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Neuroplasticity-Based Computerized Cognitive Remediation for Geriatric Depression

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Abstract

Objective—This article describes a novel treatment model designed to target specific neurocognitive deficits in geriatric depression with neuroplasticity-based computerized cognitive remediation (NBCCR).

Method—The recent National Institute of Mental Health (NIMH) report "*From Discovery to Cure"* calls for studies focusing on *mechanisms* of treatment response with the goal of arriving at new interventions for those who do not respond to existing treatments. We describe the process that led to the identification of specific executive deficits and their underlying neurobiology, as well as the rationale for targeting these symptoms as a part of a strategy intended to improve both executive dysfunction and depression. We then propose a strategy for further research in this emerging area

Results and Conclusions—Despite significant developments, conventional antidepressant treatments leave many older adults still depressed and suffering (Thase, Entsuah et al. 2001). Psychotherapy may be effective in some depressed elders, although a recent review concluded that none of the available treatment studies meets stringent criteria for efficacy in the acute treatment of geriatric depression(Kiosses, Leon et al.). Appropriately developed and targeted NBCCR, has the potential to serve as a novel treatment intervention for geriatric depression. Pathophysiological changes associated with executive dysfunction may be an appropriate target for NBCCR. Examining both behavioral changes and indices of structural integrity and functional change of networks related to cognitive and emotional regulation may lead to a novel treatment and elucidate the role of specific cerebral networks in geriatric depression.

Keywords

Executive function; computerized cognitive remediation; geriatric; depression; neuroplasticity

Introduction

Despite significant developments, conventional antidepressant treatments leave many older adults still depressed and suffering(Thase, et al. 2001). Antidepressants developed in the past 20 years are safe but their efficacy is no better than that of tricyclics. The onset of antidepressant action is slow, improvement of symptoms is often incomplete and unstable, and remission occurs in only one third of patients(Alexopoulos 2005). Psychotherapy may be effective in some depressed elders, although a recent review concluded that none of the

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available treatment studies met stringent criteria for efficacy in the acute treatment of geriatric depression(Kiosses, et al. 2011). The recent National Institute of Mental Health (NIMH) report "*From Discovery to Cure"* calls for studies focusing on *mechanisms* of treatment response with the goal of arriving at new interventions for those who do not respond to existing treatments.

Pathophysiological changes leading to executive dysfunction may be an appropriate target for novel treatments for geriatric depression. Studies, including ours, suggest that elderly patients with major depression often exhibit deficits in select executive functions that predispose them to poor antidepressant treatment response, increase the risk of relapse(Alexopoulos, et al. 2004; Kalayam and Alexopoulos 1999), and promote disability and suicidal ideation (Dombrovski, et al. 2008). In addition, executive dysfunction often persists despite remission of mood symptoms(Murphy and Alexopoulos 2004), leaving patients perpetually vulnerable to disability(Kiosses, et al. 2000; Kiosses, et al. 2001) and relapse(Alexopoulos et al. 2004; Kalayam and Alexopoulos 1999). Further, the identified executive deficits appear to rely on similar cerebral networks, indicating a possible target for intervention. Identifying the impact of select executive deficits on clinical outcomes and their shared underlying neurobiology in geriatric depression is an essential step in the development of novel and targeted treatments that may improve clinical outcomes.

A model intended to organize research in geriatric depression proposed that factors contributing to this disorder can be divided into "mediating mechanisms", "predisposing brain abnormalities" and "etiological contributors"(Alexopoulos 2005). Accordingly, symptoms and signs of geriatric depression are mediated by hypometabolism in dorsal neocortical structures including the DLPFC and dACC, and hypermetabolism of some limbic structures. In this model, abnormalities underlying executive dysfunction may lead to depression directly by promoting the metabolic changes mediating the depressive syndrome or by serving as factors predisposing to these metabolic changes(Alexopoulos 2005).

