Advances in Neurocognitive Rehabilitation Research from 1992 to 2017: The Ascension of Neural Plasticity

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\textbf{Abstract}

\textbf{Objective}—The past 25 years have seen profound changes in neurocognitive rehabilitation and that continue to motivate its evolution. Although the concept of nervous system plasticity was discussed by William James (1890), the foundation for experience-based plasticity had not reached the critical empirical mass to seriously impact rehabilitation research until after 1992. The objective of this review is to describe how the emergence of neural plasticity has changed neurocognitive rehabilitation research.

\textbf{Method}—The important developments included (a) introduction of a widely available tool that could measure brain plasticity (i.e., fMRI), (b) development of new structural imaging techniques that could define limits of and opportunities for neural plasticity, (c) deployment of non-invasive brain stimulation to leverage neural plasticity for rehabilitation, (d) growth of a literature indicating that exercise has positively impacts neural plasticity, especially for older persons, and (e) enhancement neural plasticity by creating interventions that generalize beyond the boundaries of treatment activities. Given the massive literature, each of these areas is developed by example.

\textbf{Results}—The expanding influence of neural plasticity has provided new models and tools for neurocognitive rehabilitation in neural injuries and disorders, as well as methods for measuring neural plasticity and predicting its limits and opportunities. Early clinical trials have provided very encouraging results.
Conclusion—Now that neural plasticity has gained a firm foothold, it will continue to influence the evolution of neurocognitive rehabilitation research for the next 25 years and advance rehabilitation for neural injuries and disease.

Keywords
Neural Plasticity; Neurorehabilitation; Neuroimaging; Non-Invasive Brain Stimulation; Aerobic Exercise

Introduction: Neurocognitive Rehabilitation and Neural Plasticity in 1992

25 years ago during the 100th anniversary of the American Psychological Association (APA), neurocognitive rehabilitation for brain injury and disease was a growing discipline. In the previous decade, the increase in survival of persons with traumatic brain injury (TBI) spurred the founding of the National Head Injury Foundation, now the Brain Injury Association of America (BIAA, 2016). Interest in the work of Goldstein (1943), Luria (e.g., 1962), and Zangwill (1945) on traumatic brain injury in war was reemerging within this context. The New York University Head Trauma Program for rehabilitation, based on experiences in brain injury rehabilitation from the 1973 Yom Kippur War, had been in operation for 15 years (Ben Yishay, et al. 2003), and variants of this program were spawned around the United States and the world.

From the standpoint of aphasia, enough data already existed in 1992 to support a meta-analysis concluding that aphasia therapy was efficacious relative to no treatment, but the data were not adequate to make specific statements about efficacy for different types of aphasia therapy or different kinds of aphasias (Robey, 1994). Methods for treating other kinds of neurocognitive and related problems had been or were being developed by 1992. Examples of such problems include visual neglect (e.g., Pizzamiglio et al., 1992; Rossi et al., 1990), social/emotional problems after TBI and frontal lobe injury (e.g., Ben-Yishay et al., 1985), attention (e.g., Sohlberg & Mateer, 1987), and memory (e.g., Glisky, 1992). However, the evidentiary base for such treatments lagged well behind that of aphasia.

The literature on neurocognitive rehabilitation between 1992 and 2017 has been voluminous. Treatments in all areas mentioned above have been developed and tested. This evidence is far too vast to cover comprehensively in a single review. Instead, we will focus on one of the most important developments in neurorehabilitation during this time period: the introduction and development of the concept of neuroplasticity into neurorehabilitation research. Further, to make the scope of this review manageable and relevant to the Journal’s readership, we will focus specifically on neurocognitive rehabilitation.

In 1992, the neurosciences were on a positively accelerating growth curve, as demonstrated by scientific attendance at the annual meeting of the Society for Neuroscience in Anaheim 2.5 times greater than that of 10 years earlier (Society for Neuroscience, 2016). At this time, however, the world of neurocognitive rehabilitation seemed to be in a perpetual redshift relationship with neuroscience research, which seemed to be accelerating away from the scientific base of neurorehabilitation research at an ever-increasing rate. Yet, in spite of the illusion of an increasing distance between the neurosciences and neurocognitive...
rehabilitation, the gravitational attraction of the neurosciences was actually pulling the
discipline of neurocognitive rehabilitation toward it. The scientific foundation laid by the
neurosciences was an irresistible force, bound to test the veracity of neurocognitive
rehabilitation constructs, forever changing the field as it did so.

Critically, this neuroscientific foundation consisted largely of studies on neuroplasticity. The
work of Merzenich, Nudo, and colleagues contributed much to this area. For example,
Merzenich and colleagues (1984) published a study showing remapping of adjacent digits
into cortex previously associated with amputated digits. This group produced subsequent
papers showing that repetitive intracortical microstimulation could induce remapping of
motor cortex in rodents (Nudo et al., 1990), and peripheral hand stimulation induced
plasticity in the somatosensory cortex of primates (Jenkins et al., 1990). This work was a
precursor to landmark papers by Nudo and colleagues on use-dependent alterations in
primate motor-cortex representations (Nudo et al., 1996a) and the neural underpinnings of
rehabilitation in primate models of movement (Nudo et al., 1996b) published only four years
after 1992. These and similar studies have provided a strong impetus to understand the role
of neuroplasticity in neurocognitive rehabilitation and to employ techniques to induce neural
plasticity in the service of rehabilitation.

The foundation for other notable events to have an impact on neural plasticity-related
research in neurocognitive rehabilitation had been or was being laid in 1992:

1. The beginnings of functional magnetic resonance imaging (fMRI) were almost
   coincidental with APA’s 100th anniversary. Multiple laboratories had been
   working “simultaneously” on an intrinsic blood contrast that could be used to
   demonstrate activity in visual cortex evoked by visual stimulation or activity in
   motor cortex by finger thumb opposition, and blood oxygenation level dependent
   (BOLD) contrast was born (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et
   al., 1992). Although Belliveau and Kwong were to publish a paper demonstrating
   that gadolinium-based contrast agents also could be used for dynamic
   susceptibility fMRI of visual and somatosensory cortex (Belliveau et al., 1991),
   BOLD contrast fMRI was to become the dominant fMRI methodology because
   of the practicalities and relative safety of using an endogenous as opposed to an
   exogenous contrast. The introduction of fMRI was a revolutionary change for the
   study of human cognition, but it also provided neurocognitive rehabilitation with
   a tool to map neuroplastic changes resulting from rehabilitation.

2. By 1992, Naeser and colleagues were already using a technique to correlate
   lesion location with cognitive deficits (e.g., Naeser et al., 1989). Although this
technique involved a subjective rating system of the amount of lesion in brain
regions, it was accurate enough to demonstrate correlations between language
deficits and left-hemisphere ischemic strokes. This technique was later to be used
to predict aphasia treatment outcomes (Naeser et al., 1998). However, a few
years later, a more quantitative and objective lesion mapping technique was
developed (see below). Lesion mapping information has a profound potential to
help define the possibilities and limitations of neuroplastic processes necessary
for neurocognitive rehabilitation.
Some foundations for non-invasive brain stimulation (NIBS) techniques had been laid by 1992. One landmark study for transcranial direct current stimulation (tDCS) was the work of Albert (1966a, 1966b) showing that pulsating anodal and cathodal currents applied to medial cortex of rodents could facilitate or block retention of avoidance responses. However, it was not until after 1992 that a technique with the potential to be deployed for clinical purposes was developed. Regarding repetitive transcranial stimulation (rTMS), another NIBS technique, Barker and colleagues (1985) had described the method and equipment used for transcranial magnetic stimulation (TMS) of the motor cortex and referenced experiments that had been performed with the technique in the three years prior to their article. rTMS had been introduced in 1989 (Wasserman, 1998), and Pascual-Leone and colleagues (1991) demonstrated that high-frequency rTMS (up to 25 Hz) could induce speech arrest when language eloquent cortex was stimulated during speech. The potential for various clinical applications, including neurocognitive rehabilitation, was soon obvious.

Though the landmark review of the effects of fitness on cognition by Colcombe and Kramer (2003) was still 11 years off, studies of the positive effects of exercise on cognition in aging were reported in 1992 (e.g., Hassmén et al., 1992; Hawkins et al., 1992; Shay & Roth, 1992). Such work eventually would lead to studies of the neural underpinnings of these exercise-induced effects (see below).

By 1992, the literature on generalization was prolific for behavioral treatments used in psychiatric patients and children with speech problems, autism, or intellectual disabilities. Although much less common in the literature on neurocognitive rehabilitation, generalization as a topic of research had found its way into some rehabilitation studies. For example, by that time, there was evidence of generalization in the aphasia literature, as well as its limitations (e.g., Doyle et al., 1989; Wambaugh & Thompson, 1989). The linkage of generalization to neural plasticity in rehabilitation, however, would await development of neuroplasticity as a theme in the rehabilitation literature.

