ABSTRACT

The current review addresses the need for increased use of evidence-based, nonpharmacological therapies for individuals with dementia. To facilitate understanding of the potential efficacy of nonpharmacological therapies on cognitive functioning for individuals with dementia, the mechanisms of action for selected therapies are described, including the assessment method used to identify the mechanism. The strength of evidence supporting each therapy was evaluated, with some therapies demonstrating strong support and others only moderate support for their effectiveness and mechanism of action. Therapies with the strongest support include (a) cognitive training/stimulation, (b) physical exercise, and (c) music. Therapies with moderate support include (a) biofield, (b) meditation, (c) engagement with a naturally restorative environment, and (d) social engagement. Although the strength of evidence varies, together these therapies offer treatments designed to improve cognitive functioning, have low risks and adverse effects, and have the potential for widespread accessibility, thereby increasing the potential range of therapies for individuals with dementia.

Aging is associated with structural and functional changes in the brain, which can lead to poor cognitive function and neurodegenerative disorders in older adults (Arking, 2006). Brain changes in aging related to cognitive functioning include (a) decreased brain weight, size, and synaptic density, resulting in decreased synaptic activity and complexity; (b) decreased expression of neurotrophic factors, specifically decreased brain-derived neurotrophic factor (BDNF) in the hippocampus; (c) reduced neurotransmitters in the hippocampus, substantia nigra, striatal pathway, and thalamus, with changes in the hippocampus being especially apparent; and (d) decreased neurogenesis, particularly in the dentate gyrus (Arking, 2006; Burke & Barnes, 2006; Mora, Segovia, & del Arco, 2007).

Specifically in dementia, cerebral neuropathological changes include cerebral atrophy; decreased regional cerebral blood flow; and a decreased number of working neurons, synapses, and neurotransmitters in multiple cortical and subcortical regions (Reisberg, Franssen, Souren, Auer, & Kenowsky, 1998). Autopsy studies have shown that, in individuals with dementia, the brain often displayed cortical atrophy in the neocortex and hippocampus, which led to cognitive dysfunction, including memory impairment, poor executive function, and a deficit in spatial navigation (Gearing et al., 1995; Savva et al., 2009). In addition, several neuropathological changes are associated with Alzheimer’s disease, including neuritic plaques, neurofibrillary tangles, and amyloid angiopathy (Savva et al., 2009).

With aging, the role of stress hormones (i.e., cytokines and glucocorticoids) and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis are associated with cognitive impairments, including those seen in dementia (McEwen, 2006, 2007; Sotiropoulos et al., 2008). The brain plays a key role in determining organ stress, with the amygdala, hippocampus, and prefrontal cortex being affected by chronic stress responses (McEwen, 2006). In older adults and individuals with dementia, the stress response often becomes maladaptive due to disrupted or failed negative feedback loops, exposing the individual to high (i.e., toxic) levels of glucocorticoids (Sotiropoulos et al., 2011). Glucocorticoids are associated with regulation of mood and cognition and may result in cognitive disorders when secreted at high levels, such as those seen in stress responses with impaired HPA axis regulation (de Kloet, Joels, & Holsboer, 2005). These collective changes in function and resulting cognitive decline set the stage for an increased understanding of the mechanisms of action for nonpharmacological therapies directed at improving cognitive function in individuals with dementia.
zation, termed brain plasticity. Plasticity is described as the brain’s ability to change its structure and function to allow the central nervous system to obtain new information, learn new skills, establish new neuronal networks in response to environmental stimulation, and recover from brain injuries (Mora et al., 2007; Silva et al., 2012). Results of animal studies reported since the mid-1980s provide evidence of plasticity and the brain’s capacity to respond structurally to external stimuli (Black, Sirevaag & Gre- ennough, 1987; Briones, 2006; Fillit et al., 2002). Although the magnitude of plasticity in older adults is much lower than in young individuals, current literature suggests that neural plasticity does not disappear in aged brains (Aslan et al., 2012; Fillit et al., 2002). Although plasticity decreases with age, external factors have been shown to counterbalance the effects of aging and dementia-related pathology and consequently enhance plasticity and preserve cognitive function in older adults with dementia (Mora et al., 2007). Enriched and varied stimulations (e.g., physical activity, cognitive-stimulating activity, social engagement, environmental enrichment) are widely supported behavioral and environmental factors. Specifically, theories of neurological functioning and regeneration support many of the therapies included in the current review.

In humans, the production of new neurons has been shown to continue even into later years. Based on animal studies and clinical trials in humans, plasticity theory suggests that both rehabilitative and pharmacological interventions may facilitate neuronal reorganization and recovery of function (Albensi & Janigro, 2003; Bach-y-Rita, 2003a,b). Studies using human subjects tested the effectiveness of enriched environments on the preservation of neuronal function, including the slowing of cell death (Bach-y-Rita, 2003b). Robertson and Murre (1999) reviewed human studies regarding brain plasticity and concluded that the adult brain can undergo dramatic changes in neural structures, including dendritic and axonal sprouting. Swaab, Dubelaar, Scherder, van Someren, and Verwer (2003) examined evidence from a variety of studies that indicates neurons do not die in dementia, but instead in atrophy, indicating cells may continue to be stimulated. An increasing body of evidence also indicates that metabolic impairment may contribute to neuronal dysfunction and atrophy in dementia. Therefore, stimulation of neurons both pharmacologically and nonpharmacologically is a promising strategy in the treatment of dementia.

Although some nonpharmacological therapies affect cognitive function through neurophysiological mechanisms, some therapies require capacity of learning. Studies have shown that individuals with dementia can learn (Bozoki, Grossman, & Smith, 2006; De Vreese, Neri, Fiorvanti, Belloi, & Zanetti, 2001), with increased awareness of deficits being associated with an increased likelihood that an individual can benefit from cognitive rehabilitation (Clare, Wilson, Carter, Roth, & Hodges, 2004). Evidence of brain plasticity and retained awareness and ability for learning in dementia supports the potential benefits of nonpharmacological therapies.