We have previously proposed two interrelated models that illustrate a research strategy for identifying targets for novel treatment for geriatric depression. These models are based on the assumption that both age- and disease related neuroinflammation (Alexopoulos and Morimoto 2011; Morimoto and Alexopoulos 2011), and cerebrovascular disease(Alexopoulos 2006) promote changes in cerebral networks leading to geriatric depression. These neurobiological processes function as the "etiological contributors" either by damaging corticolimbic structures predisposing to depression or by directly promoting metabolic changes (hypometabolism in some dorsal neocortical structures and hypermetabolism of some limbic structures) mediating the depressive syndrome. The treatment strategy we propose in this article is an attempt to intervene at the level of "predisposing brain abnormalities" by directly targeting and changing the function of cerebral network abnormalities that predispose to poor treatment outcomes. We suggest that this strategy is likely to produce neurobiological changes leading to a clinically meaningful improvement of depressive symptoms.

This article describes a novel treatment model designed to target specific executive deficits in geriatric depression with neuroplasticity-based computerized cognitive remediation (NBCCR). Below we describe the process that led to the identification of such deficits and their underlying neurobiology, as well as the rationale for targeting these specific deficits as a part of a strategy intended to improve both executive dysfunction and depression. Recent research suggests that computerized cognitive remediation based on the principles of neuroplastic reorganization can induce neuroplasticity in the aging brain(Mahncke, et al. 2006). Therefore, neuroplasticity-based cognitive remediation may change the functioning of these identified circuits, thereby, changing the clinical outcomes of the disorder. We will

first describe the rationale for such an intervention, and then propose guidelines and specific parameters likely to result in therapeutic neuroplastic change in the older-adult brain. We base these parameters on data on the induction of neuroplasticity in aging animals, in normal aging humans, and in patients suffering from schizophrenia. We then propose a strategy for further research in this emerging area.

Computerized Cognitive Remediation (CCR)

The term “cognitive remediation” encompasses a wide variety of interventions. Currently, computerized cognitive remediation is based on multiple, divergent theoretical perspectives, and, accordingly, utilizes both diverse administration techniques and design parameters. Further, computerized cognitive remediation interventions for psychiatric populations vary by whether they serve as stand-alone treatments, as adjunct treatments to another psychosocial intervention, or as an augmentation strategy to medications. Available programs differ in their prescribed dose (how many hours); duration (over what period of time), and intensity (how challenging and individualized the programs are and how frequent the treatment sessions are) (Lustig, et al. 2009). In addition, the outcome measures of CCR interventions are often quite disparate. Therefore, comparing efficacy or outcomes across studies is complex and yields mixed results (Lustig et al. 2009).

Neuroplasticity Based Computerized Cognitive Remediation (NBCCR)

During most of the 20th century, the general consensus among neuroscientists was that brain structure was relatively immutable after a critical period during early childhood. This belief has been challenged by new, converging findings suggesting that given stimulation of the right nature, intensity and duration, many aspects of the brain remain plastic even into late adulthood.

Neuroplasticity is a fundamental property of the nervous system. The term refers to the ability of the brain to change structurally and functionally as a result of both input from the environment and perturbations including injury(Kolb and Teskey 2010). Neuroplasticity may occur on multiple levels of cortical organization; from cellular changes, to increased dendritic branching, to large-scale network alterations (e.g. cortical re-mapping after stroke). Neuronal mechanisms of neuroplasticity include Hebbian learning, dendritic modifications (in length, branching, or spine density), synaptic modifications, glial size and number, axonal and neuronal growth/regrowth, and metabolic activity.

Neuroplasticity can be measured in multiple ways. Structural changes can be quantified with imaging techniques (i.e. morphometry, diffusion tensor imaging). Function changes, or changes in connectivity, can be quantified with functional imaging. Further, neuroplasticity may be reflected in measurable behavioral changes such as learning or memory.

NBCCR, as opposed to other CCR interventions, is theoretically founded in basic neuroscience research on animal models of neuroplasticity-based learning in the adult brain. Training techniques are based on behavioral and biological determinants of therapeutic neurophysiological change. Therefore, clinical effects of NBCCR interventions are assumed to be mediated via changes to neural network functioning and alterations in synaptic connectivity in the adult brain (i.e. neuroplasticity). NBCCR paradigms rely on what is known about the organization of neural function of the targeted circuit/s and often utilize cognitive neuroscience paradigms as the bases for training stimuli and tasks.