The introduction of neuroplasticity as a dominant theme in neurocognitive rehabilitation research is arguably the most significant development in this literature since the 100th anniversary of the APA. This acceleration of research in this area has been made possible not only by development of the neuroscientific underpinnings, but also by development of tools to measure and induce neural plasticity and determine its limitations, and by demonstration of neural plasticity in cognitive and behavioral paradigms. Nonetheless, we are only beginning to develop the necessary knowledge for this area of inquiry to impact how we deliver neurocognitive rehabilitation interventions for brain injury and disease. Hence, we are a long way from realizing the full impact of this development. The purpose of this review is to survey developments in the study of neural plasticity during neurocognitive rehabilitation across the past 25 years, and to give the reader a concept of both the state of the art and the potential for the future.

The vast literature in this realm is far too great to provide comprehensive coverage in a journal-length review. Rather, we cover major trends, developing them by a few examples of
disease, injury, or syndrome, and then briefly expand the discussion to other research models. These trends are as follows: (a) functional magnetic resonance imaging (fMRI) as a measure of neuroplasticity, (b) structural neuroimaging as a method for defining the limits of neural plasticity, (c) NIBS as method for inducing neuroplasticity, (d) aerobic exercise as a means for inducing neuroplasticity, and (e) generalization of training and its relationship to neural plasticity. We will close with a few conclusions about where the field is heading.

Measuring Neural Plasticity: Functional Neuroimaging

While positron emission tomography (PET), magnetoencephalography (MEG), electroencephalography (EEG), and near infrared spectrography all have been used to study neural plasticity, functional MRI (fMRI) has become the dominant method for imaging neural plasticity in rehabilitation, in part because of its versatility and its wide-spread availability. Hence, we will develop our discussion around fMRI. Although fMRI has provided scientists a tool for exploring neural plasticity, the nature of information provided by it should be briefly addressed. In particular, fMRI cannot be used to measure synaptogenesis, a hallmark of neural plasticity. Instead, fMRI is used to detect changes in regional brain activity and changes in the brain connectivity and systems over time. The way in which such changes have been studied has varied depending on the nature of the question and the population studied; hence, the purpose of this discussion is to illustrate the diversity of fMRI methodologies that can be applied to different questions.

To develop this theme, we have selected studies in two different populations: amnestic mild cognitive impairment (aMCI), which is often considered to be prodromal dementia, and aphasia after stroke. aMCI is a relatively recent area of inquiry for neurocognitive rehabilitation and was selected, in part, because recent findings show some promise in re-engaging structures known to be involved in memory. Aphasia was chosen because fMRI in patients with stroke presents unique challenges, which have evoked a variety of solutions tailored to the experimental questions. Taken together, these two examples will illustrate a range of fMRI analysis techniques that can be applied to other populations and problems in neurocognitive rehabilitation.

Amnestic Mild Cognitive Impairment

A commonly used fMRI approach involves conducting some statistical comparisons on all brain voxels in a functional image data set. Recent versions of such analyses involve multi-level modeling, where “lower level” analyses (e.g., each condition vs. baseline) are done first, and only those voxels meeting significance criteria are promoted to the next analysis level (e.g., comparison amongst conditions). Hampstead et al. (2011) used this approach to assess changes in brain networks that occurred with a successful intervention for pairing names with novel faces in patients with multiple modality amnestic mild cognitive impairment (aMCI). (Mild cognitive impairment involves decline in cognitive function in older individuals that is not yet severe enough to interfere with daily functioning. In aMCI, the ability to form new memories is specifically involved.) In this study, subjects learned a set of face-name pairs over three sessions by associating a salient facial feature with the name using visual imagery and a nick name that emphasized the relationship between the
fMRI sessions were conducted before and after training, where
subjects were asked to remember face-name pairs that were trained during the intervention,
face-name pairs that were not trained, and two control face-name pairs that were repeatedly
alternated. The baseline condition was rest. Regions of interest (ROIs) that activated relative
to baseline were promoted to the next analysis level. Two comparisons were made at the
second level: (1) ROIs that showed greater increases from pre- to post-training for trained
than untrained face-name pairs were designated as training specific, and (2) ROIs that
showed greater increases from pre- to post-training for untrained than repeated faces were
designated as non-specific changes. The most robust training-specific changes showed
increased activity in the pre-callosal medial frontal cortex and in the posterior cingulate/
precuneus region, known to be involved in the “default network”. (The default network is
comprised of brain areas including the posterior cingulate/precuneus region which often
show activity decreases from a simple baseline, such as rest, to a more complex task.) One
possible interpretation for these changes involved increased engagement of attentional
mechanisms; however, it should be noted that the portion of the posterior cingulate gyrus
activated was in the retrosplenial region, and retrosplenial cortex has been implicated in
memory and amnestic syndromes (e.g., Heilman et al., 1990; McDonald et al., 2001;
Valenstein et al., 1987). Effective connectivity between training-specific ROIs was measured
at pre- and post-training using Granger causality analysis. An increased number of
connections were shown from pre- to post-treatment scans, including increased connectivity
between the anterior precuneus and multiple other areas. Hence, this study demonstrates a
network approach to connectivity as well as a whole-brain analysis approach.

When interventions are likely to affect specific brain regions, hypotheses regarding those
ROIs can be tested. Given the ubiquitous presence of the hippocampus in the memory
literature, Hampstead et al. (2012) focused on hippocampal response to memory training in
aMCI. In three sessions, Hampstead et al. (2012) trained aMCI patients and normal controls
to remember object locations in pictures of rooms by associating the object with a salient
feature in the room near the object, using a verbal reason to relate the object to the feature,
and forming an associated visual image. For both neurotypical adults and aMCI patients,
there was also a control group exposed to the same pictures and recall attempts, but without
the memory strategy. Participants improved performance for trained items from pre- to post-
intervention, and no difference in performance improvement emerged between aMCI and
control participants. In pre- and post-intervention fMRI scans participants saw trained,
untrained, and repeated stimuli. During encoding scans, participants tried to remember the
objects’ location and during retrieval scans, they picked the correct location among 3
choices. For within group analyses of encoding scans, only the aMCI memory strategy
group showed increased activity post-treatment in the left hippocampal body for both trained
and untrained stimuli. During retrieval scans, aMCI memory strategy patients showed
bilateral activity increases in the hippocampal body and tail for trained stimuli, and for
untrained stimuli, both the aMCI and control memory strategy groups showed increased
hippocampal activity, restricted to the left side in the aMCI patients. These two studies
provide some reason for optimism that neural plasticity can be evoked in the service of
improving memory in aMCI. Indeed, when memory strategies are used, the second study
specifically indicates re-engagement of the hippocampus, a structure vulnerable in aMCI (e.g., Whitewell et al., 2007).

**Aphasia**

Other examples of neuroplasticity research can be found in the aphasia rehabilitation literature. Aphasia is impairment of language and communication functions caused by brain injury or disease. Speaking, aural comprehension, reading, and writing can be affected in different ways depending on the role damaged regions play in language systems. In this section, we will address aphasia caused by stroke. This population presents a very different set of neuroimaging challenges from aMCI. A complete exposé of these challenges and solutions to them is beyond the scope of this review, but these issues have been addressed elsewhere (e.g., Crosson et al., 2007; Meinzer et al., 2013; Rapp et al., 2013). For the current purposes, we will address methods that have been tailored to different experimental questions. We also take into account different sizes, shapes, and locations of lesions causing aphasia. This conundrum is present in any study involving rehabilitation in stroke. Essentially, it can be difficult to use whole-brain voxel-wise comparisons of groups or conditions in the lesioned hemisphere, such those discussed for aMCI (Hampstead et al., 2011), because areas of perilesional activity in some patients may be located in areas occupied by lesions in other patients, which could lead to underestimation of the importance of the area to rehabilitation because when such areas are lesioned in some patients, they result in zero activity change, thus pulling down the mean change.

Fridriksson et al. (2010) avoided this conundrum by using voxel-wise correlations of activity changes with outcome measure changes. In other words, their experimental question was in which brain areas were activity changes associated with therapeutic change. They did 30 hours of aphasia therapy for patients with various types of aphasia. The intervention involved picture naming using phonological and semantic cuing hierarchies, and the fMRI task involved naming a subset of the trained pictures. For each voxel, change in activity from pre- to post-intervention was correlated with change in picture naming. In voxels occupied by lesion, activity changes from pre- to post-intervention should be zero. If activity changes in such an area are important to rehabilitation, then the lack of activity change due to a lesion should hamper rehabilitation-related changes in behavior. Hence, voxels in which there are lesions contribute meaningful data points to the correlational analysis because the inability to evoke activity changes will hamper rehabilitation. Fridriksson et al. found that activity increases in left inferior parietal lobule, left superior parietal lobule, left middle frontal gyrus, left pars opercularis, left precentral gyrus, and precuneus bilaterally were associated with improved picture naming.