**NONPHARMACOLOGICAL THERAPIES**

Widely used therapies that have been shown to have a potential positive impact on cognitive functioning are included in the current review, with most therapies being tested specifically with individuals with dementia. For each therapy presented, the research was reviewed if published from the early 1990s to the present and tested the effects of the therapy on cognitive functioning. From the reviewed research, published reports were then examined for testing and identification of a specific mechanism of action. The strength of the evidence (Table 1) for effects on cognitive functioning and identification of the mechanism of action were reviewed and rated. The strength of the evidence supporting each therapy is described and categorized as demonstrating either strong or moderate support for their effectiveness and mechanism of action. Reviewed therapies with the strongest support include (a) cognitive training/stimulation, (b) physical exercise, and (c) music. Therapies with moderate support include (a) biofield, (b) meditation, (c) engagement with a naturally restorative environment (NRE), and (d) social engagement. These therapies have identified mechanisms of action that support their effects on cognitive and neuronal functioning, including potential neurogenesis. An overview of the mechanisms of action specific to each treatment is found in Table 2.

**Therapies With Strongest Evidence**

*Cognitive Training/Stimulation.* Cognitive training involves individual or group activities to stimulate an individual’s cognition through association and categorization (Olazaran et al., 2010). In addition, cognitive training often involves teaching strategies with an emphasis on problem solving to enhance specific cognitive function (e.g., memory, reasoning, processing speed) and has been widely tested with individuals with dementia (Aguirre, Woods, Spector, & Orrell, 2013; Hopper et al., 2013; Olazaran et al., 2010; Sitzer, Twamley, & Jeste, 2006).

*Cognitive stimulation* refers to the characteristics of an individual’s continuous learning and adaption to environ-
mental stimuli (Yevchak, Loeb, & Fick, 2008). It is suggested that the elements of cognitively stimulating activities require (a) multiple function involvement, (b) attention control, and (c) complicated tasks (Yevchak et al., 2008). This type of activity can refer to professional work (e.g., driving a taxi, teaching, conducting research) or leisure activities (e.g., travel, extensive reading, watching performances) (Frick & Benoit, 2010). Specific to individuals with dementia, the encoding and retrieval tasks have been most consistently examined in relation to identifying the mechanisms underlying therapeutic responses to cognitively stimulating therapies (Schwindt & Black, 2009).

The concept of "use it or lose it" has been applied to cognitive aging and suggests that specific cognitive functions are more likely to be promoted or preserved when individuals experience more cognitive stimulation and frequently operate that specific function (Kramer et al., 1999; Yevchak et al., 2008). In fact, research suggests that decreased cognitive performance in older adults is not due to the brain's inability to change, but rather a result of a lack of stimulation (i.e., training) or insufficient interaction with the environment (Yevchak et al., 2008). The extant literature supports this concept, including findings that cognitive stimulation significantly benefits cognitive function, and the benefits are seen in individuals at any age (i.e., older adults, individuals with dementia, nursing home residents with more advanced disease) (Frick & Benoit, 2010; Spector et al., 2003). Recent meta-analyses indicate common outcomes of cognitive therapies include (a) improved memory and mental ability; (b) errorless learning achievement; (c) verbal and visual learning; (d) improved executive functioning, language, and attention; (e) improved functioning in activities of daily living; and (f) lower depression (Aguirre et al., 2013; Hopper et al., 2013; Olazaran et al., 2010). Long-term benefits have also been described, including improved cognitive abilities compared to controls specific to training as long as 5 years after treatment (Willis et al., 2006). However, findings from these analyses did not include reports of physical findings or mechanisms of action.

Bach-y-Rita (2003a,b) reported findings that support that the human brain can reorganize after being damaged and result in functional improvement. Mechanisms through which this reorganization can occur have been identified through studies of individuals with both mild cognitive impairment (MCI) and dementia that use measures of cortical imaging (i.e., functional magnetic resonance imaging [fMRI] and positron emission tomography [PET] scans), cerebral blood flow, and diffusion tensor imaging for assessing white matter tracts as well as performance on measures of cognitive functioning (Aslan et al., 2012; Belleville et al., 2011; Forster et al., 2011; Schwindt & Black, 2009). Reported findings from imaging studies reveal increased activation of specific brain regions, including areas of the parietal, occipital, frontal, and temporal lobes (Belleville et al., 2011; Nyberg et al., 2003; Schwindt & Black, 2009), prefrontal cortex, cerebellum, and basal ganglia (Belleville et al., 2011). Increased blood flow to specific brain regions has also been identified, including the parahippocampal gyrus and bilateral inferior frontal gyri, as well as increased connectivity (i.e., white matter) in the uncinate fasciculus and forceps minor (Aslan et al., 2012). Positive cognitive outcomes reported in these studies include face–name associative encoding (Celone et al., 2006; Diamond et al., 2007), visuospatial paired associate learning (Gould et al., 2006), abstract pattern recall (Grön, Bittner, Schmitz, Wunderlich, & Riepe, 2002), free word recall (Becker et al., 1996), attenuated decline (Mini-Mental State Exam [MMSE] and Alzheimer's Disease Assessment Scale-cog), and word recall for patients with MCI (Belleville et al., 2011; Forster et al., 2011). Specific to individuals with MCI, a systematic review of 20