NBCCR developed for humans adapts training parameters that have been shown to be effective in inducing neuroplastic change in aging animals. For example, there are four critical principles of NBCCR interventions designed for the adult brain. These principles are

based on the theory that neuroplasticity in an aged brain requires intensive practice coupled with the heightened neurotransmission associated with reward, and with executive control processes (i.e. dopamine, and norepinephrine)(Bao, et al. 2001). To be maximally effective, NBCCR behavioral training paradigms should engage targeted cerebral networks with sensory, motor and cognitive tasks that are: 1. increasingly challenging; 2. individually adaptive; 3. attention demanding; and 4. immediately rewarding, with the goal of reorganizing and refining cortical representations (Bao, et al. 2004).

Proof of Concept: Reversal of normal age-related cognitive decline

Recent findings from both human(Bherer, et al. 2006; Erickson, et al. 2007; Mahncke et al. 2006; Smith, et al. 2009) and animal (de Villers-Sidani, et al. 2010) studies suggest that the aging brain can make neuroplastic changes with enhanced activity (Bao et al. 2004; Mora, et al. 2007). For example in a study of older rats, behavioral paradigms designed in the manner described above reversed all measured age-related functional and structural declines in the primary auditory cortex(de Villers-Sidani et al. 2010). In humans, age-related reductions in cognitive functioning likely result from both deficits in early sensory processing resources (“bottom up”), and a failure to engage relevant executive functions such as cognitive control (“top down”) (Jones, et al. 2006). Converging evidence suggests that top down cognitive processes such as attention involve the integration of multiple more basic neurocognitive functions including sensory processing in the primary sensory cortex(Kastner and Ungerleider 2000). Conversely, age-related degradation of neural representations of incoming sensory information impairs cognitive processing and performance by both transmitting unreliable information, and by taxing executive functioning systems such as working memory(Schneider, et al. 2002).

Indeed, NBCCR designed to target both processes has been shown to reverse age-related declines in information encoding and processing and induce change in the underlying neural functions (Erickson et al. 2007; Mahncke et al. 2006). NBCCR based on the four principles improves basic cognitive functions of older adults such as memory (Smith et al. 2009), and processing speed (Smith et al. 2009), as well as executive functions such as cognitive control (Bherer et al. 2006), task shifting, resolving interference(Persson and Reuter-Lorenz 2008), and dual task processing (Bherer, et al. 2008). Further, NBCCR training “generalizes” and induces both proximal and distal transfer (Bherer et al. 2008; Smith et al. 2009). Effects of NBCCR are also sustainable, with benefits remaining at least three months after training (Mahncke et al. 2006) .

Finally, NBCCR appears to induce changes on measures of “neuroplasticity” in the aging brain. NBCCR-induced changes in brain activation in the elderly are similar to neurobiological effects in young adults. Elders show a training-dependent reduction in diffuse brain activation and increases in specific prefrontal areas, which are correlated with improved performance (Erickson et al. 2007), perhaps a result of a change in strategic processing. NBCCR of executive functions in older adults has been associated with increased resting cerebral blood flow in the prefrontal cortex(Mozolic, et al. 2010). Finally, increases in white matter indices (fractional anisotropy and mean diffusivity) in the ACC and the corpus callosum were observed in DTI studies of older adults who underwent NBCCR training, which correlated with improvements in cognitive performance(Lovden, et al. 2010; Takeuchi, et al. 2010).

NBCCR in Schizophrenia

In psychiatry, NBCCR has been most investigated in the treatment of cognitive deficits in schizophrenia. Meta-analyses, have repeatedly demonstrated moderate effect sizes of NBCCR treatment in improving cognition in these patients compared to active control

conditions(Genevsky, et al. 2010). Further, remediation induced improvements above and beyond the effects of non-specific computer stimulation (Bell, et al. 2001; Fisher, et al. 2009; Twamley, et al. 2003). Effects of NBCCR transfer beyond training measures to gains in distinct neurocognitive domains other than those directly trained (Twamley et al. 2003), including social cognition(Grynszpan, et al. 2011). NBCCR training also improved functional outcomes such as employment (Bell, et al. 2005), and persisted at 6 and 12 month follow-up after the conclusion of treatment.(Wexler and Bell 2005) Programs found to be effective for this population are dually focused; that is, they integrate bottom-up restoration of degraded perceptual processing with top-down training of executive functions.(Adcock, et al. 2009)

Imaging studies in schizophrenia are consistent with clinical observations. Increased training-dependent activations in the BOLD signal were noted in the DLPFC, ACC, and frontopolar cortex, of patients and activation correlated with behavioral improvement (Haut, et al. ; Wexler, et al. 2000). These results indicate that the long-recognized hypofrontality in this disorder may be reversed with appropriately targeted training. Hypometabolism in frontal structures (dorsal neocortical, including the DLPFC and OFC) is also important in the pathophysiology of geriatric depression. These findings suggest that cognitive remediation designed to target similar behavioral functions and underlying frontal abnormalities in geriatric depressed patients may hold promise to produce similar salutary changes.