Benjamin et al. (2013) did 30 sessions of aphasia therapy pairing complex left-hand movements with word-finding trials (picture naming for 20 sessions followed by category-member generation for 10 sessions) in patients whose verbal output showed at least some nonfluent characteristics. The idea was to shift activity during word-finding from left to right lateral frontal cortex, allowing right-hemisphere mechanisms to assume language functions for their damaged left-hemisphere counterparts. A control group performed the word-finding treatments without the left-hand movements. The fMRI task involved category member
generation, consistent with the last 10 sessions of training. Because middle cerebral artery lesions were of different sizes, shapes, and locations, the authors used large ROIs in both hemispheres (lateral frontal, medial frontal, and posterior perisylvian) to assess changes in laterality from pre-to post-intervention. At post-treatment, laterality only in the experimental group had shifted significantly toward the right hemisphere for the lateral frontal but not the other ROIs. However, it was greater rightward shift in posterior persylvian activity that predicted greater improvement in category member generation probes from pre-treatment to the end of the experimental treatment.

The most recent studies using fMRI to detect activity changes related to aphasia treatment are beginning to emphasize network analyses, a trend that is increasingly prevalent in fMRI literature in general. For example, Duncan and Small (2016) gave patients with aphasia six weeks of an imitation treatment, which involved audio-visual presentation of words and phrases followed by repetition of these stimuli by the patients (Lee et al., 2010). Resting state fMRI scans were done at roughly 3-week intervals (3 pre-, 1 during, 3-post intervention). Resting state scans are done when subjects are not performing any experimental task. An independent components analysis (ICA) using all scans identified eight relevant networks, consisting of a total of 230 areas (nodes). These networks and their nodes were used to compare average modularity from the pre-intervention scans to average modularity from the post-treatment scans. Modularity is a graph theoretic metric describing the degree of discreteness in activity among multiple networks. Networks with high modularity tend to have greater connectivity within network nodes than between nodes of different networks. The behavioral outcome measure was correct information units from a narrative language sample. These investigators found that increased modularity was associated with increased correct information units (CIUs) from pre- to post-intervention, indicating that more successful intervention outcomes are associated with increasing discreteness of functional networks in the resting state.

These studies indicate different imaging approaches to study neural plasticity resulting from aphasia treatment. Generally, results have been positive, though analyses differed depending on the nature of therapy and the research questions regarding neural plasticity. Although the literature on neural plasticity resulting from cognitive rehabilitation is not prolific in MCI, the growing literature on neural plasticity resulting from aphasia therapy has been reviewed periodically (e.g., Crinion & Leff, 2007, 2015; Meinzer et al., 2011). In the most recent of these reviews, covering 15 months of research, Crinion and Leff (2015) concluded that improvement in aphasia treatments are most often accompanied by increased left-hemisphere perilesional (frontal-temporal) activity. Though the meaning of such changes is still questioned, right-hemisphere increases in activity from pre- to post-intervention also occur, especially in the inferior frontal gyrus. These conclusions generally are consistent with previous reviews. Benjamin and colleagues’ (2013) findings indicate that the potential value for right-hemisphere participation in neural changes underlying aphasia treatment outcomes deserves further attention.

In this brief discussion, we highlighted different analysis approaches used to answer diverse questions in neurorehabilitation studies for aMCI and stroke-induced aphasia. These populations represent a small sample of problems that fMRI has been used to study.
example, improved performance accompanied by left-hemisphere activity increases have been documented for developmental speech and language disorders such as stuttering and dyslexia (Neumann et al., 2005; Odegard, Ring, Smith, Biggan, & Black, 2008). Research with temporal lobe epilepsy (TLE) has indicated that fMRI may be useful for predicting post-surgical outcomes and non-invasively lateralizing language dominance prior to surgery in children and adults with refractory seizures (Rabin et al., 2004; Suarez et al., 2014). Long-term frontal and hippocampal activity changes, accompanied by positive cognitive changes, have been shown several months after anterior temporal lobectomy (Bonelli et al., 2012). For TBI, Arnemann et al. (2015) found that a successful intervention (5-week attention regulation and goal-orientation attention training) was predicted by higher baseline modularity, and positive outcomes also were associated with increase executive function tasks performance. Thus, fMRI studies of are yielding substantive insights into the topography of neural plasticity for numerous disorders using data acquisition and analysis methods tailored to the experimental question.

Structural Imaging and Plasticity in Stroke Rehabilitation

When a brain area involved in functions like language or attention to visual space is damaged, the impact on these functions depends upon its contributions to the system and the effects on other brain areas up- and down-stream of the affected area in cognitive processes. Typically, the degree to which the affected function can be rehabilitated depends on what intact brain areas can be recruited to perform it, or what alternative mechanisms are available to compensate for the loss of function. It follows that optimal neurocognitive rehabilitation interventions can be developed if we have a good understanding of what brain areas and systems are damaged that are likely to have a major impact on the limitations and induction of neural and behavioral plasticity. The relationship between localization of damage and rehabilitation potential is particularly salient in ischemic stroke, where large brain regions may be completely destroyed. In this section, we explore how structural imaging can help inform rehabilitation models and predict outcomes. We develop this theme primarily by using the examples of aphasia and neglect after stroke.

Prior to the early 2000’s, brain-behavior relationships in stroke survivors often were assessed by grouping patients either by lesion or by behavior. Grouping the patients by lesion involves clustering groups of subjects that have a similar lesion location (e.g. inferior parietal lobule), and comparing cognition and behavior to a control group (Friedrich, Egly, Rafal, & Beck, 1998). This approach can provide pertinent information about how a brain region relates to behavioral measures, but depending on the size and shape of the region, may not provide high spatial specificity. This approach may also miss important brain areas that are outside of the lesion location. Grouping patients by behavior implies clustering patients by their behavioral deficits and then mapping their lesions to a common template space (Dronkers, 1996; Freedman, Alexander, & Naeser, 1984). Lesion areas shared between patients with a common behavioral deficit are compared to lesion locations of patients without the deficit. Identifying brain regions that are associated only with the behavior can help identify brain regions that are involved in a specific cognitive skill, but require a cut-off on continuous behavioral data. This is a subtle but important point, because
the continuity of behavioral measures can help assess varying degrees of deficits, and imposing an artificial cut-off might bias the structure-behavior associations.

Within the last two decades, methods were introduced that provide improved lesion-behavior mapping, including Voxel-based Lesion Symptom Mapping (VLSM) (Bates et al., 2003). The technique uses high resolution anatomical MRI scans on which an experienced operator can manually demarcate the lesion. This is performed on multiple participants with different lesion locations. The area of the lesion is then binarized into a participant-specific mask, registered into a common atlas space, and entered into a voxel-wise analysis to determine lesion locations associated with specific cognitive or behavioral deficits. VLSM is a simple, yet elegant, semi-automated algorithm to define structure-behavior associations that allows for aggregation of data across participants in a more objective way than previous methods. Diffusion weighted imaging (DWI) is another structural MRI image that can be used to quantify white matter integrity or to track white matter pathways connecting gray matter structures. DWI data also can be used to map anatomical networks.

In this section, we focus on mapping cognition-brain relationships in stroke using two syndromes: (1) Work in mapping the relationship between brain regions and domain-specific and domain general functions related to language in aphasia is a relatively mature endeavor with good examples of how this kind of mapping can be related to language therapies. (2) By contrast, the therapeutic implications of mapping hemispatial neglect-brain relationships is a relatively nascent area. By contrasting these two areas of research, we can see how the potential of VLSM or DWI might be brought to bear on defining limitations and opportunities in neurocognitive rehabilitation, depending on the stage of development of the research area. Finally, we will broaden the discussion to other rehabilitation populations and structural imaging modalities.

**Aphasia**

Aphasia therapy can improve ‘real-world’ outcomes for patients with aphasia (Bhogal, Teasell, and Speechley 2003, Basso et al., 2013), even when therapy is administered in the chronic stages (Moss & Nicholas, 2006). Structural imaging techniques such as VLSM or DWI can be used to identify which persons with aphasia are most likely to benefit from a specific treatment. With respect to VLSM, two studies by Fridriksson and colleagues contrast how prediction of treatment response might provide useful information to therapists. In the first study (Fridriksson et al., 2010), persons with aphasia received a treatment emphasizing graded semantic and phonological cueing hierarchies for picture naming, with 15 hours dedicated to each type of training. VLSM analysis indicated that patients with lesions at the junction of the left angular and middle temporal gyri predicted limited improvement with this treatment. It is worth noting that fMRI of picture naming also was performed in this study (as noted above) and that areas of increased activity in the parietal and frontal lobes predicted improvement in picture naming. Since these areas would have to be intact for activity to increase, this study shows how information from multiple neuroimaging modalities provide complementary information in terms of what brain regions need to be intact or engaged to respond positively to treatment.
Fridriksson et al. (2015) had persons with left-hemisphere stroke (with and without aphasia) do a standard picture description task and a speech entrainment task in which they mimicked an audiovisual presentation of a speaker in real time. Speakers produced short narrative scripts about generic topics and only the mouth was visible. For both tasks, the number of different (unique) words produced per minute was measured. VLSM showed that improvement in words produced for speech entrainment relative to standard picture description was associated with lesions in the left inferior frontal gyrus. While this was not a treatment study per se, it is likely that improvement in production during speech entrainment could be an indicator of ability to respond to this exercise as a treatment. This extrapolation suggests that some lesions could predict positive response for some treatments, unlike the previous example (Fridriksson et al., 2010) in which lesion predicted poor response to treatment. Further, most of the participants who improved with speech entrainment had Broca’s aphasia; however, some had anomic aphasia instead. Hence, this example indicates how language behavior and VLSM might be combined to assess the probability of treatment success.