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Evidence from well-designed meta-analysis or well-done systematic review with results that consistently support a specific action (e.g., assessment, intervention, treatment)</td>
</tr>
<tr>
<td>A2</td>
<td>Evidence from one or more randomized controlled trials with consistent results</td>
</tr>
<tr>
<td>B1</td>
<td>Evidence from high-quality, evidence-based practice guideline</td>
</tr>
<tr>
<td>B2</td>
<td>Evidence from one or more quasi-experimental studies with consistent results</td>
</tr>
<tr>
<td>C1</td>
<td>Evidence from observational studies with consistent results (e.g., correlational, descriptive studies)</td>
</tr>
<tr>
<td>C2</td>
<td>Inconsistent evidence from observational studies or controlled trials</td>
</tr>
<tr>
<td>D</td>
<td>Evidence from expert opinion, multiple case reports, or national consensus reports</td>
</tr>
</tbody>
</table>

Note: A1 and A2 = strong evidence; B1 and B2 = moderate evidence; C1, C2, and D = weak evidence.
|----------------------------|----------------------------------|----------------------|-------------------|-----------------|---------------------------------|
| Cognitive training/stimulation | MRI, fMRI, PET, and FDG-PET scans | • Increased activation to brain regions, including the parietal, occipito-parietal, frontal, and temporal lobes, and the cerebellum, basal ganglia, and prefrontal cortex  
• Increased blood flow to specific brain regions  
• Increased connectivity (white matter) | Non-impaired older adults with MCI and mild to moderate dementia | A1 | Improved word recall, face-name association encoding, attenuating mental decline (MCI), visuospatial paired learning, and abstract pattern recall |
| Physical exercise | Serum BDNF, cortisol, and insulin-like growth factor (IGF-1) levels; MRI and fMRI scans; brain autopsy | • Increased BDNF secretion  
• Increased neurogenesis, specifically in the dentate gyrus and hippocampus  
• Increased IGF-1  
• Increased clearance and delayed accumulation of brain amyloid β (Aβ)  
• Anti-inflammatory effects  
• Diminished stress responses; decreased cortisol secretion  
• Increased hippocampal volume  
• Increased synaptic connectivity | • Animal models  
• Non-impaired older adults  
• Adults with MCI and mild to advanced dementia | A1 | Increased verbal fluency and verbal communication, and improved executive function |
| Music therapies | Neurotransmitter secretion analysis; cytokine, melatonin, salivary cortisol, CgA, and immunoglobulin levels; PET and fMRI scans | • Modulated immune response  
• Buffers the hyper-secretion of the corticosteroid associated with stress and impaired HPA axis regulation  
• Activates neurotransmitter secretion | • Non-impaired older adults  
• Adults with mild to advanced dementia | A2 | Improved short-term recall and language abilities (improved MMSE scores) |
| Biofield therapies | Salivary cortisol and IgA; EEG; heart rate variability; natural killer cell activity and number; neuropsychological testing | • Buffers the hyper-secretion of the corticosteroid associated with stress and impaired HPA axis regulation  
• Increased immune function leading to reduction in neuroendocrine stress responses  
• Increased alpha-band activity in the frontoparietal lobes | • Cellular studies  
• Adults with mild to moderate dementia and MCI | B2, A2 | Improved mood and cognitive scores (MOCA; AMMSE), and decreased behavioral and psychological symptoms (RMBPC) and agitation |
TABLE 2 (CONTINUED)

|---------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------|---------------------------------|
| Meditation therapies      | EEG; MRI; serum melatonin, serotonin, and urinary cortisol levels | • Higher gamma-band activity in the medial frontoparietal lobes  
• Increased left-sided anterior activation  
• Thickening of the prefrontal cortex and right anterior insula  
• Increased gray matter in the left hippocampus, posterior cingulated cortex, temporoparietal junction, cerebellum, and putamen  
• Increased melatonin compared to controls  
• Increased antibody titers  
• Reduced urinary cortisol in TM practitioners | Non-impaired adults and older adults | A2 | Increased attentional performance and decreased negative affect and autonomic arousal |
| Natural environment interactions | fMRI scans; salivary cortisol levels; EEG and EKG (HR); skin conduction; neuropsychological testing | • Increased alpha activation indicating relaxation; decreased autonomic arousal  
• Activation of specific neural regions including: superior and middle frontal gyri, superior parietal gyrus, precuneus, basal ganglia, superior occipital gyrus, anterior cingulate gyrus, superior temporal gyrus, and insula  
• Decreased cortisol levels  
• Faster recovery from sympathetic activation  
• Restored attention capacity | Non-impaired older adults and adults with mild to advanced dementia | B2, B2 | Increased attention capacity and speed of processing; improved memory, calculation, semantic word fluency, orientation, and mood; and decreased agitation |
| Social engagement         | Brain autopsy; MRI and fMRI scans; electrophysiology | • Increased hippocampal neurogenesis  
• Increased synaptic plasticity in the hippocampus | • Animal models  
• Non-impaired adults and older adults  
• Adults with mild to advanced dementia | A2, C1 | Decreased risk of dementia and improved global cognitive function, semantic and working memory, spatial learning, and functional level |

Note. MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; FDG = Fluorine-18-Fluoro-deoxyglucose; PET = positron emission tomography; MCI = mild cognitive impairment; BDNF = brain-derived neurotrophic factor; HPA = hypothalamic–pituitary–adrenal; CgA = Chromogranin A; MMSE = Mini-Mental State Exam; EEG = electroencephalography; MOCA = Montreal Cognitive Assessment; AMMSE = Annotated Mini-Mental State Exam; RMBPC = Revised Memory and Behavior Problems Checklist; TM = transcendental meditation; EKG = electrocardiogram; HR = heart rate.
studies revealed fMRI findings indicating changes in brain activation specific to areas associated with memory (i.e., frontal, temporal, and occipital lobes), as well as increased connectivity in the medial temporal gyrus and precuneus (Simon, Yokomizo, & Bottino, 2012). These meta-analyses and reports of imaging studies provide support for cognitive training and stimulation therapies as beneficial for individuals with MCI and mild dementia, although the potential also exists for benefits for individuals at later disease stages.

