Dual Task physical activity and its relationship to spatial working memory in early-stage Alzheimer's Disease.

ABSTRACT

It has been suggested that physical activity and cognitive stimulation are significant protective factors against the modifiable risk of mild Alzheimer's disease. Although many studies have investigated cognitive effects in dual-task conditions, showing improved cognitive function of the executive function and spatial working memory, those that include physical activity combined with cognitive stimuli are low in number and vary in design and replicability. The aim of the present work is to analyse the effect of a dual-task multimodal intervention on a complex validated cognitive battery test, with the purpose to share new insight on the treatment of adults with early-stage Alzheimer's disease to improve spatial working memory.

Dementia is an umbrella term used to describe a group of neurodegenerative symptoms, these include, global deterioration of intellect, cognition and behaviour, which can arise across different forms of the condition. Increases in the number of people with dementia attracts global health policy attention, particularly across developed countries (Wimo, Winbald, Aguero-Torres & von Strauss, 2003). Around 50 million people have dementia worldwide, with the most common form, Alzheimer's disease counting for approximately 60% of cases (WHO, 2020). Other forms of dementia include vascular dementia, Lewy body dementia, frontotemporal dementia, focal dementias (such as progressive aphasia), subcortal dementias (such as Parkinson's disease) and mild cognitive impairment, identified as an early stage of dementia and common in general ageing.

Ageing is associated with a progressive decline in cognitive function, which occurs according to heterogeneous trajectories, dependent on multiple physiological and environmental components (Fjell, et al., 2009). The human brain begins to atrophy in the third decade of life, and there is disproportionate age-related atrophy in the frontal, parietal, and temporal regions (Graff-Radford et al., 2021). Normal age-related changes in executive function include decline in tasks that involve attention-switching (multitasking), difficulty in instrumental activities of daily living, slower response times, reduced speed of information processing, and reduced inhibitory control (Westlye, et al., 2009).

Classifications can be made of cognitive impairment, commonly in later life, through identifying different stages along the dementia pathway aid in diagnosis and prognosis, as well as the development of interventions (Innes & Manthorpe, 2013). Diagnostic testing, such as brain scans, psychological tests or semi-structures interviews of the person or a family member, can identify stages and transitions along a suggested linear pathway of dementia (Crisp et al., 2000).

Dementia is a clinical syndrome characterised by the impairment of multiple cognitive domains, where the cognitive impairment must include loss of memory and one or more of the following: aphasia, apraxia, agnosia or executive dysfunction (Anderson, 2014). This is often severe enough to affect every day social or occupational functioning. The hippocampus is important for memory formation and spatial navigations. Loss of memory arises from early degeneration or death of neurons, starting at the entorhinal cortex in the hippocampus. These can be identified as key indicators or hallmarks of Alzheimer's disease (AD), where disorientations, confusion and memory lapses are common (Lyman, 1989). The inability to enquire, encode and retrieve memories is present at all stages of the AD, where grossly impaired cognitive performance has been evident on a range of laboratory tasks over decades of research (Miller, 1977). Using the model of working memory proposed by Baddeley (1974), neuropsychological evidence for the impairment of WM in AD is evaluated below.

Working memory (WM) is a system that enables the temporary maintenance of limited information, where that information is kept on-line or available for immediate access by other cognitively demanding tasks. This kind of active maintenance is essential for a variety of tasks such as language comprehension and problem-solving (Baddeley and Hitch, 1974.) Unlike short term memory which a passive mechanism, a system for holing a single, small amount of information for a limited duration, with no other significant other cognitive processing occurring at the same time (Miller, 1979), WM contains two elements, storage and active processing (Baddeley and Hitch, 1986.) The concept of WM shares many similarities with short-term memory but attempts to address the oversimplification of short term-memory by including the role of information manipulation (Baddeley, 2012).