While interpretation of VLSM analyses often emphasize gray matter regions, it is important to remember that cognitive and behavioral functions are possible because information in brain systems travels along white matter pathways between regions that play unique roles in such functions. By using diffusion tensor imaging (DTI) and related techniques on DWI images, the integrity of white matter pathways can be assessed. Using probabilistic tractography to quantify connectivity between brain regions, Bonhilla et al. (2016) studied how structural connectivity between brain areas was associated with treatment outcome. They found that the degree of preservation of global brain connectivity as well as how well left temporal regions remain connected to the remaining global networks predicts positive treatment outcomes (improved picture naming). In other words, when the global and temporal pathways are available to promote neural plasticity, the cueing hierarchy treatment used in this study is more likely to succeed. Hence, VLSM and DWI analyses provide synergistic information about the brain’s structure, lesion location, and how they both relate to aphasia treatment outcome.

**Hemispatial neglect**

Neglect has not reached the same stage as aphasia in use of structural imaging to predict treatment outcome. Nonetheless, it is worth briefly considering VLSM studies relating lesion location to neglect symptoms because such studies are useful in building neurocognitive models of neglect that, in turn, can be used to develop neurorehabilitation strategies. Hemispatial neglect is a condition in which patients fails to report, orient toward, or respond to sensory stimuli in contralesional space that cannot be attributed to sensory or motor dysfunction. Hemispatial neglect more often involves the left side of space relative to the patient. As with aphasia, different types of neglect can be defined depending on how perception of space or action into or on one side of space are affected (Heilman, Watson, & Valenstein, 2012).

Recent lesion-symptom mapping studies have added important information regarding structure-function relationships that force us to consider traditional models emphasizing the
frontal and parietal and frontal lobes in neglect (e.g., Heilman et al., 2012). For example, Karnath et al. (2011) showed that damage to superior and middle temporal gyri were prominent in predicting neglect symptoms in both the acute and chronic phases of right-hemisphere stroke. Basal ganglia lesion showed a similar predictive value. The inferior parietal lobule predicted neglect primarily in the acute as opposed to the chronic phase. Reports over the past two decades also indicate the importance of white matter damage as a predictor of neglect and recovery (Doricchi & Tomaiuolo, 2003; Karnath et al., 2009).

One critical caveat about correlating neglect measures (or any other cognitive measures) with anatomy should be noted. The array of measures used to measure neglect has been impressive and includes line bisection (e.g., Albert, 1973), letter cancellation (e.g., Lezak et al., 2012), reading (e.g., Halligan, Cockburn, & Wilson, 1991), drawing (e.g., Kinsella, Olver, Ng, Packer, & Stark, 1993), mental imagery (e.g., Bisiach & Luzzatti, 1978), attention to the body (e.g., Beschin & Robertson, 1997), and naturalistic action tasks (e.g., Schwartz et al., 1999). Given that VLSM requires the cognitive scores to obtain structure-behavior associations, it is important to note that different tests may tap different aspects of neglect, which can affect the areas identified by VLSM. Indeed, most typical measures of neglect are multi-dimensional. For example, Na et al. (1998) showed that both line bisection and cancellation tasks, typical clinical and experimental measures of neglect have both sensory-attentional (failure to respond to sensory information in the left hemispace) and action-intentional (failure to initiate action in the left hemispace) that can be separated experimentally. Hence, any VLSM study using traditional versions of these measures will confound sensory-attentional and action-attentional neglect, which are assumed to have different anatomic substrates (Heilman et al., 2012). This concern of confounding different aspects of neglect with multidimensional measures should be considered carefully in picking outcome measures for future studies to predict outcome using VLSM.

Verdon et al. (2010) demonstrated one way in which the concern of multidimensionality could be addressed. They used the elegant approach of performing factor analysis on the cognitive scores, and the factor scores, taking into account differential weighting of various tests, were subsequently used in VLSM analysis. Their results identified factors indicative of the dichotomy identified by Na et al. in that they were able to derive perceptive visuo-spatial and exploratory visuo-motor factors. While this approach is very promising, we must remember that the tests entered into the factor analysis must reflect varying degrees of different neglect components to be successful.

Development and application of structural imaging approaches are not exclusive to aphasia and neglect, or even stroke research. For example, white matter integrity is a particularly salient issue in TBI because diffuse axonal injury resulting from mechanical shearing forces is prevalent (Jennett & Teasdale, 1981). Sidaros et al. (2008) used DWI metrics to quantify microstructural integrity in TBI found that higher fractional anisotropy (indicating higher integrity) in the cerebral peduncle in the late subacute phase post-injury predicted better functional outcomes one year following injury. It is also worth noting that structural imaging measures may vary depending on the population involved and the nature of damage incurred. Specifically, VLSM may not be applicable to every rehabilitation population because some individuals (e.g., those with Parkinson’s disease, Alzheimer’s disease, MCI,
aging, or mild TBI) do not have the type of lesion that can be quantified on typical structural MRI scans, in which case other methods have been used. For example, voxel based morphometry (Ashburner & Friston, 2000) has demonstrated local gray matter density differences between groups of MCI patients and age-matched neurotypical controls affecting medial as well as neocortical temporal regions and the cingulate gyrus (e.g., Chételat et al., 2002; Pennanen et al., 2005). As noted above, initial findings regarding memory training in aMCI are promising; hence, correlating VBM gray matter densities with treatment outcome in this population might eventually provide predictive information useful in selection of treatment options. As another example of structural imaging techniques, in a one-year aerobic exercise (walking) study of older adults, Erickson et al. (2011) found that changes in hippocampal volume correlated positively with increased memory function. Given that amygdalar and hippocampal volumes are related to subjective family assessment of memory in MCI (Fyock & Hampstead, 2015) and that MCI patients show increased hippocampal activity during memory tasks as a result of memory intervention (Hampstead et al., 2012), changes in hippocampal volumetrics as a result of extended memory intervention with MCI might be a fruitful topic for inquiry. As an example of yet another structural imaging approach, Ailion et al. (2016) found that the interaction between cerebellar lesion size and cerebellar atrophy predicted processing speed in adult survivors of childhood cerebellar tumor. If these variables can explain long-term cognitive outcomes, they may also be capable of predicting rehabilitation intervention outcomes.

To summarize, VLSM and DWI based measures of white matter have proven useful in predicting cognitive outcomes in stroke rehabilitation. Different structural imaging measures have been used as appropriate with other populations. Findings indicate that structural imaging measures will be fertile ground for revealing limitations and opportunities in future neurocognitive rehabilitation research.

Noninvasive Brain Stimulation and Neural Plasticity: Transcranial Direct Current Stimulation and Transcranial Magnetic Stimulation in Dementia

The last two decades not only have yielded methods for measuring neural plasticity during rehabilitation and defining its limits but also have seen the emergence of non-invasive brain stimulation (NIBS) techniques that can induce neural plasticity. Given space limitations, the discussion will be limited to the most commonly used NIBS techniques: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both techniques modulate cortical excitability, but through very different mechanisms. Through rapid changes in magnetic fields, rTMS induces an electrical current strong enough to fire neurons in the target cortex (Nitsche et al., 2008; Clark et al., 2011). Whether rTMS increases or decreases cortical excitability depends on the timing of repeated stimulation relative to excitatory and inhibitory phases of neural firing, with high frequency rTMS (e.g., 10 Hz) increasing cortical excitability and low frequency rTMS (e.g., 1 Hz) decreasing it (Kozyrev et al., 2014). On the other hand, Jackson et al. (2016) noted that tDCS currents are too weak to fire neurons; rather, tDCS works by depolarizing or hyperpolarizing neuronal membrane potentials, thereby making neuronal firing more or less likely. tDCS currents hyperpolarize parts of a neuron where current enters and depolarize the parts where the

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current exits (Jackson et al., 2016). Thus, the effect of a direct current on a neuron depends on the orientation of the neuron relative to the current. Of course, populations of neighboring neurons with similar orientations relative to the applied current will be affected in the same way, leading to regional effects with respect to increasing or decreasing excitability. Jackson et al. (2016) warned that the model that tDCS decreases excitability of neurons under a cathode and increases excitability under an anode is too simplistic. Further, there may be critical dose-response effects with cathodal tDCS where a 1 mA current decreases excitability of underlying cortex while a 2 mA current increases excitability (Batsikadze et al., 2013). A final, but important point is that both rTMS (Lenz & Vlachos, 2016) and tDCS (Jackson et al., 2016) have shown lasting changes in cortical excitability indicative of neural plasticity, though much research is needed to characterize these changes.