**Exercise Therapies.** Substantial evidence suggests that physical activity and exercise, primarily aerobic exercise (e.g., walking, jogging, bicycling) and activities that require a memory for muscle movement (e.g., Tai Chi, dance), improve cognitive outcomes in older adults and individuals with dementia. A number of epidemiological studies have also supported the benefits of exercise for risk reduction for dementia, with significantly lower dementia rates for older adults who exercised more than three times per week, controlling for dementia risk factors such as APOE genetic predispositions (Larson et al., 2006; Podewils et al., 2005; Scarmeas et al., 2011; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). Mechanisms of action have been examined to identify the cellular and molecular pathways to explain these positive exercise effects on the brain.

Several meta-analyses and systematic reviews describe the effects of exercise on the brain using animal models. The complexity of the mechanisms underlying exercise-induced cognitive plasticity is supported by a recent review by Foster et al. (2011). Some of the basic exercise effects identified through animal studies include increased length and number of dendritic connections ( Cotman & Berchtold, 2002); neurogenesis in the dentate gyrus; increased BDNF levels in the hippocampus and dentate gyrus ( Adlard, Engesser-Cesar, & Cotman, 2011; Berchtold, Castello, & Cotman, 2010); increased brain uptake of insulin-like growth factor (IGF-1) (Trejo, Carro, & Torres-Aleman, 2001); and mediation of inflammatory processes ( Neman et al., 2006). Exercise has also been reported to delay amyloid β (Aβ) accumulation and improve memory in transgenic mice (Lazarov et al., 2005). Although primarily aerobic exercise has been studied, acrobatic exercise was another exercise type with positive effects on neurogenesis and synaptic plasticity, requiring motor learning compared to forced exercises (e.g., running, exercising on a treadmill) (Ball & Birge, 2002). These findings suggest that forms of exercise that require attention or motor learning, such as Tai Chi or dance, may positively affect cognitive functioning.

A number of human studies have examined the neuropathological mechanisms of physical activity on cognitive function; however, most studies, including meta-analyses, have included older adults without dementia (Colcombe & Kramer, 2003; Erickson et al., 2009; Foster et al., 2011; Kramer et al., 2006; Rockwood & Middleton, 2007). Colcombe et al. (2006) examined the association between aerobic exercise and brain structure using MRI. Study findings included increases in the volume in gray matter brain areas in the exercise group but not in the control group. Similar findings were reported by Erickson et al. (2009, 2011) when testing the effects of aerobic exercise on hippocampal volume and spatial memory in older adults. The researchers reported that a higher exercise level was positively correlated to higher hippocampal volume (increased by 2%) and increased BDNF serum levels after controlling for demographic characteristics. In addition, higher exercise and hippocampal volumes were correlated to better spatial memory. In older adults (mean age = 67.3), improved executive functioning was found following a 12-month walking exercise, along with increased connectivity between frontal, posterior, and temporal cortices using fMRI data ( Voss et al., 2010). Improved immune function with exercise has also been suggested in older adults participating in cardiovascular exercise training (Woods et al., 2009). These protective effects suggest exercise may help preserve cognitive function in older adults ( Graff-Radford, 2011).

In studies including individuals with dementia, Heyn, Abreu, and Ottenbacher (2004) examined the positive effects of exercise training and found a significant effect size for cognitive performance across studies; however, none of the studies reviewed assessed potential mechanisms of action congruent with the cognitive outcomes. Reported cognitive benefits were minimal, with primary outcomes being improvements in word fluency and verbal communication ( Friedman & Tappen, 1991; Molloy, Richardson, & Crilly, 1988). In individuals with MCI, high-intensity aerobic exercise has resulted in improved executive functioning and glucose metabolism and reduced cortisol secretion for women only, with increased IGF-1 for men only (Baker et al., 2010). Conversely, Podewils et al. (2007) found no associations between physical activity and white matter lesions using MRI data in a sample of older adults, including individuals with dementia and MCI. Systematic studies including animals and older adults without dementia provide support for benefits of exercise on cognitive functioning. However, the need exists for more systematic studies that examine exercise effects and the
mechanism of action, specifically with individuals with MCI or dementia.

Music Therapy. Music therapy is an individual or group intervention that has the potential to affect neuropsychiatric disorders, including organic disorders (e.g., dementia). Music therapies have been designed to improve self-reported quality of life of individuals with dementia in various domains, including cognitive functioning and using music experiences (e.g., singing, listening to and discussing music, moving to music) (Simmons-Stern, Budson, & Ally, 2010). Music therapy can be performed in a group setting or on a one-on-one basis using either relaxing music or the individual’s preferred music. The music therapy model is based on neuroscience called neurological music therapy (NMT). NMT is defined as the influence of music on the individual’s preferred music. In other words, NMT (a) studies how the brain is with and without music stimuli, (b) measures the differences, and (c) uses these differences to document changes in the brain through music that will eventually affect the individual with dementia nonmusically (Boso, Politi, Barale, & Enzo, 2006).

Several reviews of the effects of music therapy have found positive effects on older adults and individuals with dementia (Boso et al., 2006; Fukui & Toyoshima, 2008; Lin et al., 2011; McDermott, Crellin, Ridder, & Orrell, 2013). Studies have been conducted with community-based older adults (i.e., generally outpatient settings) and nursing home residents, with most studies using randomized, controlled study designs, although sample sizes have tended to be small (i.e., N = 20 to 87). Specific to individuals with dementia, studies have been conducted across the disease stages; however, no studies were found specific to individuals with MCI. Positive outcomes across studies have included (a) reductions in behavioral symptoms (Sakamoto, Ando, & Tsutou, 2013), anxiety, and depression (Chu et al., 2013; Raglio et al., 2010); (b) increased engagement, socialization, attention, and verbalization (Thompson, Moulin, Hayre, & Jones, 2005); and (c) heightened or improved hormonal and physiological parameters, including modulated stress responses (Khalfa, Bella, Roy, Peretz, & Lupien, 2003). Most recently, in individuals with advanced dementia, music interventions have been shown to increase short-term parasympathetic activity and reduce behavioral symptoms, suggesting continuing benefits of music therapies into the later disease stages (Sakamoto et al., 2013). One brief analysis also suggested positive cost benefits of music therapies (Bellelli, Raglio, & Trabucchi, 2012).

