AOT confers functional gains in chronic stroke that are maintained over the longterm

This study expands upon our preliminary findings [20]; using a standard therapy control group and including measurements at the maintenance stage; to provide further evidence that AOT may be efficacious in improving motor function following stroke. It is also complemented by studies showing observation/practice techniques leading to improvements in motor learning in healthy individuals [41]; adult stroke [21]; Parkinson's disease [42] and children with cerebral palsy [43]. AOT is also associated with increased force generated and increased excitability of the motor cortex [44]; suggesting that AOT leads to a higher level of brain activity than motor imagery or physical training [45].

AOT was developed following discovery of the mirror neuron system; as a biologically-based method that combines observation of object-manipulation with subsequent imitation of the same goal-oriented action. Although the mechanistic underpinnings are still unclear; one hypothesis implicates the neurophysiological response to experience mediated by motor imitation; i.e. repetitive actions triggered by visual input leading to alterations in neuronal activity [15,46]. In this context, it is possible to consider activities of daily living as well-rehearsed motor activities; thus categorizing people as "experts" at completing these tasks [47]. Therefore; it has been suggested that the brain maintains very specific representations of these activities [47]; and thus the associated network should be particularly strong. The goal of AOT therefore is to activate the mirror neuron networks associated with these ADLs; thus priming them for increased contribution to subsequent motor activity.

Significantly, the current findings indicate maintenance of AOT-induced gains over the longterm. It is all too common for gains made in a standard acute rehabilitation program to be lost in the long term. Indeed, Paolucci and colleagues found nearly 40% of patients experience a decline in mobility status at the 1-year follow-up [3]. In addition; long-term gains can vary greatly between individuals. These results indicate that AOT may be particularly effective in facilitating long-term maintenance of gains; even within a heterogeneous population.

Interestingly, this study found that individuals receiving AOT showed significantly better scores than the NDT group at maintenance on the nine-hole peg test (NHPT); The NHPT is a measure of fine manual dexterity [48]; which is a major component of the movements AOT aims to impact. Indeed; AOT is specifically designed to target skilled; fine motor hand movements (i.e. finger individuation); as it emphasizes manipulation of common objects with finger and wrist movements. In contrast; the other measures used in this study; (Fugl-Meyer and WMFT); include hand dexterity as one of several measures of upper extremity function; including shoulder; elbow; forearm; and wrist [49]. These measures thus put greater reliance on proximal/gross motor movements; decreasing the likeliness that differences will be seen between the two treatment groups. The NHPT is a valid; reliable measure of upper extremity functions following stroke [50]; and has a high degree of correlation with other measures of hand function [51]. Notably, differences in NHPT scores were seen at the maintenance phase; thus supporting our hypothesis that AOT is particularly effective at preventing regression of gains in the long-term.

Although AOT conferred greater motor benefit than NDT on several measures; it is interesting that only the maintenance-phase NHPT was found to be significantly greater in individuals receiving AOT than those receiving NDT. One of the complicating issues in stroke research is the large variance of functional ability commonly seen in study populations [52]; and this was also true in the current study (FM range: 3-52; WMFT FA range: 16-74). Such variance makes it particularly difficult to find significant differences; unless the study is restricted to include only a narrow range of baseline functions. Therefore, while our decision not to stratify subjects by functional ability serves as a more representative sample for a wide range of stroke outcomes; this high variance may explain the lack of significant differences between the two groups on many of the reported measures. However, the fact that differences were still found in such a varied cohort may in fact attest to the effectiveness of AOT to facilitate long-term functional gains.

There are several reasons why AOT may be more effective at maintaining functional gains over the long term (see Small, et al. 2013 for a review [15]). In particular; it has the potential to facilitate the neural substrate required for functional recovery. While the exact mechanism is still unknown; AOT may; through the recruitment of mirror neurons; facilitate the activation of neural circuitry used for everyday movements. This theory is based on the process of indirect remediation [53]; in which the mirror neuron circuitry is recruited via observation of activations (as evidenced by lower motor evoked potential thresholds); thus providing an increased role in subsequent motor output. In addition; although AOT and NDT are alike in that they both involve gradual and incremental training using identical; skilled; uni or bimanual tasks; AOT focuses on a specific goal (e.g. pick up the orange) without trainer intervention regarding the movements; whereas NDT emphasizes the movements used (e.g. flex the wrist to pick things up) as guided by the trainer. In this context, AOT could serve to facilitate neural networks that underlie these movements; whereas NDT might rely on the development of compensatory strategies to accomplish the motor tasks.