We will develop the theme of NIBS in rehabilitation by discussing promising research in dementia, which is characterized by the combination of cognitive and functional deficits that represent a significant decline from the individual’s previous level of functioning. Dementia and prodromal dementia (MCI) were selected not only because of promising recent neurocognitive rehabilitation research, but also because of the importance of the problem. The aging of our population will create an increasing burden of dementia. Estimated rates of dementia vary widely based on factors such as age (e.g., 13.9% of those over age 70; Plassman et al., 2007) and global region (e.g., 2–4% in sub-Saharan Africa; 8.5% in Latin America; Prince et al., 2013). A number of models predict a marked increase by 2050 (Prince et al., 2013). With healthcare related costs in the final five years of life exceeding those of notable diseases like heart disease and cancer (Kelley et al., 2015) and the lack of any disease modifying/arresting agent on the horizon, comes the need for other treatment options. Non-pharmacologic approaches, including NIBS, are increasingly being recognized for their potential to mitigate cognitive deficits.

We focus specifically on Alzheimer’s disease, MCI, and Frontotemporal dementia given their prevalence and the primary cognitive deficits that characterize these etiologies. While the findings detailed below are generally encouraging and support the presence of neuroplasticity even in advanced disease stages, there is striking lack of information on dose-response relationships, efficacy across the disease continuum, and other vital methodological factors that currently limit the clinical translation of these techniques.

**Alzheimer’s dementia**

Alzheimer’s disease (AD) is diagnosed in one out of nine U.S. adults aged 65 years or older (Alzheimer’s Association, 2016) and is characterized by learning and memory deficits in the early stage, with widespread cognitive and functional impairment in later disease stages. The disease is defined by neurofibrillary tangles that begin in the transentorhinal cortex of the medial temporal lobes as well as beta-amyloid plaques that are distributed in the basal portions of the frontal, temporal, and parietal cortices (Braak & Braak, 1991; McKann et al., 2011; Perl, 2010; Serrano-Pozo et al., 2011).

Both tDCS and rTMS have been used for cognitive “enhancement” purposes in AD, with generally positive results over both short- and long-term follow-up. A recent meta-analysis found 11 studies that had used either tDCS or rTMS in those with AD (Hsu et al., 2015).
Impressively, the authors reported a mean effect size (ES) of 1.35 (95% CI of 0.86–1.84) that remained large and clinically meaningful even after adjusting for publication bias (ES=0.78). Several factors were found to affect treatment response including stimulation timing, such that stimulation delivered concurrent with task performance yielded an ES of 1.79, whereas for tasks performed after stimulation, the ES was 1.04. Single session ES was 1.49, whereas the ES was 1.2 in studies that provided multiple sessions. There was a clear effect of TMS frequency with high (ES=1.64) being superior to low frequency (ES=0.23) in studies that generally targeted the prefrontal cortex (PFC) and evaluated outcome using global screening measures (e.g., MMSE, ADAS-Cog), confrontation naming, auditory comprehension, and various executive abilities (e.g., Trail Making Test).

Rahman-Filipiak et al. (in press) recently reviewed tDCS research in dementia and found that the effects of tDCS vary by cognitive domain. For example, global cognitive functioning, as measured by the MMSE or ADAS-Cog, improved only when tDCS was paired with memantine (Khedr et al., 2014) and not when it was used as a stand-alone treatment (Boggio et al., 2012; Suemoto et al., 2014). Likewise, tDCS had no effect on visual attention (Ferrucci et al., 2008) or psychiatric symptoms such as mood disorders, apathy, social isolation, and “personality” changes (Suemoto et al., 2014).

Such null findings raise the possibility of a critical mismatch between the targeted brain region(s), presence and severity of disease pathology in the region, and the associated cognitive domain. In this respect, consistent evidence has emerged that tDCS applied to the lateral temporal cortex enhances aspects of memory functioning in AD. For example, Boggio et al. (2009) found a selective improvement in visual recognition memory, but not simple attention or inhibitory control, following a single 30-minute session in which the anode was placed over either the left dorsolateral prefrontal cortex or the left temporal lobe. These effects were replicated and found to persist at a one-month follow-up in subsequent study that used a bitemporal montage and provided five consecutive daily 30-minute sessions with 2mA of current (Boggio et al., 2012). Similarly, word recognition memory improved following a single 15-minute session that provided 1.5mA over the lateral temporal cortices bilaterally in two separate studies (Ferrucci et al., 2008; Marceglia et al., 2016); an effect that was accompanied by neurophysiological change as revealed by increased high-frequency alpha and beta oscillations in the temporoparietal area on EEG (Marceglia et al., 2016). A recent case study of a patient with early onset AD reported increased verbal memory recall after 12, 30-minute sessions (2 sessions/day for 6 days) at 2mA over the left lateral temporal cortex (Bystad et al., 2016).

**Mild Cognitive Impairment (MCI)**

MCI due to AD is a pre-dementia clinical state that is characterized by subjective report of cognitive decline, objective evidence of such decline (especially in learning and memory), but preserved everyday functioning (Albert et al., 2011). Intervention at this stage may enhance and/or prolong functioning by capitalizing on neural networks that are relatively preserved compared to the more advanced stage of dementia. To date, only one randomized controlled trial has been published using tDCS in patients with MCI. Meinzer et al. (2015) reported that, relative to a sham session, a single 20-minute session of 1mA with the anode
over the left lateral PFC enhanced semantic word retrieval and was accompanied by reduced blood oxygen level dependent (BOLD) signal on fMRI, which is generally interpreted as a sign of increased neural efficiency.

Hampstead et al. (unpublished; NCT01958437) recently completed a double blind, randomized controlled trial that used a crossover design to evaluate the effects of High Definition (HD)-tDCS on the neural networks underlying spatial navigation in healthy older adults and MCI. Allocentric spatial navigation is known to decline with age and further in AD (Moffat, 2009 & Lithfous et al., 2013) and occurs within the context of the well-established “posterior to anterior shift” in BOLD signal during aging (Davis et al., 2008) that indicates dysfunction of “posterior” brain regions. Building on their earlier findings that tDCS altered BOLD signal in a polarity dependent manner in healthy young adults (Hampstead et al., 2014), Hampstead et al. targeted the right superior parietal lobule using HD-tDCS (2mA for 20 minutes with center anode over site P2) in an attempt to facilitate spatial processing. Outcome was measured offline (i.e., post-tDCS) at the behavioral (i.e., memory test performance) and neurophysiological levels using both task-based and resting-state fMRI. Preliminary analyses suggest that, relative to sham, active HD-tDCS altered the pattern of task-related BOLD signal within left-hemisphere regions that are associated with successful memory encoding. Likewise, active HD-tDCS reduced resting-state functional connectivity between the targeted right parietal region and the right dorsolateral prefrontal cortex, relative to sham. Interestingly, these effects appeared dependent on cognitive phenotype such that the effects were largely driven by patients with MCI.

As discussed earlier, tDCS alters the probability of neuronal activity and thereby makes cognitive (or other) activities more or less likely. An intriguing possibility, supported by the motor literature, is that tDCS can be used to enhance and prolong the activity associated with tasks or interventions. In this regard, cognitively-based interventions are rapidly gaining interest for use in aging and dementia and have been shown to enhance cognitive performance and BOLD signal in both neocortical regions (Belleville et al., 2011; Hampstead et al., 2011) and the hippocampus (Hampstead et al., 2012). However, such approaches have well-documented limitations in regard to near- and far-transfer of the trained techniques. An ongoing study (NCT02155946) aims to overcome such limitations by pairing HD-tDCS with mnemonic strategy training in patients with MCI using a parallel groups, double blind RCT design. Specifically, this study uses HD-tDCS to target a lateral PFC region, known to be important in memory encoding and mnemonic strategy use, and then shapes this expected effect using mnemonic strategy training. Outcome is evaluated using ecologically-relevant memory tests and fMRI following 5 consecutive training sessions and again at 3-months.

**Frontotemporal Dementia**

Frontotemporal dementia (FTD) encompasses a heterogeneous group of disorders that disproportionately affect the frontal and temporal lobes (Bott et al., 2014). FTD has an earlier onset than AD, most commonly between 50 and 60 years old (Saykin & Rabin, 2014), with the behavioral variant (bvFTD) accounting for half of all FTD cases. Primary progressive aphasia (PPA) encompasses the other half of FTD cases and, as the name
implies, is characterized by language deficits, specifically affecting motor-speech and grammatical knowledge in the nonfluent variant (nfvPPA) and the semantic knowledge in the semantic variant (svPPA) (Gorno-Tempini et al., 2011). While a logopenic variant (lvPPA) characterized by word-finding difficulty exists, it is generally believed to be associated with AD.