In studies examining the mechanisms of action for music therapies specifically in individuals with dementia, positive outcomes have been documented using primarily PET or fMRI (Fukui & Toyoshima, 2008); neurotransmitter secretion analysis (Kumar et al., 1999; Sakamoto et al., 2013); cytokine levels (Okada et al., 2009); melatonin levels (Kumar et al., 1999); and salivary cortisol, immunoglobulin, and Chromogranin A measures (Chu et al., 2013; Khalfa et al., 2003; Suzuki, Kanamori, Nagasawa, Tokiko, & Takayuki, 2007; Takahashi & Matsushita, 2006). Findings from these studies suggest that music therapies may benefit cognitive functioning through their modulation of the stress response, buffering the hyper-secretion of the corticosteroid associated with stress and impaired HPA axis regulation, as described previously (de Kloet et al., 2005). Increased secretion of melatonin and neurotransmitters associated with autonomic activation (i.e., norepinephrine and epinephrine) are proposed to result in both relaxing and activating responses (Kumar et al., 1999). In studies measuring the mechanism of action and cognitive outcomes, positive outcomes have included improved short-term recall (Chu et al., 2013) and improved language ability using the MMSE language subscale (Suzuki et al., 2004) in addition to improved behavioral outcomes (Sakamoto et al., 2013; Suzuki et al., 2007). In systematic studies conducted with individuals with dementia, findings suggest several mechanisms of action for the positive effects of music therapies, with an identified need for further studies, including additional measures (e.g., electroencephalography [EEG]), to document specific areas of the brain stimulated through music therapies (Boso et al., 2006).

Therapies With Moderate Evidence

Biofield Therapy. Historical accounts of hands-on healing and energy-based interventions have been found in numerous cultures around the world (Jain & Mills, 2010; Wang & Hermann, 2006). Termed biofield therapies, these interventions involve a practitioner using his or her hands, either on or off an individual’s body, to facilitate general health and well-being through modification of the human energy field by the direction of healing energy (Jain & Mills, 2010). These therapies include Reiki, Therapeutic Touch, Healing Touch, and others, many of which are practiced by health care professionals, particularly nurses (Anderson & Taylor, 2011). Requiring no effort on the part of the patient, biofield therapies may be an appropriate intervention for individuals with dementia over more cognitive interventions (e.g., guided imagery, meditation). Recent reviews have found that earlier studies
of biofield therapies lack adequate design features, such as appropriate controls, blinding, and sufficient sample sizes; however, results of these studies are promising and warrant further research (Anderson & Taylor, 2011; Jain & Mills, 2010). More recent studies of biofield therapies have started to address these issues, enhancing study rigor (Lu, Hart, Lutgendorf, Oh, & Schilling, 2013). Because of the variability in methodology, the aspects of the intervention that need to be present, including dosage and duration, remain to be established in specific patient populations, including those with dementia.

In vitro studies have begun to elucidate cellular mechanisms involved in mediating the effects of biofield therapies. Biofield therapy significantly reduced cytotoxicity induced by oxidative damage in primary retinal neurons, offering a protective effect, and increased the gene expression of IGF-1 (Yan et al., 2004). As previously discussed, IGF-1 is believed to mediate the effects of BDNF as well as increase the clearance of Aβ. Studies by Kiang, Marotta, Wirkus, and Jonas (2002) and Kiang, Ives, and Jonas (2005) have demonstrated that biofield therapies increase intracellular Ca²⁺ concentrations in leukemic Jurkat cells via L-type calcium channels (LTCCs). LTCCs are essential for synaptic plasticity and spatial memory in the hippocampus (Anekonda & Quinn, 2011). Aging and Aβ promote the influx of Ca²⁺ into neurons via LTCCs, leading to impaired neuronal function, adversely affecting synaptic functions in Alzheimer’s disease. Moreover, dysregulation of intracellular Ca²⁺ may contribute directly to the expression of clinical symptoms in Alzheimer’s disease (Anekonda & Quinn, 2011). Although speculative, biofield therapies may positively affect the homeostatic regulation of calcium in hippocampal neurons, thereby improving cognitive function. In a pilot study by Uchida, Iha, Yamaoka, Nitta, and Sugano (2012), biofield therapy increased mean power spectral values in the alpha range versus placebo in the frontal and central cortical regions (i.e., brain regions associated with cognitive function and the stress response) (McEwen, 2006).

Reports of studies in other chronic disease populations measuring physiological parameters in response to biofield therapies reflect positive changes in heart and respiratory rates and blood pressure (Post-White et al., 2003), and heart rate variability (Kemper, Fletcher, Hamilton, & McLean, 2009); these changes suggest relaxation is reflected in the reduction of sympathetic tone and a shift to a more parasympathetic response, influencing activity of the HPA axis, which plays a role in the stress response (as described previously), as well as in exacerbating the behavioral and psychological symptoms expressed by individuals with dementia. Biofield therapies appear to exert effects through a psychoneuroimmunological framework by reducing stress and improving immune function. Biofield therapies have been reported to increase salivary immunoglobulin A (Wilkinson et al., 2002) and increase the activity (Lutgendorf et al., 2010) and number of natural killer cells (Coakley & Duffy, 2010). Moreover, as biofield therapies often involve touch and nontouch techniques, positive effects on the immune system may be secondary to the documented beneficial effects of physical contact on both the immune response and neuroendocrine stress hormones by manual therapies (e.g., massage) (Post-White et al., 2003), leading to a decrease in HPA activity.