WM deficit has been shown in individuals with AD across different neuropsychological battery tests. These have shown reduced span for words, letters and digits (Belleville, Peretz, & Malenfant, 1996; Cherry, Buckwalter & Henderson, 1996; Dannenbaum, Parkinson & Inman, 1988; Kopleman, 1985). Immediate memory for spatial working memory (SWM) information has also shown impairment in AD, assessed in research using traditional special memory tasks such as the corsi block tapping test combined with other visuospatial pattern tasks (Grossi et al., 2009). SWM processes have shown to be present in early stages of AD and progress in severity as the disease progresses (Sangal, 1992). In addition, measures have shown substantial cognitive deficits, such as the Brown-Peterson task, a recall task with or without a distractor task and interval to allow for rehearsal (Belleville, Peretz, & Malenfant, 1996; Kopleman, 1985) as well recency effect, also reduced in AD individuals (Carlesimo et al., 1996; Miller, 1971).

While Baddeley and Hitch's original theory of WM (1974) originally had three components; the phonological loop; the visuo-spatial sketchpad; and the central executive. WM was also described as hosting a unitary component, the central executive (CE), which is in charge of handling and processing information, and by two slave systems, the phonological loop and the visuospatial sketchpad, which is responsible for storing and keeping available verbal and visuospatial information.

Research has directly shown deficits affecting the central executive in AD, predominantly using a dual-task paradigm, finding that AD individuals are particularly impaired when performing simultaneously two different tasks, which according to Baddeley (1986), constitutes the most important functions of the central executive. Specific research focusing on the phonological store (Collette et al., 1989; Morris, 1984, 1987 & 1994; Morris & Baddeley, 1988), measured the size of phonological similarity effect in both auditory and visually presented letters and digits. Results showed reduced span for words, letters and digits was not caused by an impairment affecting the phonological store nor the articulation rehearsal system, but rather by dysfunction of the central executive system (Morris, 1994).

Logie's model of the Visio-spatial sketchpad system (VSSP) (1995, 2005 & 2008) comprises of a visual temporary store which is subject to decay and interference from new information, and a spatial temporary system, which can be used to plan or rehearse the new information stored above. Whilst contemporary research continues to show significant decline in verbal and visuospatial working memory (Lee at al., 2018), evidence is established for the two components of the Visio-spatial sketchpad system (Klauer & Zhao, 2004), there is, however, limited research from the cognitive psychology perspective on AD and Logie's sketchpad system.

Further limitations in the phonological loop and Visio-spatial sketchpad system components was found that they are not suited to serial recall, or where long-term memory is recruited and used to integrate constituent words into smaller chunks (Miller 1966) with capacity being set by the number of chunks rather than the number of words. Nor does it have scope for a combination of visual and phonological information (Baddeley, 2000). Chunking or clustering is a common strategy in the recruitment of semantically related words (Wegesin et al., 2000), involving gathering items into larger groups, based on meaning (semantic) and relationships between items (words) and on the basis of previous experience (long-term-memory) (Brown & Craik, 2000), whilst retaining the list in the mind.

An additional component to WM, the episodic buffer was therefore proposed by Baddeley (2000), regarded as a temporary storage system that modifies and integrates different sensory content. Baddeley suggests the existence of a store that is capable of drawing information from the phonological loop, Visio-spatial sketchpad system and long-term memory, and holding it in some integrated form, assuming a role of consciousness in binding these component's in the process of WM. Baddeley (1993) shares evidence from those with short term memory deficits from decline in series recall and the recall of prose suggest the need of a further back up or storage. Thus, reflecting Tulving (1989) episodic memory, the episodic buffer is controlled by executive function through the medium of conscious awareness. (Pearson, 2006; Soto & Silvanto, 2014; Zhongyi, 2008).

Tests of episodic memory and learning demonstrate established evidence in cognitive science (Collie & Maruff, 2000; Mouline et al., 2004; Carlesimo et al., 2005). Disfunction in the episodic buffer may provide a partial explanation for the difficulty's experienced in individuals with AD, when learning new information. That is, AD individuals may have an absence of the strategic organisational skills associated with the episodic buffer, that clunks units of information in order to enhance the amount of information held at any one time. Research has found that individuals at different stages of AD struggle to manipulate, integrate and organises (clunk) relevant features of new information and that this is inefficient processing, adversely impacting on their ability to learn new information (Carlesimo et al., 1998).