An NBCCR Strategy for Geriatric Depression

What follows is an example of a research strategy for the development of NBCCR targeting cognitive deficits associated with poor treatment response of geriatric depression. We present findings that identify potential target functions and underlying target networks, and briefly describe a research strategy designed to evaluate whether NBCCR is a viable alternative treatment for geriatric depression.

The Role of Executive Dysfunction

Among the impairments in cognitive function that accompany geriatric depression, executive dysfunction has been consistently associated with poor outcomes(Alexopoulos, et al. 2005; Alexopoulos, et al. 2000; Kalayam and Alexopoulos 1999; Kiosses et al. 2001; Morimoto, et al. 2010; Sneed, et al. 2010; Sneed, et al. 2008; Sneed, et al. 2007). Executive dysfunction is common in geriatric depression(Lockwood, et al. 2002), with up to 40% of patients exhibiting decrements in performance(Alexopoulos, et al. 2002). Deficits in some executive functions predict poor remission rates with selective serotonin reuptake inhibitors (SSRI's) and other medications (Alexopoulos et al. 2000; Kalayam and Alexopoulos 1999). Further, executive deficits persist after depressive symptoms and signs subside leaving patients with disability(Kiosses et al. 2000; Kiosses et al. 2001) and increased propensity to depressive relapse(Alexopoulos et al. 2004; Kalayam and Alexopoulos 1999; Sneed et al. 2007).

Executive Functions Predicting Poor Clinical Outcomes

Decrements in performance on the Initiation/Perseveration (I/P) subtest of the Dementia Rating Scale (DRS) predict poor response to antidepressant treatment in geriatric depression (Alexopoulos, et al. 2003; Kalayam and Alexopoulos 1999). A meta-analysis examining the relationship between pretreatment cognitive impairment and response to antidepressant medication demonstrated that only the DRS I/P subtest was a reliable predictor of poor antidepressant treatment response(McLennan and Mathias 2010). Though not a classical test of executive function, the I/P portion of the DRS tests multiple coordinated cognitive skills that require executive functioning. A recent study, showed that, among the function tested

by the I/P, only the Complex Verbal portion (CV/IP) predicted remission during treatment with escitalopram (Morimoto et al. 2010). The CV/IP tests word generation ability by asking patients to name all of the items they can think of in a supermarket (i.e. semantic fluency). Performance on speeded verbal tasks such as the CV/IP can be improved by the use of strategies, such as the organization of responses into super ordinate verbal categories (semantic organization) e.g. replying with words belonging to the same category (fruit) e.g. grapes, strawberries, bananas, oranges, etc. rather than separate categories e.g.: " bread, bananas, milk, etc. Completing strategic semantic tasks such as the CV/IP also requires selection of words from multiple activated responses, and suppression of semantically or phonemically related but inapplicable words. In the above study, the use of semantic strategy, explained performance differences between remitters and non-remitters(Morimoto et al. 2010).

Another commonly reported neuropsychological deficit associated with geriatric depression is in episodic memory dysfunction (Hickie, et al. 2005). A study exploring semantic strategy on a classic test of verbal memory, the Hopkins Verbal Learning Test Revised (HVLT-R), showed that patients who remitted while treated with escitalopram utilized more semantic clusters (grouping semantically related words together during recall) than those who did not remit. Further, the remitters' clustering scores increased during the three learning trials suggesting a recognition or initiation of strategy, where as non-remitters use of clustering strategy remained constant and significantly lower throughout the three learning trials(Morimoto, et al. 2011). The two analyses described above identified *semantic strategy* as a discrete domain of executive dysfunction related to antidepressant response, regardless of the task by which it is elicited (i.e. verbal memory or semantic fluency).