Relaxation, decreased anxiety and stress, and improved mood are the most common effects and hallmarks of biofield therapies, and frequently have been reported in various study populations, including individuals with dementia (Anderson & Taylor, 2011; Jain & Mills, 2010; Lutgendorf et al., 2010). In studies involving individuals with dementia, biofield therapies have been shown to decrease agitation (Hawranik, Johnston, & Deatrich, 2008) and salivary cortisol (Wang & Hermann, 2006; Woods & Dimond, 2002). By reducing cortisol levels, biofield therapies may have a positive impact on cognitive function. Using a quasi-experimental design, a 4-week biofield therapy intervention improved cognitive function and behavioral and psychological symptoms of individuals with dementia (Crawford, Leaver, & Mahoney, 2006). More recently, a 6-month biofield therapy intervention using a randomized controlled trial design was shown to reverse cognitive decline and improve mood significantly in individuals with dementia (Lu et al., 2013).

**Meditation Therapies.** The effects of meditation on cognitive functioning have been increasingly studied in older adults, with findings suggesting potential benefits for improved or sustained cognitive functioning, including potential benefits for individuals with dementia. Models supporting the efficacy of meditation therapies have focused on the positive effects on attention and information processing, including activation of specific areas of the brain (Hu, Chang, Prakash, & Chaudhury, 2011). Several types of meditation practices have been examined in adult populations, including objectless mindfulness (Davidson et al., 2003; Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004), insight meditation (Lazar et al., 2005), Sahaja and Vihangam yoga (Aftanas & Golosheykin, 2005; Prakash et al., 2010; Prakash et al., 2012), Zen meditation (Pagnoni & Cekic, 2007), and transcendental meditation (TM) (Walton
As described in a review of meditation therapies, the effects on cognition have been studied across age groups, including older adults (Xiong & Doraiswamy, 2009). These studies included both advanced and beginning practitioners, with some controlling for length of total meditation experience (Davidson et al., 2003).

Study methods have varied and included testing meditation interventions over 8 to 12 weeks (Alexander, Chandler, Langer, Newman, & Davies, 1989; Davidson et al., 2003; Holzel et al., 2011) to comparing long-term meditation practitioners to untrained controls, with long-term practitioners often engaging in meditation daily (Lazar et al., 2005; Walton et al., 2004). Studies have primarily taken place in community settings, although older adults in nursing and retirement home settings have also been included (Alexander et al., 1989). Across studies, the cognitive benefits of meditation therapies have been documented using a wide range of standardized tests. In an early study, Alexander et al. (1989) demonstrated that, in older adult participants (mean age = 81), TM resulted in improved cognitive flexibility and paired associate learning. Positive cognitive outcomes for yoga meditation practices have included increased attention, processing speed, alternation ability, and performance on interference tests (Prakash et al., 2010; Prakash et al., 2012), whereas Zen meditation has resulted in improved attentional processes (Prakash et al., 2009). These studies included both advanced and beginning meditation practitioners compared to controls, with long-term practitioners often engaging in meditation daily (Lazar et al., 2005; Walton et al., 2004). Studies have primarily taken place in community settings, although older adults in nursing and retirement home settings have also been included (Alexander et al., 1989). Across studies, the cognitive benefits of meditation therapies have been documented using a wide range of standardized tests. In an early study, Alexander et al. (1989) demonstrated that, in older adult participants (mean age = 81), TM resulted in increased left-sided anterior activation on EEG (participants’ mean age = 36) (Davidson et al., 2003). Using MRI, structural changes in the brain have been reported, with the prefrontal cortex and right anterior insula being thicker in long-term practitioners using insight meditation (mean age = 38), with more pronounced effects in older practitioners (Lazar et al., 2005). These brain regions are associated with attention and sensory processing, which is consistent with findings of increased attentional capacity in meditation practitioners. In addition, the thickness of the inferior occipitotemporal visual cortex was correlated with years of meditation experience, controlling for age and average thickness of the right hemisphere. More recently, in meditation-naïve participants (i.e., non-dementia), mindfulness-based stress reduction practitioners (8-week treatment) demonstrated MRI structural changes, including increased gray matter concentrations in the left hippocampus, posterior cingulated cortex, temporo-parietal junction, cerebellum (Holzel et al., 2011), and putamen (Pagnoni & Cekic, 2007) compared to controls.

Metabolic stressors have also been examined, with melatonin secretion being greater in TM practitioners compared to controls; however, melatonin secretion began to decline in TM practitioners after long meditation—an effect that was not explained (Solberg et al., 2004). In post-menopausal women (mean age = 75), following an administered metabolic stressor (glucose), long-term TM practitioners displayed significantly lower cortisol levels compared to non-practicing, age-matched controls (Walton et al., 2004). Interestingly, along with activation of specific brain regions, increases in antibody titer following an influenza vaccination were also found in practitioners compared to controls, suggesting positive effects on immune functioning (Davidson et al., 2003).

Although studies are lacking meditation specifically with individuals with dementia, these findings have identified mechanisms of action with the potential to positively impact cognitive functioning, including changes in brain structure and stress responses. As cortical thinning occurs with aging and more aggressively in dementia, the preservation of cortical thickness in specified brain regions may buffer or attenuate this thinning in individuals with dementia (Hu et al., 2011). The positive effects of TM on cortisol response and melatonin secretion may reduce the well-documented harmful effects of stress-induced cortisol secretion in the hippocampus, including atrophy. EEG findings suggest a second, positive effect on improved attentional capacity and the ability to regulate negative emotions, further lowering autonomic arousal and decreasing the cortisol response. Although cost-effectiveness studies have not been conducted, one study reported higher levels of mind–body therapies in adults with neurological conditions, including dementia, supporting the potential acceptance of these therapies by individuals with dementia (Wells, Phillips, & McCarth, 2011).