An early tDCS trial with a mixed sample of 10 patients with FTD found no effect of a single tDCS session (2mA for 40 minutes; anode over the left PFC) on verbal fluency (Huey et al., 2007). However, persistent improvements in the FTD Rating Scale and functional activities (e.g., speech output, household chores) were noted throughout a 7-month follow-up period in a patient with bvFTD who underwent ten, 20-minute sessions (2 sessions/day for 5 consecutive days) at 2mA with the anode over the left PFC (Agarwal et al., 2016). tDCS effects in PPA-FTD appear promising as evidenced by improvements in speech production and grammatical comprehension (Gervits et al., 2016), spelling (Tsapkini et al., 2014), and naming (Cotelli et al., 2014; Cotelli et al., 2016; Manenti et al., 2015; Wang et al., 2013). Despite the promising findings, these studies varied widely in tDCS dosage (1–15 sessions for 20 – 40 minutes per session at 1.2 to 2mA), montage and targeted brain regions, and sample characteristics. While neuroplasticity can be inferred by the behavioral/cognitive changes, none of the studies included methods of evaluating neurophysiological responses. In the only published study of svFTD and tDCS to date, Teichmann and colleagues (2016) demonstrated that stimulation over either the left or right temporal pole improved semantic matching relative to sham; however, only stimulation with the cathode over the right temporal pole improved processing speed.

The emerging literature for tDCS with other clinical populations is promising, but results can be variable at times. For example, the potential of tDCS for TBI rehabilitation has recently garnered empirical interest with mixed results at times (Dhaliwal et al., 2015). In a pilot study, Leśniak et al. (2014) found that repeated tDCS accompanied by daily cognitive rehabilitation did not significantly improve cognitive performance compared to sham controls. Another TBI study revealed increased cortical excitability and cognitive performance in response to 10 sessions of “anodal” stimulation (Ulam et al., 2015). Severity of injury and time of intervention may be important considerations for future research in tDCS for TBI rehabilitation (Dhaliwal et al., 2015). A promising example in another population is the use of tDCS in gait therapy for children with cerebral palsy (Grecco et al., 2014). For future NIBS research in general, a framework for predicting the physiological mechanisms of induced neuroplasticity and characterizing conditions that affect cortical excitability is necessary, as exemplified by research with healthy populations indicating age-specific considerations for tDCS optimization (Moliadze et al., 2015). More research on early neurorehabilitation interventions with NIBS techniques also would be a welcome development.

The Influence of Exercise on Neurobehavior and Plasticity

Although techniques for NIBS that could be applied to rehabilitation have been developed mainly during the past two decades, another potential means of inducing neural plasticity, physical exercise, was prominent even in ancient cultures. Pioneers of Western medicine
such as ancient Greece’s Hippocrates and his mentor Herodicus (5th century BC) regularly prescribed exercise for medical treatment (Tipton, 2014). In spite of this historical precedent, up until the mid-1990’s, there had been some controversy as to whether or not exercise improved cognition, particularly in older adults (Blumenthal et al., 1989; Dustman et al., 1984; Elsayed et al., 1980; Hughes, 1984; Madden et al., 1989; Spirduso, 1975). The idea of this controversy is an anathema to neuroscientists working in 2017, as consistent evidence has shown Hippocrates prophetic, but this was a very real debate in 1992. So, what happened over the last 25 years to bring us back to the opinion voiced in the fifth century BC?

For the most part, the collection of evidence regarding underlying mechanisms of physical exercise that might support neural changes awaited development of the empirical and conceptual framework for neural plasticity, and once that foundation was laid, a robust literature on the effects of exercise in aging was built upon it. The following discussion will focus on aging-related changes in behavior respective of underlying neural processes. Aging was selected as a focus for this section for two reasons. First, although not traditionally considered a target for neurocognitive rehabilitation, aging-related declines in cognitive functioning appear responsive to exercise as an intervention. However, second, we have recently presented evidence that aging-related diseases such as stroke or Alzheimer’s disease interact with aging processes (Crosson et al., 2015). Our review suggests that treating the aging-related component of this interaction can have positive rehabilitative effects.

Up through 1992, much of associated research into the role of exercise on cognition focused on paper and pencil testing of participants probing the cognitive constructs of crystallized versus fluid intelligence (Blumenthal et al., 1989; Elsayed et al., 1980; Madden et al., 1989). The comparisons in much of associated work involved somewhat broad assays of cognition that may or may have not been associated with aging-related declines. An important pivot made in the mid-1990’s respective of aging research was the identification of specific aspects of behavior associated with poorer performance in aging (e.g., Salthouse, 1996). Quickly thereafter, having identified reliable measures of declines in aging, the focus shifted to characterizing prophylaxis from and reversal of these aging-related performance impairments. This change coincided with the migration of cognitive psychology towards mechanistic neuroscience during the “Decade of the Brain” in the 1990’s and with the rapid development of novel technologies to index neurological function. Over the past 25 years, these techniques and results from their deployment have made the aforementioned debate a historical footnote, at least within the context of aging.

Recent investigations on the relationship between exercise and behavioral outcomes have demonstrated improved performance for psychomotor and processing speed, working memory, task switching, inhibition, verbal fluency, and spatial memory (Erikson & Kramer, 2009; Holzschneider et al., 2012; McGregor et al., 2013; Nocera et al., 2015; Prakash et al., 2014; Wasylyshyn et al., 2011). Critically, all these domains are associated with aging-related performance declines in sedentary older adults. These data are of great importance by themselves; however, modern neuroscience has paired behavioral assessment with techniques that describe the underlying neural anatomy and physiology. In the above studies, researchers used structural and functional MRI to probe the potential mechanism of aging-
related declines and, importantly, how exercise might slow or even reverse these deficits. This technology (MRI) has provided direct brain mapping and neurophysiological evidence of the beneficial effects of physical activity on brain health and cognition. We will explore some of the major work in this modality, as its deployment has perhaps more than any other method or technology furthered our understanding of how exercise facilitates neural plasticity.

Seminal works from MRI and from a brain structure standpoint have highlighted the neuroplastic capabilities of exercise, providing compelling evidence for the powerful effects of exercise on brain structure in older adults (Colcombe et al 2003). The advent of voxel-based morphometry (VBM) on structural MRI data has shown increased volume in overall brain mass as well as white and gray matter, specifically areas of the frontal cortex and hippocampus in physically active vs. sedentary older adults (Colcombe et al., 2003; Zlatar et al., 2015). Importantly, exercise interventions have also shown morphometric differences in these areas from pre-to post-exercise intervention (Colcombe et al., 2006; Erickson et al., 2011) with corresponding increases in cognitive function.

While MRI had been in general use for over a decade, the advent of functional MRI (fMRI) in the early 1990’s offered a powerful tool to understand patterns of brain activity during tasks. Task-based fMRI became the dominant method of neurocognitive investigation and the impact of aging on brain activity began to receive greater attention in the early 2000’s (D’Esposito et al., 2003). Models of neural activity during task-based fMRI evolved over the next decade indicating that the aging brain showed distinctive differences in cortical recruitment as compared to younger adults (Cabeza, 2002; Davis et al., 2007; Park & Reuter-Lorenz, 2009; Wierenga et al., 2008). However, groups of researchers interested in exercise and aging began to note that older adults who engage in regular aerobic exercise tend to show patterns of brain activity more similar to younger adults (Zlatar et al., 2013). The seminal work in the cognitive domain in these regards showed that older adults with high aerobic capacity produced activity patterns in dorsolateral prefrontal areas similar to those of young adults during an executive function task (Colcombe & Kramer, 2003). That same group performed an exercise intervention over six months and found that previously sedentary older individuals were able to alter patterns of brain activity in the same task from those characteristic of aged individuals to those of young adults (Colcombe et al., 2004). Similar findings arose in multiple domains including tasks involving: motor control (McGregor et al., 2009), category member generation (Nocera et al., 2017), semantic memory (Smith et al., 2011) and color-word interference tasks (Prakash et al., 2011). In aggregate, these studies indicate that increased physical activity may be a prophylactic vector for maintaining neuroplasticity in the aging brain, which can be indexed by fMRI.

Other modern techniques have informed our understanding of how exercise affects the aging brain with respect to cognition. Transcranial magnetic stimulation has shown differences in measures of inter- and intra-hemispheric inhibition respective of level of aerobic exercise engagement in acute, single session intervention (Singh et al., 2014) and in cross-sectional studies of physically fit vs. sedentary adults (McGregor et al., 2011; McGregor et al., 2013). These changes are associated with differential motor performance on dexterity tasks potentially indicating modulation of excitatory tone as a result of aerobic activity. In
addition, near infrared spectroscopy (NIRS) has also shown exercise-induced differences in laterality of dorsolateral prefrontal activity in older adults exhibiting improved performance on color-word interference tasks (Hyodo et al., 2012). Electroencephalography (EEG) also has shown changes in oscillatory frequencies in older adults depending on level of physical activity (Dustman et al., 1996; Lardon & Polich, 1996; Endo et al., 2006).