This research used a word-list learning task, a common memory test, in which one of the lists consisted of unrelated words, and the other of related words drawn from four semantic categories, although the related words were not presented sequentially. Participants attempted to learn the list of words across five learning trials, followed by a 15-minute delayed recall trial. As compared with healthy controls, the AD group recalled a similar number of words from the related and unrelated lists, showing little benefit from the opportunity to use semantic clustering to improve performance for the related wordlist. Although only a small sample was used in this study, this study does not explore the challenges of active switching attention, as experienced in everyday life. Contemporary measurements, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) offer an advancement on these methods, using automatised computerised tests, less influenced by the administrator, accessible to those with mild-moderate AD and shown to be a more sensitive tool for the identification of subtle differences in cognitive performance (de Jager, Milwain, & Budge, 2002). In addition, computerised testing, often conducted on devices such as Ipads, is thought to be suited to application with older adults and is being used more extensively (Erkison et al., 2019).

In early-stage AD, the central executive is impaired and can be more challenged under divided-attention tasks (Logie et al., 2004), allowing for little attention resource for new learning (Fernandes & Moscovitch, 2000; Moscovitch, 1992 & 1994). These findings suggest a learning deficit in early-stage AD may related to small deficits in attention allocation efficiency, episodic buffer function or both combined. Therefore, the in- ability to chunk information progresses through the stages in AD. Evaluating the efficiency of the episodic buffer and learning in new information under divided or full attention conditions has been in investigated (Germano et al., 2007), adding to the body of evidence that indicate the staging of WM impairment in early AD. The small sample size of healthly aging adults, adults with mild AD and those with more advanced AD is a limitation in this study, especially with issues in measurement of stages of AD. Further limitations exist across studies (Fernandes & Moscovitch, 2000; Collie & Maruff, 2000; Mouline et al., 2004; Carlesimo et al., 2005), where the accuracy of dementia stage is often undefined in studies, where there exists criticism of the index of severity used (Green et al., 1996).

Many of the studies above, referred to the Mini-Mental State Examination (MMSE) for diagnosis of severity of AD. This brief 30-item test first appeared in 1975 and is frequently used as a quick and easy method to diagnose dementia and Alzeimers disease (Folstein, 1975). It is however strongly influenced by non-cognitive domains (Devenny & Hodges, 2017) and does not translate reliably across cultures or education levels, including literacy and numeracy (Espino, 2001). The MMSE also lacks component sensitive to executive function and the screen for spatial working memory replies on just one item (Devenny & Hodges, 2017). In the UK, a revised criteria for diagnosing dementia and mild cognitive impairment (MCI), now labelled major and mild neurocognitive disorders (NCDs) in the DSM-5, is more prevalent. It shows a clearer criteria and larger weight on objective measures, meaning it could be easier to operationalise in large-scale studies of ageing and AD. Algorithmic methods to identifying neurocognitive disorders are particularly valuable in resource-intensive health practice, population studies (Tschanz, 2000) and in settings where there is limited access to biomarkers and clinical services, where globally, most dementia circumstances occur in such settings (Eramudugolla, 2017).

There can also be considerable variability between individuals, the rate and extent of cognitive decline, reinforcing the value longitudinal studies, narrative studies or methodologies in social psychology. Social psychology has done much to remind researchers and health professionals of the importance of focusing on the individual person with dementia (Sabat, 1994). It highlights possible therapies and interventions that might be useful for individuals, carers, volunteers and professionals to help them support the person with dementia, including that provided by peer support groups (Kitwood 1988,1990; Sabat & Hare, 1992). Debates exist to the influence of the various perspectives that inform our understating of dementia and alzeimers. Predominantly a biomedical and cognitive understanding has influenced health care and policy, where brain pathology, identification of symptoms, rather than reaction to the social milieu in the individual with AD lives. These evidence based social psychology perspectives, predominantly interview methods or the individual with AD or a family member, have advanced more recently (Burns & Lliffe, 2009), can aid both researchers to identify potential risks or protective factors for AD.