**Interacting With the Natural Environment.** Multiple studies have shown that interacting with the natural environment produces attention-restoration effects, thus improving cognitive function (Hartig, Evans, Jamner, Davis, & Garling, 2003; Kaplan, 1995, 2001). Interactions with
nature may include any activity that stimulates one or more of the senses either through natural or man-made stimuli (Gibson, Chalfont, Clarke, Torrington, & Sixsmith, 2007; Herzog, Chen, & Primeau, 2002). Natural environments have been shown to improve attention and memory more effectively than built environments (Korpela & Hartig, 1996; Lauman, Garling, & Stormark, 2003). The NRE can be experienced indoors or outdoors and can include gardening, aromatherapy, light therapy, a walk in nature, viewing nature through windows, and listening to bird or water sounds. NRE interactions provide cognitive, physical, and emotional stimulation and spiritual enhancement (Cox, Burns, & Savage, 2004; Lee & Kim, 2008; Ottosson & Grahn, 2005). NRE elements are a rich source of multisensory stimulation and range from physically passive to active engagement and individual or social stimulation (Bengtsson & Carlsson, 2005; Sugiyama & Ward-Thompson, 2007).

As noted previously, studies demonstrate that attention control is an important mechanism in cognition, especially for individuals with dementia (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Gorus, De Raedt, Lambert, Lemper, & Mets, 2006; Perry & Hodges, 1999). Attention has been correlated with memory, executive functions (e.g., planning, decision making), motor function, and way-finding (Baddeley et al., 2001; Parasuraman & Haxby, 1993; Perry & Hodges, 1999). Selective or directed attention is the ability that allows directing responses to salient stimuli and processing information without interference from irrelevant stimuli (Perry & Hodges, 1999). The control of cognition (i.e., executive functioning) and emotions (i.e., self-regulation) share limited resources (Baumeister, Vohs, & Tice, 2007; Kaplan & Berman, 2008; Cimprich, 1993; Cimprich & Ronis, 2001, 2003; Herzog et al., 2002; Tennessen & Cimprich, 1995). Other studies not using a dementia sample have found correlations between improved attention capacity and interventions using nature with use of backward digit span testing or attention network task tests (Berman, Jonides, & Kaplan, 2008; Cimprich, 1993; Cimprich & Ronis, 2001, 2003; Herzog et al., 2002; Tennessen & Cimprich, 1995). Lauman et al. (2003) demonstrated decreased autonomic arousal by viewing natural versus urban settings by measuring inter-beat intervals (via EKG) and improved orienting task performance.

There have been fewer studies for populations with dementia, but they still show evidence of cognitive benefits. Using indoor gardening activities, Lee & Kim (2008) demonstrated significant improvements in cognitive scores on the Revised Hasegawa Dementia Scale. Support for positive cognitive effects in individuals with dementia was demonstrated in a quasi-experimental study by Tse (2010). NRE therapies have demonstrated a variety of additional benefits for individuals with dementia, including decreases in agitation (Cohen-Mansfield, 2007; Detweiler, Murphy, Kim, Myers, & Ashai, 2009; La Garce, 2002; Mather, Nemecek, & Oliver, 1997; Mooney & Nicell, 1992; Riemersma-van der Lek et al., 2008; Whall et al., 1997); de-
creased psychotropic drug use and falls (Detweiler, Murphy, Myers, & Kim, 2008; Detweiler et al., 2009); circadian rhythm normalization (i.e., sleep patterns and quality) (Lee & Kim, 2008); as well as increased socialization, life satisfaction, and positive affect (Heyn et al., 2004; Jarrott & Gigliotti, 2010; Rappe & Topo, 2007; Tse, 2010).

In summary, growing evidence supports NRE therapies as having benefits for cognitive functioning for older adults, including individuals with dementia. The mechanism showing the most robust support is that of stress mediation, although due to the multidimensionality of NRE interventions, other mechanisms may contribute to the overall effects. Components of chronobiology, physical activity, social interactions, sensory stimulation, practicing remembered skills/hobbies, and sense of accomplishment and meaningfulness may play a role in the influence of NRE on cognition. NRE interventions are multidimensional activities; therefore, identifying the precise mechanisms of action for NRE need to be viewed in light of the overall impact.

Social Engagement. Social engagement is conceptually defined as staying socially connected, frequently participating in social activities, and a feeling of being socially supported (Cacioppo & Hawkley, 2009). It is generally accepted that individuals with higher social engagement have higher cognitive function and are less likely to have dementia, whereas social isolation and loneliness contribute to impaired learning and executive functions and increased risks for cognitive decline and dementia (Cacioppo & Hawkley, 2009). The positive effects of social engagement have been supported in both animal and human studies.

In animal models, rats housed in groups performed better on spatial learning tasks compared to socially isolated rats (Lu et al., 2003). In addition, the study by Lu et al. (2003) revealed that group-housed rats had significantly increased neuron proliferation in the dentate gyrus of the hippocampus and synaptic plasticity in the hippocampus. Some recovery of cognitive function also was found, with the rats previously isolated for 4 weeks and then subsequently reared in groups for another 4 weeks, showing recovered performance in spatial learning tasks (Lu et al., 2003). These early findings were supported by a later study by Madroñoal et al. (2010), in which increased hippocampal neurogenesis was observed in young mice (age = <3 months) caged in groups, providing social engagement. However, this same effect was not found in adult mice, suggesting the benefit of social engagement on associative learning and related hippocampal neurogenesis is more pronounced at younger ages (Madroñoal et al., 2010).