A second executive function consistently associated with poor antidepressant treatment response is susceptibility to cognitive interference (Sneed et al. 2010; Sneed et al. 2008; Sneed et al. 2007). The Stroop Color-Word Test, the classic measure of this function has been associated with poor response in depressed patients aged 75 years and older (Sneed et al. 2007). These findings have been replicated (Simpson, et al. 1998). The Stroop Color-Word Test consists of three blocks of trials. In the first block (word condition), printed color names (red, blue, green) are presented in black. In the second block (color condition), a string of the letter X is presented in different colors (red, blue, green). In the third block, color names are again presented, but this time printed in incongruous colors. This final task requires the suppression of a habituated (prepotent) response, i.e., naming the ink color that incongruously named color words are printed in. The increase in time taken to perform the latter task compared with the basic task is generally considered a measure of inhibitory control (Anderson 2003; Van der Elst, et al. 2006).

Selection of a Target Network for NBCCR

The executive functions associated with poor antidepressant response(Morimoto et al. 2010; Sneed et al. 2008; Sneed et al. 2007) are mediated, at least in part, by the Strategic Semantic Control Network (SSCN). In normal adults, *semantic fluency* is associated with activations in the left inferior and the middle frontal gyrus, especially when semantic strategies ("clustering") are applied(Bor, et al. 2004). Use of *semantic strategy* and higher word production are associated with greater dorsal anterior cingulate cortex (dACC) activation(Kaneda and Osaka 2008). Semantic organizational strategy (mental reorganization of verbal material) is associated with activation of the dorsolateral prefrontal cortex (DLPFC)(Long, et al. 2010; Owen 2000). *Verbal strategy initiation* is associated with activation of the orbitofrontal cortex (OFC) and activation is correlated with subsequent memory performance (Savage, et al. 2001). *Conflict detection and resolution* of irrelevant verbal memory traces are mediated by the dACC and DLPFC(Basho, et al. 2007). Further, the prefrontal regions mediating semantic processing may influence emotional control

processes (i.e. emotional regulation) in older adults(Ritchey, et al. 2011). Dysfunction in the SSCN may produce multiple downstream behavioral manifestations that are similar (semantic strategy deficits vs. cognitive interference deficits) but not identical due to individual differences in network abnormalities, pre-morbid network characteristics and network interactions with other brain systems necessary for completion of tasks.

SSCN, Aging, and Depression

The SSCN network is adversely affected by aging (Meinzer, et al. 2009; Wierenga, et al. 2008). Older adults perform worse than younger adults on tasks requiring semantic strategy including semantic fluency(Brickman, et al. 2005; Meinzer et al. 2009) and verbal memory, during both encoding and retrieval(Dunlosky, et al. 2005; Shing, et al. 2010). Moreover, aging preferentially damages prefrontal SSCN structures including the DLPFC, and OFC(Raz, et al. 1997). Older adults show inefficient recruitment of the task-dominant prefrontal cortical areas (primarily left), and disinhibition of non-specialized networks (primarily right) on tasks requiring semantic strategy(Meinzer et al. 2009; Wierenga et al. 2008). Moreover, aging induces region-specific alterations in dendritic morphology, cellular connectivity, gene expression and other neuroplastic processes that ultimately affect SSCN function(Burke and Barnes 2006).

Geriatric depression occurs in the context of abnormalities in brain structures central to SSCN. Older depressed adults have bilateral damage to SSCN structures and their connections including the OFC, ACC, and DLPFC compared to elderly controls (Ballmaier, et al. 2004; Gunning-Dixon, et al. 2008). Further, older adults with major depression have greater deficits in verbal fluency, and cognitive control than depressed young adults, which persist after symptom improvements (Elderkin-Thompson, et al. 2003; Herrmann, et al. 2007; Lockwood et al. 2002).