Factors associated with increased risk of central executive function include, but are not limited to, diabetes (Biessels et.al, 2006; Lu et al., 2009), smoking (Anstey, 2007; Choi, Choi & Park, 2018) and depression (Burk et al., 2018; Ownby et al., 2006). Factors showing an association with decreased risk of AD and cognitive decline were cognitive engagement (Slatter, Schönknecht, & Schröder, J. 2012) and physical activity (Nagamatsu et al., 2013; Santos-Loranzo et al., 2016). Whilst a consistent association for risk or protective factors does not imply findings are robust and where methodologies are varied, data is limited and quality of evidence often judged to be low, the risk and protective factors can still influence further studies and health policy and practice.

With an increase in sedentary behaviour across generations (Owen, 2020), this in-active time spent sitting at work or for travel, combined with increased life expectancy, contributes to the increased prevalence of diabetes (Garneau & Aguer, 2019), musculoskeletal impairment (Rezus et al., 2017) cardio-vascular disease (Green et al., 2017) a range of cancers (Ninot et al., 2020) as well as a broad range of other preventable health outcomes related to a sedentary lifestyle (WHO, 2020) including the long term risk of dementia (Magnon et al., 2018; Ekblom et al., 2019; Coelho et al., 2020)

Physical activity interventions have shown to improve cognition and reduce cognitive decline (Stillman et al., 2020). As a low-cost and safe non-pharmalogical strategy, evidence for aerobic and less so for strength training show positive effects on cognitive function (Erkison et al., 2019). Multi-modal training (Northey et al., 2018) is recommended is several studies for its contribution to cognition (Forte et al., 2013) and physical function (Cadore & Izquierdo, 2013). A common limitation in this literature, however is related to the nature to the studies, with variability in design and duration of intervention.

In healthy older adults, simultaneous mental and physical tasks (dual-task) has shown to be efficient in increasing cognitive function (Eggenberger et al., 2015; Falbo et al., 2016; Lauenroth et al., 2016; Herold et al., 2018) this is particularly effective if mental tasks are performed simultaneously with multimodal physical activity (Northey et al., 2018), for example dance or Thai Chi, which require more coordinative abilities and sequence recall (Hamacher et al., 2015). However, because of the wide variation between protocols, the lack of detailed methodological description (baseline levels of physical fitness, and training intensity) and small sample sizes in some studies.

A moderate-intensity multimodal physical activity program performed simultaneously to a complex previously validated cognitive stimulation is proposed as an effective intervention program to improve spatial working memory in adults with early-stage Alzheimer's disease.

Research Proposal

Dual Task physical activity and its relationship to spatial working memory in early-stage Alzheimer's Disease.

As prevalence of Alzheimer's disease is up in the UK and globally, as is the understanding across psychological perspectives of protective factors such as cognitive activities (Slatter, Schönknecht, & Schröder, J. 2012) and physical activity (Nagamatsu et al., 2013; Santos-Loranzo et al., 2016). Interventions that offer dual task (moving and thinking) activities could contribute to the range of treatments for patients at risk of AD low-cost and a safe non-pharmalogical strategy. Cognitive effects of exercise and cognitive stimulation in dual-task paradigms are indefinite (Ansai et al., 2017; Wollesen et al., 2020) there is a need for more sensitive cognitive testing batteries as outcome measures to assess the influence of dual-task interventions (Wollesen et al., 2020)

This research hypothesises that a moderate-intensity multimodal physical activity program performed simultaneously to a complex previously validated cognitive stimulation is an effective intervention program to improve spatial working memory in adults with early stage Alzheimer's disease. The results from this research offer a novel approach, with the inclusion of family or support members as well as referral from their GP; acknowledging the role of social support (Kitwood 1988,1990; Sabat & Hare, 1992).

Participants

Purposeful and opportunistic sampling will be used to identify participants. Participants (n=10) referred from their GP via social prescribing scheme will be allocated not randomly to either the Dual-Task Exercise (DTEx) or Control (CG) groups. Participants will be given the opportunity to choose to take part in the DTEx or CG prior to baseline assessments, based on their availability and convenience to attend interventions at the local facility and their ability to stay committed to the regular sessions.

To be eligible, participants are required to be >60 years and judged through local GP method (either MMSE or DSM-5) to be in early stages of Alzheimer's, an available family member or support person was also deemed to be a requirement of eligibility. They also should report no history of traumatic brain injury, stroke and be physically in-active (no regular exercise for at least 4 months prior to the assessments.