The benefit of social engagement on brain functioning has been further supported by evidence generated from multiple large-scale human studies (Amieva et al., 2010; Bennett, Schneider, Tang, Arnold, & Wilson, 2006). An early longitudinal, 12-year study of 2,812 home-dwelling older adults revealed that individuals with more social ties had a lower incidence of cognitive decline compared to their less socially connected counterparts (Bassuk, Glass, & Berkman, 1999). Similarly, another longitudinal study found that older adults with poor social connections, lower participation in social activities, and social disengagement were at high risk for cognitive decline (Zunzegu Gui, Alvarado, Del Ser, & Otero, 2003). Moreover, Bennett et al. (2006) reported that social network size can modify the association between dementia pathology and cognitive function; individuals with a larger network size showed higher cognitive function despite having more severe dementia pathology. This effect was especially pronounced for semantic and working memory, controlling for relevant mediating factors (e.g., depression). In a later cross-sectional study, Krueger et al. (2009) examined 838 institutionalized older adults without dementia and found that a higher frequency of social activity and perceived social support were significantly associated with higher global cognitive function, including memory, perception speed, and visuospatial ability.

Taken together, evidence (from animal and human studies) supports that social engagement is associated with higher cognitive function (including learning, executive function, and hippocampus-related memory), as well as improved neurogenesis and synaptic plasticity in the hippocampus (animal studies only). Moreover, the possibility exists that decreased cognitive functioning resulting from isolation may be reversed through later social interaction. These collective findings are promising; however, there is a lack of intervention trials testing social engagement as therapy for individuals with dementia (Flickr, 2009).

DISCUSSION

Although not exhaustive, the current review includes a variety of nonpharmacological therapies with evidence of the underlying mechanism of action on cognitive functioning from cellular, animal, and human studies (Table 2). A conceptual view of the various mechanisms of action on cognitive functioning is included (Figure), providing an overview of the mechanisms of action identified from the reviewed research. From this conceptual model, it is clear that a variety of mechanisms from nonpharmacological interventions impact cognition, with many addressing
age- and dementia-related neuropathic changes described previously. For example, increases in actual brain size and cortical thickness were demonstrated in studies testing the effects of cognitive training, physical exercise, and social engagement, whereas neurotrophic factors, including increased BDNF, were found to be modulated following physical exercise and music therapies. Changes (i.e., increases) in cerebral blood flow have also been found following cognitive therapies. Impaired HPA axis function was also positively affected by a number of therapies, including music, biofield, physical exercise, meditation, and interacting with a natural environment. The current review identifies the links between nonpharmacological therapies and their effects on specific mechanisms of action and cognitive function, many of which have been identified as being associated with aging and cognitive decline (Arking, 2006; Burke & Barnes, 2006; Mora et al., 2007). These findings underscore the understanding that many nonpharmacological interventions designed to improve cognitive functioning are theory-driven and supported by empirical research findings.

Findings from the current review also have relevance for clinical practice. By increasing our understanding of the potential benefits of nonpharmacological therapies, the implicit hope is to advance support for combined therapies for individuals with dementia, using drug and non-drug therapies with identified positive effects on neuronal functioning. Although medication therapies have been available to treat dementia for approximately two decades, the limits of these drugs have been well-established, increasing the potential importance of adding non-drug therapies to treatment plans (Tschans et al., 2011; Zec & Burkett, 2008).

As many of these therapies (i.e., cognitive training, exercise, and meditation) have preventive actions, they provide the older adult with choices for self-care actions, with benefits for disease prevention as well as maintenance of cognitive functioning. For those newly diagnosed with dementia, these therapies provide the opportunity to select treatment options that fit with the individual's preferences and previous activities. Clinically, recommending dual therapies allows the patient more treatment options, including therapies that can be individualized, based on an individual's domain of cognitive impairment and preferences, with a possible non-drug treatment plan (Table 3). As most non-drug therapies have no or few adverse effects and can be made available in many community settings, the potential benefits of incorporating non-drug therapies may far exceed the potential costs, as many of these therapies are also considered pleasant activities (e.g., music, social engagement, interacting with the natural environment).

The implications of these findings for research are evident, including the need for head-to-head studies examining the effects of dual therapies compared to medication-only therapies, especially in individuals with MCI or early-stage dementia. Research that includes
samples of individuals with MCI or early-stage dementia diagnoses are especially lacking in biofield and meditation therapies, indicating the need to increase controlled, randomized trials testing these two therapies. Studies examining combined therapies (i.e., multi-modal studies) are also indicated as suggested by the rather unique mechanisms of action found for some therapies. For example, the mechanisms of action identified for cognitive therapies have little overlap with those identified for music therapies, suggesting that these combined therapies may produce a synergistic effect on cognitive functioning. Cost-effectiveness studies are indicated as well, given the potential to improve overall functioning and decrease the need for assistive care. These findings also suggest the importance of examining the mechanism of action underlying any nonpharmacological therapy to better understand the effects on the brain and ensure the therapy has the potential to positively impact cognitive functioning in older adults, especially individuals with cognitive impairment.

CONCLUSION

The current analysis and overview provides a beginning understanding of the potential positive effects of a variety of nonpharmacological interventions on neuropsychology and cognitive function. Collectively, the variety of therapies reviewed allows for tailoring of a treatment plan based on individual strengths and preferences, providing a guide for health care providers to use in recommending nonpharmacological therapies. The current findings add to the growing body of research identifying protective or preventive factors and therapies that may be beneficial prior to the onset of memory loss or dementia. Findings may also point to the importance of future research testing nonpharmacological therapies to ameliorate pathology and potentially improve cognitive functioning in individuals with dementia.

REFERENCES


Amieva, H., Sotykova, R., Matharan, E., Helmer, C., Antonucci, T.C., & Dartigues, J.-F. (2010). What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. Psychosomatic Medicine, 72, 905-911. doi:10.1097/PSY.0b013e3181f5e121


Bach-y-Rita, P. (2003b). Late postacute neurologic rehabilitation:


Mora, F., Segovia, G., & del Arco, A. (2007). Aging, plasticity and environmental enrichment: Structural changes and neurotransmitter...
dynamics in several areas of the brain. Brain Research Reviews, 55, 78-88. doi:10.1016/j.brainresrev.2007.03.011