Another issue regarding exercise-induced neural plasticity is the role of brain derived neurotrophic factor (BDNF), which is a substrate for neural plasticity in the brain. Animal studies have shown that exercise increases BDNF activity in the hippocampus (Neeper et al., 1995; Vaynman et al., 2004) and have unambiguously linked the benefits of exercise to BDNF activity. For example, Vaynman et al. (2004) showed that by blocking binding of BDNF to the TrkB receptor in the hippocampus, they reduced the effects of exercise on rodent memory to the level of sedentary controls. However, translation of these findings to human research has not been as uncomplicated as might be hoped. Part of the problem may be that BDNF is measured in serum in humans as opposed to in specific brain regions for animals. For example, Erickson, Voss, Kramer, and colleagues did not find increases in serum BDNF for a one-year aerobic exercise (walking, 60–75% of heart reserve, 40 minutes, three times/week) compared to a stretching and toning control group (Erickson et al., 2011; Voss et al., 2013). Nonetheless, Erickson et al. did find that increases in hippocampal volume were positively associated with BDNF increases for this walking program, with BDNF changes accounting for 13–14% of the changes in hippocampal volume. Change in hippocampal volume, in turn, is positively associated with both increases in fitness and in spatial memory. These latter findings suggest that the role of BDNF in exercise-induced neural plasticity for aging humans is worth further investigation, though methodological challenges exist.

Although aging has not typically been considered a target for rehabilitation, the literature consistently has shown that cognitive decline accompanying aging, particularly in sedentary adults, can be mitigated by aerobic exercise. Hence, it is only natural that we attempt to apply exercise to more traditional targets for neurocognitive rehabilitation. Indeed, the fact that the effects of aging and an aging-related disease may interact (Crosson et al., 2015) suggests that the effects of exercise on aging might transfer to persons with stroke. Recent studies show that aerobic exercise can generally improve cognition in stroke survivors, though there is variability in what specific cognitive functions improve (Blanchet et al., 2016; Marzolini et al., 2016; Quaney et al., 2009; Tang et al., 2016; Zheng et al., 2015). However, whether aerobic exercise in humans can be used as an adjuvant to improve cognitive training for stroke-induced deficits is an open question. Physical activity exerts positive influence in recovery following TBI as well, including facilitation of neuroplasticity and attenuation of cognitive impairments (Archer, 2011). However, the benefits of exercise as an intervention tool in TBI may have time-sensitive boundaries for when it may be most effective or even deleterious. Increases in basal BDNF are moderated by the timing of exercise intervention after insult in animal models (Griesbach, 2011). More research is needed in dose-response relationships as well as time-window effects of exercise as a rehabilitative tool in TBI.
To summarize, in aggregate, there is now compelling evidence that aerobic exercise has direct and profound capacity to improve behavior, function, and health in the aging brain. Attempts to apply exercise to more traditional neurocognitive rehabilitation targets, like stroke and TBI, show promise but also indicate limitations. Looking ahead, the relationship between exercise and brain health in children and young adults needs more exploration. Similarly, across the life span, future inquiry should aim to increase the understanding of the dose-response relationship as well as the impact of various exercise approaches, modalities, and multimodal interventions. The utility and limitations of exercise as an adjuvant to improve cognitive rehabilitation deserves further exploration. Over the next 25 years, exciting technological advance in our approaches and understanding of genetic and epigenetic approaches as well as multimodal brain imaging techniques will undoubtedly deepen our understanding exercise effects on cognition and behavior in a variety of conditions.

**Neural Plasticity and Generalization**

In the context of neurocognitive rehabilitation, generalization refers to the accrual of the benefits of therapy to items and situations beyond the therapeutic endeavor. Given space limitations, the following discussion will focus on intrinsic generalization. Nadeau and colleagues (McClung et al., 2010; Nadeau et al., 2008; Nadeau et al., 2015) have defined intrinsic generalization as application of knowledge or procedures instantiated during therapy to other knowledge, procedures, or situations that share features, sequences, or contexts with the trained knowledge or procedures. In other words, the shared content between trained and untrained knowledge or procedures allows for propagation of therapeutic gains to the untrained knowledge or procedures. In contrast, extrinsic generalization entails the intentional, strategic application of knowledge or procedures gained during therapy to rebuild neurocognitive functions. The ability to generalize to untrained items or processes is a highly desirable characteristic for rehabilitation therapies because, realistically, it is impossible to train every item, context, or procedure which a rehabilitation participant might wish to use or might encounter. Hence, generalization multiplies the benefits of therapy. Intrinsic generalization has a neural equivalent, transference, in which plasticity in a circuit promotes concurrent or subsequent plasticity (Kleim & Jones, 2008). Because recent developments in aphasia therapy speak clearly to the issue of intrinsic generalization, the following discussion focuses on aphasia therapy to derive principles that might be applied to other kinds of neurocognitive rehabilitation.

Unfortunately, many traditional aphasia treatment approaches produce little to no generalization to untrained targets or behaviors, e.g., words or syntactic structures not used during therapy (Nickels, 2002). However, in the past 25 years, researchers in aphasiology have developed a more comprehensive understanding and a greater focus on intrinsic generalization. A greater understanding of intrinsic generalization, and its link to experience-dependent neuroplasticity, has led to a shift in the development of novel treatment approaches in aphasia rehabilitation. New approaches capitalize on transference, which promotes intrinsic generalization by providing repeated experiences that are thought to engage circuits relevant to multiple, as opposed to a single, item or process. This opens the door for improvements in both untrained targets and behaviors, as described in further
detail by Nadeau (2015). What follows are examples of treatment approaches developed to promote generalization.

**Phonomotor Treatment**

Phonomotor treatment (PMT), developed by Kendall and colleagues, is based on the concept that production of words requires intact phoneme sequence knowledge and the loss of this knowledge contributes to anomia (Kendall, Conway, Rosenbek, & Gonzalez Rothi, 2003). PMT uses multi-modal tasks to strengthen phonological sequence knowledge. The multi-modal approach includes visual and verbal descriptions of how to produce the sound (e.g., for /p/ bring the lips together and blow them apart), identification of whether two sounds are the same or different, repetition of sounds, and sound-letter correspondence. To maintain a strict focus on the phonological system, the training progresses from sounds in isolation to one-syllable phoneme sequences (e.g., “eep”) to more complex one- and two-syllable nonwords (e.g., “froik”). Real words are only introduced in the final stage of treatment. Studies of PMT have demonstrated acquisition and maintenance of gains in confrontation naming of untrained items (Kendall, Oelke, Brookshire & Nadeau, 2015; Kendall et al., 2008) as well as improvements in discourse production (Kendall, Rosenbek, Heilman, Conway, Klenberg, Gonzalez Rothi, & Nadeau, 2008), alexia (Brookshire, Conway, Hunting Pompon, Oelke, & Kendall, 2014; Kendall et al., 2003) and apraxia of speech (Bislick, Oelke, & Kendall, 2014; Kendall, Rodriguez, Rosenbek, Conway, & Gonzalez Rothi, 2006). Broad intrinsic generalization of PMT treatment effects are thought to occur because trained phoneme sequences activate similar phoneme sequences in untrained tasks (Nadeau, 2012).

**Verb Network Strengthening Treatment**

Verb Network Strengthening Treatment (VNeST), developed by Edmonds and colleagues, is based on the concept that semantic networks can be strengthened through repeated co-activation of verbs and their “agents” and “patients” (Edmonds, Nadeau & Kiran, 2009). The treatment builds on single target verbs to form sentences. For instance, using the target verb “stirs”, the patient identifies examples of “who” stirs and “what” is stirred. One of the examples (e.g., “baker stirs ingredients”) is used to continue building the semantic network through identification of “where”, “why” and “when” (e.g., “baker mixes ingredients in bowl to make cake batter before pouring it in pan”). Studies of VNeST have demonstrated acquisition and maintenance of gains in confrontation naming of untrained nouns and verbs (Edmonds & Babb, 2011; Edmonds, Mammino & Ojeda, 2014), as well as sentences and connected speech across different aphasia types and severities (Edmonds et al., 2011; 2014; Edmonds, 2016). Nadeau (2012) suggested that broad generalization occurs with VNeST because training promotes activation of untrained nouns and verbs, both of which are building blocks for connected speech.

**Complexity Account of Treatment Efficacy**

The Complexity Account of Treatment Efficacy (CATE) refers to a theoretical framework that predicts that generalization from complex to simple structures will occur when common linguistic processes are shared. CATE has been applied in the treatment of naming deficits (Kiran et al., 2003) and syntactic deficits (Thompson et al., 2003). In naming studies, training of atypical exemplars in a category (e.g., pomegranate) generalizes to untrained
typical exemplars (e.g., grapes) (Kiran et al., 2003). In an extension of the CATE principles to a slightly different framework, Kiran et al. (2009) sought to obtain intrinsic generalization within “location” categories (e.g., hospital). They expected that training of abstract words (e.g., emergency) would generalize to concrete words (e.g., doctor) within the same category. As hypothesized, three of four participants showed generalization from trained abstract to untrained concrete words. Two of four participants were trained on concrete words in location categories, and as expected, generalization from trained concrete to untrained abstract words did not occur. Similarly, in syntactic studies, training of complex sentence production (e.g., The mouse that the cat chased is small) generalizes to untrained but related syntax (e.g., wh-questions: Who did the mouse chase?). Thus, research on CATE provides evidence that intrinsic generalization between words or syntactic structures can be achieved when there are commonalities between the treated and untreated words or structures.