Metrics of resting functional MRI stability predicts response to AOT

The current study found that; for individuals receiving AOT; baseline/pre-therapy rsFC stability was significantly related to degree of long-term motor recovery. Specifically, individuals with a greater amount of overall stability between and among brain regions prior to therapy showed greater functional improvement at maintenance following AOT (but not NDT). Given that those receiving AOT also experienced greater functional improvement than those receiving NDT; it is reasonable to speculate that this stability is; at least in part; an important mechanism underlying AOT. Stability of rsFC has been previously associated with connectivity between homotopic regions of the brain [26]; and inter hemipsheric functional connectivity is associated with post-stroke functioning [54]. In this study, the positive correlation between baseline mean stability and long-term motor measures suggests that AOT more effectively capitalizes on the stability of functional interactions between homotopic brain regions. In contrast, no such relationship was found for those receiving NDT; suggesting that NDT receives less benefit from the stability of interactions among these brain regions.

We further examined the standard deviation of stability to gain insight into the variance throughout the system. Individuals with a greater variance of temporal rsFC stability among all regions of the brain showed greater sustained response to AOT; but not to NDT. Variance of brain signals is increasingly understood to contribute to more effective processing by the brain; in that it represents a system that facilitates a greater exploration of possible interactions [55]. For example, fMRI signal variability is decreased with aging and is associated with declines in cognitive performance with age [56]. The underlying structural connectivity acts as somewhat of a constraint on functional connectivity [40,57]; and regional variations in rsFC dynamics exist [58]. Therefore it may be that AOT is more effective at harnessing the broad range of variability in rsFC; including the high stability of homotopic brain regions as well as the high variability (low stability) among other brain regions; despite a stable structural connectivity; than NDT.

These findings thus provide empiric evidence for the mechanism of functional gains following AOT. Given that there was no significant change in stability measures following either therapy; AOT does not appear to rely on new patterns of functional connectivity to produce improved motor outcomes. It may be that AOT facilitates the recruitment of previously developed neural architectures to produce maintenance of functional gains. Interestingly, this is in accordance with the intended purpose of AOT; as described above; AOT is specifically designed to influence mirror neurons with the intent of facilitating existing functional interactions that were lost to stroke; essentially reprising stroke-affected network connectivity. Conventional/standard rehabilitative therapies; such as NDT; aim to develop new; compensatory strategies; thus requiring the emergence of new functional connectivity. In sum; this differential response to functional stability may be; at least in part; due the ability of AOT to capitalize more efficiently on the existing neural architecture. This notion is supported by the fact that the strength of functional connectivity depends to some degree on the qualities of the white matter pathways between regions [57]; which are distinctly impacted by stroke and are particularly difficult to remediate.

Certain study limitations must be considered when interpreting these results. First, as the sample size is modest; these results should be considered preliminary; and warrant further investigation. Also, although AOT confers improvement in functional gains in the given cohort; it is not yet clear as to why some individuals benefit from AOT more than others. Furthermore; our method of assigning participants to treatment groups based on baseline function; age; and education led to the situation that the AOT group had a greater proportion of woman than the NDT group; however, as women tend to have poorer recovery of the upper limb than men following stroke [59]; this imbalance may in fact serve to blunt the measured benefits of AOT. Additionally, we excluded individuals with depression to remove this as a potential confound; but it remains to be seen how depression will impact gains from AOT. Finally, as described in the results; individuals receiving NDT did show some degree of functional improvement; although this was not significant after correction for multiple comparisons. NDT is widely used as current standard of care; and the results of the current study do not question the validity of this therapy; rather; these findings support the robustness of AOT.

Summary

The present study found that one-month of AOT is effective at facilitating functional gains in individuals with chronic stroke. Critically, these gains were seen not just immediately after therapy; but were also maintained over the long term. This sustained improvement is critical; as it suggests that AOT may confer functional gains well after the treatment has ended. Furthermore, the stability and variability of functional connectivity prior to therapy helped predict the response to treatment with AOT. This suggests that the functional gains following AOT may be due; at least in part; to a more effective use of post-stroke neural architecture. Taken together, these findings indicate that AOT is effective at conferring long-term functional gains following stroke; and may do so not by compensatory measures; but rather through the remediation of existing neural networks critical to motor function.

Ethical Standard

This study has been approved by the appropriate committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the study.

Acknowledgement

We thank Matthew Schiel for his technical help with data processing; as well as the Institute for Clinical & Translational Sciences at UCI for the use of their facilities (supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences; National Institutes of Health; through Grant UL1 TR000153). The present work was supported by the National Institutes of Health under grants RO1-NS-54942 and by a grant from the James McDonnell Foundation (NRG group). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Austin J Clin Neurol - Volume 4 Issue 4 - 2017
ISSN : 2381-9154 | www.austinpublishinggroup.com

Citation: Riley JD, Falcon MI, Small SL, Collins K, Chen EE, Buccino G, et al. Maintenance of Hand Motor Recovery Following Action Observation Treatment for Stroke. Austin J Clin Neurol 2017; 4(4): 1114.