Participants will be asked to provide written informed consent and have his signed by both their family or support person along with the referring GP, indicating the participant is safe to participate in a physical activity program.

Measures

The Cambridge Neuropsychological Test Automated Battery (CANTAB) an automated test battery used for mild to moderate Alzeimer's Disease will be used. This series of 4 testing battery is clinically relevant as cognitive impairments in our tests correlate with everyday function and long-term outcomes in Alzheimer's disease and offer considerable advantage over traditional measures (ADAS-cog, MMSE) for predicting and discriminating stable from deteriorating forms of suspected dementia at an individual level (de Jager at al., 2005)

- Motor Screening Task (MOT): 2 minutes
- Reaction Time (RTI): 3 minutes
- Paired Associates Learning (PAL): 8 minutes
- Spatial Working Memory (SWM): 4 minutes
- Rapid Visual Information Processing (RVP): 7 minutes
- Delayed Matching to Sample (DMS): 7 minutes
- Match to Sample Visual Search (MTS): 7 minutes

Although testing across the range of cognitive functions, data will be drawn from the SWM 4-minute test, which has significant executive function demands and provides a measure of strategy as well as working memory errors (Cambridge Cognition, 2021). This automated measurement uses an iPad and is less influenced by the administrator due to its non-verbal stimuli and response required, in addition automated tests are a more sensitive tool for the identification of subtle differences in cognitive performance (de Jager, Milwain, & Budge, 2002).

Proposed procedures

All participants DTEx and CG, will be invited to attend the local intervention on one day to complete all the cognitive and functional exercise capacity tests pre- and post-intervention. It is expected these should take no longer than 90 minutes, with rest breaks included.

The intervention group will be asked to attend a group dance exercise class once a week at a local facility, and will be given a video of dance class to repeat at home once a week.

Recruitment (via social prescriber or GP)

Assessed for Eligibility

Baseline Assessment

Intervention Group: Dual Task Exercise twice weekly for 12 weeks.	Control Group

Repeat Assessment

Permissions and ethical considerations

Ethical Approval will be sought and will abide by the British Psychological Society's Code of Human Research Ethics, the EHU Code of Practice for the Conduct of Research and Ethical Guidance for Undertaking Research with Edge Hill University Students. Consent from participants, their support or family member and GP is required by the completion of the consent form before they can take part in the study. An information sheet containing details of research purpose, procedures, confidentiality and right to withdraw will be included.

It has been taken into consideration that the results of this study may cause some distress to participants if they complete the tests and start to feel concerned. To overcome this, we will include in the information sheet and debrief the suggestions that if participants do feel significant concern after taking part in this study then they should refer themselves to their GP and we have given them a link to local & national wellbeing links, that include public aces links for services and support. Copies of all information will also be seen and signed by their GP in advance of the intervention.

Expected Timeline

Weeks 1-8	Weeks 8-9	Weeks 10-22	Weeks 22-23	Weeks 24-28
Recruitment & Eligibility	Baseline Test	Intervention	Repeat assessment	Data analysis

Challenges & Limitations

The factors that determine the participants choice on groups included the home distance to intervention facility (the main reason in the most cases), incompatibility with the training session schedule, availability of a support person and possibly difficulties in transportation to intervention site. The use of a support person and the location of facility (local to local GP) may reduce any transportation barriers.

Asking participants to complete their dance class at home may prove difficult to monitor completion, however, the recruitment of a family or support participant, along with the weekly peer interactions is expected to minimalize any effect of non-compliance.

Computerised testing is thought to be suited to application with older adults and have been used extensively (Erkison et al., 2019), where variability in administration (self or lead testing) can affect reliability of results. The selected measure offers standardisation of administration and stimulus presentation, accurate measures of response latencies. And for analysis, offers automated comparison in real-time with an individual's prior performance as well as with age-related norms.

Finally, this study is limited to the CANTAB cognitive data collection only, but offers scope for qualitative enquiry with the AD participants as well as family support members and GPs, a possible follow up study.

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