While aphasia therapies have been and are currently being designed to promote generalization to untrained items and processes, imaging of changes in neural systems has only begun. As noted above, Duncan and Small (2016) indicated that improvement in untrained narrative language samples was associated with increased network modularity from pre- to post-treatment. For a treatment designed using CATE principles, Sandberg et al. (2015) found increased connectivity of left superior medial frontal and right inferior frontal cortices to other cortical nodes for participants whose training generalized from abstract to semantically related concrete words. Benjamin et al. (2013) showed that a left to right shift in posterior perisylvian activity correlates with treatment outcome for a treatment that was designed to engage right frontal structures (pairing left hand movements with word-finding attempts) and generalized from trained to untrained categories in a category member generation task. The treatment was also found to generalize from single word production to word production in a narrative picture description at three months post-treatment (Altmann et al., 2014). Thus, preliminary findings with respect to neural substrates of intrinsic generalization in aphasia treatments are encouraging, but much work remains to be done.

As in aphasia therapies, other forms of cognitive rehabilitation aspire to foster independence by facilitating improvements in cognitive processes that translate to gains in real-world, functional activities. For example, in TBI rehabilitation, various interventions to improve executive functioning, memory, and attention have shown promise in generalization to untrained tasks, although mechanisms are still unclear and effects are typically in modest ranges (Kennedy et al., 2008; Tsaousides & Gordon, 2009). Chen et al. (2011) found that specific training in goal-directed attention resulted in improved performance on non-trained neuropsychological tests of attention and executive functioning. Further, improvements in attention regulation predicted significant improvements in learning and memory though not motor speed. Considering the CATE principle that generalization will be promoted when processes targeted in treatment are associated to those that are untreated, the overlap of benefit to learning and memory but not motor speed after training improves attention regulation is not surprising. Future application of neuroplasticity principles to neurorehabilitation are bound to improve generalization, and thereby quality of life over the next 25 years.
Conclusions

As evidenced by the above review and the fact that it covers only a sliver of the available research on neuroplasticity research in neurocognitive rehabilitation, the ascension of neural plasticity has been a highly impactful addition to the neurorehabilitation research literature. This paradigm shift has been so prolific that it would have been difficult to predict in 1992, as noted at the outset of this discourse. Nonetheless, it is true that much of the foundation that served as the conceptual basis for the progress we have described was already laid at that time. But, this was no mere paradigm shift, it was a paradigm shift built upon and leveraged by other paradigm shifts. While the principles for instantiating cognitive and behavioral change derived from basic neural plasticity research (Kleim & Jones, 2008) are affecting how we model new therapies (Nadeau, 2015), this valuable development is only a part of today’s landscape in neurocognitive rehabilitation research. Critical events in the development fMRI in 1991 and 1992 (Bandettini et al., 1992; Belliveau et al., 1991; Kwong et al., 1992a and b; Ogawa et al., 1992) sparked a revolution in cognitive neuroscience (Poldrack, 2012) that was soon to affect neurocognitive rehabilitation research. The development of quantitative structural imaging techniques to assess the effects of lesion and disease on cognition and behavior (e.g., Bates et al., 2003) has helped to define the limitations and the possibilities for neural plasticity in neurorehabilitation. The ability to evoke long-term changes in cortical excitability (i.e., neural plasticity) using NIBS (Jackson et al., 2016; Lenz & Vlachos, 2016) also has been shows promise of being a game-changing development, and research on the effects of aerobic exercise on cognition in older persons has expanded to become a well-known phenomenon since the meta-analysis of Colcombe and Kramer (2003). Literature in the entire arena of this review is so massive that we cannot fail to disappoint many rehabilitation investigators who read this review because we have not had the space to mention the technique, population, or therapy that is their passion. Nonetheless, the examples given in this review indicate that with respect to neural plasticity, scientific momentum will project well into the future.

Yet, the enormity advances in the past 25 years should make us humble with respect to prognosticating about the next 25 years. The nature and timing of the next wave of paradigm shifts is difficult to foresee, though many of them undoubtedly will relate to the ever evolving technosphere around us. A more modest, and perhaps achievable, objective would be to point to a few current trends from the current state of affairs that likely will accelerate:

(a) With respect to neuroimaging and neural plasticity, imaging neural systems and their connectivity has found its way from the cognitive neuroscience laboratory into the neurocognitive rehabilitation literature (e.g., Duncan & Small, 2016), and this trend will only accelerate in the search to understand the neural underpinnings of this kind of rehabilitation. (b) Multi-modality neuroimaging research has already occurred in the neurocognitive rehabilitation arena. An example of multiple imaging modality research is the use of fMRI together with VLSM to understand the neural mechanisms that contribute to the success of specific therapies (e.g., Fridriksson et al., 2010). Because of their ability to give us a clearer understanding of rehabilitation opportunities and limitations, look for the addition of different imaging modalities in multi-modality neuroimaging studies. For example, because cognitively normal older persons may have changes in cerebral blood flow...
(Hays et al., 2016) or significant accumulation of amyloid (Rowe et al., 2010), these are potential limiting factors in rehabilitation for persons with aging-related disease such as stroke, and there are methods available to observe their effect on neural plasticity in rehabilitation. (c) As noted above, some research is being done on definition of NIBS mechanisms that acutely change cortical excitability (e.g., Jackson et al., 2016; Kozyrev et al., 2014); however, we expect future research also to help define the mechanisms that facilitate long-term neural plasticity using NIBS techniques. (d) High definition (HD) tDCS, which allows for much more precise stimulation of cortical targets than traditional tDCS with large electrodes, is also making its way into the rehabilitation literature (e.g., Doppelmayr et al., 2016), and given the ability to target specific cortical regions, HD tDCS is likely to become more prominent in the neurocognitive rehabilitation literature. (e) By this time, the generally positive effects of aerobic exercise on cognition and behavior in sedentary older persons are well documented. Given the increases in BDNF with aerobic exercise and their positive relationship with increases in hippocampal volumes (Erickson et al., 2011) and given evidence that hippocampal activity increases and intactness of the hippocampus and its connections may be related to aphasia intervention efficacy (Meinzer et al., 2010; Menke et al., 2009), one might conclude that aerobic exercise also would prove to be a good adjuvant to neurocognitive treatments like aphasia therapy to enhance neural plasticity. To the best of our knowledge, such findings have yet to emerge in the human rehabilitation literature. We suspect that the underlying reality is not as direct or simple as it might seem, but animal analogue research suggests that break-through studies in this area may be possible (Ploughman et al., 2015). (f) Given the evidence that neurorehabilitation investigators can design treatments that generalize effects to untrained items and contexts, it is predictable that this kind of generalization increasingly will become a key outcome measure in rehabilitation research. This rising trend will motivate us to develop and deploy our understanding of the roots of generalization in neural plasticity processes to improve design of new treatments.

Finally, we must keep in mind that the end-game for neurocognitive rehabilitation is improvement functionality and quality of life for participants. Hence, investigators will need to concentrate on moving their innovations through appropriate clinical trials pipelines so that mature intervention strategies can be routinely delivered to the appropriate participants in clinical neurorehabilitation programs. This process will necessitate a re-evaluation of how we continue to translate a clinical trials structure developed largely for medicine (e.g., pharmaceuticals) to neurocognitive rehabilitation (e.g., Robey & Schultz, 1998). In particular, further consideration should be given to what is an effect size that can be translated to meaningful recommendations for clinical decision making regarding from what therapy a specific patient is most likely to benefit. Such discussion should take into account: (a) the nature of the type of comparisons in a trial (e.g., treatment vs. no treatment, novel treatment vs. standard of care, one novel treatment vs. another novel treatment, (b) whether the study was conducted under ideal circumstances (i.e., efficacy) vs. under a “typical” practice setting (i.e., effectiveness), and (c) the clinical diversity of a trial’s population (e.g., a single aphasia syndrome vs. all potential aphasia syndromes). Indeed, regarding the latter factor, research discussed above (e.g., Fridriksson et al., 2010) has indicated that high diversity and relatively large sample sizes (for neurocognitive rehabilitation research) can be
useful in identifying for what patients a specific treatment is most likely to work. Such considerations are important not only for interpreting clinical trial findings, but also for designing clinical trials. For example, a clinical trial designed to detect a small, not clinically meaningful effect size with no hope of determining a subpopulation for which the treatment works best may not be a wise investment of resources. However, such determinations can only be made if we have guidance on what effect sizes are likely to translate to clinically meaningful differences. Finally, finding the most effective treatments will be greatly facilitated if we understand the how to induce neural plasticity, the individual factors that encourage or limit neural plasticity in rehabilitation, and how to meaningfully measure and predict neural plasticity. If we can accomplish these goals, the future of neurocognitive rehabilitation will be very bright for the populations whom our research targets.

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**Public Significance Statement**

*Neural plasticity* refers to the ability of the nervous system to change in response to experience, and because it is responsible for our ability to learn new facts and procedures, it is the foundation for all neurorehabilitation. This review describes how the concept of *neural plasticity*, the application of its principles, and the ability to induce it and measure it have revolutionized neurocognitive rehabilitation research for neural injuries and disorders over the last 25 years. Developments in this area have given us a greater understanding of brain-behavior changes underlying rehabilitation, which is allowing rehabilitation scientists to devise exciting new approaches.