Neurobiological studies, including ours, utilizing diverse methods have observed that abnormalities in biological measures associated with executive dysfunction also predict resistance to an SSRI in geriatric depressed patients(Alexopoulos, et al. 2010; Alexopoulos et al. 2005; Alexopoulos et al. 2004; Alexopoulos, et al. 2008). Structural and functional neuroimaging have documented both frontostriatal impairment and the relationship between frontostriatal impairment and executive dysfunction in geriatric depression (Aizenstein, et al. 2009; Murphy, et al. 2007). A recent study found significant associations between fractional anisotropy and Stroop Color Word Interference performance in multiple frontostriatal limbic regions, providing evidence for the association of these areas with the executive dysfunction often accompanying geriatric depression (Murphy et al. 2007). A functional MRI (fMRI) study demonstrated both hypoactivation of the dorsolateral prefrontal cortex (DLFPC) and reduced functional connectivity between the DLFPC and dorsal anterior cingulate pre treatment, and persistent reduced functional connectivity following treatment on a cognitive control task (Aizenstein et al. 2009).

The above studies indicate that executive dysfunction is common in geriatric depression, and does not improve significantly when depressive symptoms and signs subside. In addition, specific executive functions influence the course of affective symptoms in patients treated with antidepressants. Studies using diverse biological methods indicate frontostriatal impairment underlies the executive deficits in geriatric depression and may predispose patients to poor antidepressant treatment response. Identifying the relationship of this neurocognitive deficit to cerebral network dysfunction to remission may serve as an essential first step providing the treatment targets for a neuroplasticity-based computerized cognitive remediation (NBCCR) intervention likely to improve both executive dysfunction and depression.

A Research Strategy for Developing NBCCR as a Treatment for Geriatric Depression

Mechanism Validation

Controlled trials testing the acceptance, feasibility, and efficacy of NBCCR in geriatric depression will be a necessary first step to establish the value of this novel intervention. Three important questions may be addressed by NBCCR studies:

Will computer based cognitive remediation be able to induce neuroplasticity in the aging brain?—Neuroplasticity within the target circuit may be measured through probed fMRI or evoked potentials. Neuroimaging methods such as morphometry or DTI may also be included in the investigation.

Are interventions targeted to clinically relevant neural circuits necessary for clinical improvement? Or is non-specific cognitive stimulation similarly effective?—Studies comparing targeted NBCCR to non-specific computer stimulation matched in length of exposure, audio-visual presentation, computer use, and contact with research staff, will help to differentiate between active and non-specific effects of the intervention. In addition to non-specific control interventions, CCR targeted to neurocognitive functions not found to be predictive of clinical outcomes may improve our understanding of the mechanisms of this intervention. For example, based on the observation that patients with geriatric depression exhibit episodic memory impairment compared to normal older adults, a few studies have been undertaken training memory function in depressed older adults. These studies demonstrate improvements in the targeted function (i.e. memory), but no effect on depression, or other clinical symptoms (Naismith, et al. 2010). To our knowledge, there are no studies implicating memory impairment in the relationship to remission of symptoms. In addition, we have demonstrated previously, that episodic memory impairment in geriatric depression may be at least partially explained by executive dysfunction, specifically the deficient use of verbal strategies(Morimoto et al. 2011). Studies like these may help to demonstrate whether CCR targeted to clinically relevant neural circuitry is necessary to change affective functioning.

Which targeted circuits or functions are necessary to produce clinically relevant change?—Precise targets may improve understanding of principles (what and where?) of neuroplastic change in the adult brain. Advances in basic cognitive and affective neuroscience and behavioral studies, and their interactions may be parlayed into the identification of novel targets for NBCCR. Studies of the nature of the target systems are of priority in this inquiry. As is true for any new treatment, an understanding of the neurobiological underpinnings and behavioral manifestations of the dysfunctional networks might improve the accuracy of targets and design of NBCCR. Studies identifying neurocognitive functions, or cerebral networks necessary and sufficient for the reliable prediction of remission (and the ones that do not), across neuropsychological tests are needed to improve the targets, and outcomes of NBCCR. Perturbation of selected, clinically relevant circuits may guide our understanding of the etiological significance of such circuits in the treatment of geriatric depression.

Target Validation

Of equal importance to the *content* of the NBCCR are the *mechanisms* related to its efficacy. Measures embedded within the computer programs designed to assess intervention design parameters should be included in studies of any NBCCR intervention. This performance data can be used to improve an intervention's efficacy and efficiency by allowing

researchers to identify and maximize key components and to remove extraneous or ineffective components. To our knowledge there are no published studies in NBCCR for psychiatric populations that include information on whether the design parameters utilized by computer programs are necessary or sufficient for producing desired clinical or cognitive changes. Analysis of design elements such as: Dose, duration, intensity, reward schedule, speed, plateau and graduation criteria should be included in the analyses. For example, consider the impact of "dose" on outcome. The magnitude of cognitive plasticity in a particular intervention may vary by length or frequency of treatment. Incremental performance data like those we suggest will provide the researchers the information to assess necessary and sufficient "dosing." This data may then guide the researchers to improve the intervention's clinical impact by adding "booster sessions", or increasing the frequency of training to increase the magnitude, or prolong the benefit of positive results.

Trial design

Neurobiological measures (e.g. EEG, fMRI, and MRI) pre- and post NBCCR training will add an important additional dimension to behavioral data. These measures may identify the engagement of patient-specific cerebral networks in individuals exhibiting similar neurocognitive or behavioral patterns. For example, neuroimaging measures may reveal improved efficiency within the brain network processing the task (i.e. unilateral vs. bilateral engagement) even when neurocognitive performance remains unchanged pre- and post training. Further, as opposed to simply measuring absolute performance improvement, neuroimaging measures may help to differentiate individual benefits of NBCCR, as patients may exhibit a range of cognitive improvements. Last, neurobiological measures may also permit a more direct inquiry into neuroplastic possibility in the depressed adult brain. For example recent data suggest that CCR targeting executive functioning in normal older adults is associated with increased resting cerebral blood flow in the prefrontal cortex(Mozolic et al. 2010), and increased white matter indices (fractional anisotropy and mean diffusivity) in the ACC and the corpus callosum in DTI studies(Lovden et al. 2010).

Defining clinically relevant outcomes will be important in both developing and comparing NBCCR interventions. Simply identifying neurocognitive gains will be insufficient; future research ought also to focus on "far transfer" and/or functional effects of training. Meta-analyses in other psychiatric disorders have shown that even small neurocognitive gains impact patients' functional capacity(Wykes, et al. 2011). Therefore, disability may be another appropriate distal outcome measure in NBCCR studies. Patients with geriatric depression exhibit significant disability related to executive functions which leaves them vulnerable to future relapse(Kiosses et al. 2001). The systematic measurement of changes in patients' every day functioning as it relates to changes in targeted cognitive functions will be essential in designing future treatments for this disorder that induce long-term remission of symptoms.

Single Treatment vs. Augmentation Strategy

As geriatric depression tends to be difficult to treat, research in this area may also aid in determining whether NBCCR can function as a stand alone intervention, or whether it can and should function as an augmentation to other treatments, such as antidepressants or psychological/behavioral treatments. For example, we have reported that a version of problem solving therapy (PST) is more effective than supportive psychotherapy in reducing depression and disability in depressed older adults with executive dysfunction(Alexopoulos, et al. 2011). If effective, NBCCR may be used in parallel with PST to accelerate rehabilitation of executive deficits whereby improving participation in problem solving exercises and influencing clinical and functional outcomes. Similar adjunct treatments (CCR

plus behavioral treatment) have been effective in treatment of schizophrenia(Bell et al. 2005).

Conclusion

NBCCR based on principles of neuroplastic reorganization may induce neuroplastic changes in the aging brain. Appropriately developed and targeted NBCCR, has the potential to serve as a novel treatment intervention for geriatric depression. Pathophysiological changes associated with executive dysfunction may be an appropriate target for NBCCR. Examining both behavioral changes and indices of structural integrity and functional change of networks related to cognitive and emotional regulation may lead to a novel treatment and elucidate the role of specific cerebral networks in geriatric depression.

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Key Points

Studies suggest that elderly patients with major depression often exhibit deficits in select executive functions that predispose them to poor antidepressant treatment response, increase their risk of relapse, and promote disability and suicidal ideation.

Pathophysiological changes leading to executive dysfunction may be an appropriate target for novel treatments for geriatric depression.

Recent research suggests that computerized cognitive remediation based on the principles of neuroplastic reorganization can induce neuroplasticity in the aging brain

Neuroplasticity-based cognitive remediation targeted to the cerebral networks underlying executive deficits, may change the functioning of these identified circuits, thereby, changing the clinical outcomes of the disorder.