ICT FOR ASSESSMENT AND REHABILITATION IN ALZHEIMER'S DISEASE AND RELATED DISORDERS

EDITED BY: Philippe Robert, Iracema Leroi and Valeria Manera
PUBLISHED IN: Frontiers in Aging Neuroscience

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88919-778-1
DOI 10.3389/978-2-88919-778-1

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: **researchtopics@frontiersin.org**

ICT FOR ASSESSMENT AND REHABILITATION IN ALZHEIMER'S DISEASE AND RELATED DISORDERS

Topic Editors:
Philippe Robert, CMRR Centre Mémoire – CHU CoBTeK Université de Nice Sophia Antipolis, Association Innovation Alzheimer and Institut Claude Pompidou, France
Iracema Leroi, University of Manchester, UK
Valeria Manera, University of Nice Sophia Antipolis, France

ICT and the future of clinical practice: simple objects to improve patients' assessment and stimulation. Image By Vincent Robert

Information and Communication Technologies (ICT) are no longer objects gathering dust on a shelf; instead, they have become intrinsic in our everyday lives. They are now even taking on an indispensable role in many clinical and rehabilitation settings. In the past decade there has been a surge of interest in using ICT with elderly people, both with and without dementia, in various clinical and research settings. On the one hand, ICT can supplement the assessment of functional ability by more precisely evaluating the nature and extent of functional impairment; on the other hand, ICT can be used to support elderly people in their everyday activities, as well as to ameliorate symptoms and improve quality of life through stimulation and rehabilitation. This is the intention driving the development of Serious Games (SG), which are digital applications (often based on Virtual Reality) specifically adapted for purposes other than entertaining, including rehabilitation, training and education. Finally, ICT can also play a key role in the development of interactive educational programs to support caregivers of people living with dementia.

A handful of interesting studies have started to investigate the effectiveness of employing ICT in people with different types of dementia, such as Alzheimer's disease (AD). It is therefore timely to attempt to scope this newly emerging field, as well as to foster a dialogue among the different professionals, including academics, clinicians and computer engineers, working in the area. With this in mind, the Research Topic "ICT for assessment and rehabilitation in Alzheimer's disease and related disorders" aims to provide new and interesting insights into the current use of ICT in healthy and pathological aging. The intent is also to identify challenges and new perspectives in the field, gather recommendations for the application of ICT in AD and related disorders in clinical practice, and to showcase cutting edge clinical research.

The articles included in this Frontier Research Topics have more than achieved this aim and are a perfect illustration of how ICT can be used to enhance the lives of people living dementia and their caregivers.

Citation: Robert, P., Leroi, I., Manera, V., eds. (2016). ICT for Assessment and Rehabilitation in Alzheimer's Disease and Related Disorders. Lausanne: Frontiers Media.
doi: 10.3389/978-2-88919-778-1

Table of Contents

frontiers in Aging Neuroscience

EDITORIAL
published: 20 January 2016
doi: 10.3389/fnagi.2016.00006

Editorial: ICT for Assessment and Rehabilitation in Alzheimer's Disease and Related Disorders

*Philippe Robert[1,2], Iracema Leroi[3] and Valeria Manera[1]**

[1] CoBTeK Laboratory (Cognition, Behaviour, Technology), University of Nice Sophia Antipolis, Nice, France, [2] Centre Mémoire de Ressources et de Recherche, CHU de Nice, Nice, France, [3] Institute of Brain, Behavior and Mental Health, University of Manchester, Manchester, UK

Keywords: information and communication technology, aging, Alzheimer's disease, serious games, virtual reality, assessment, rehabilitation, online education

The Editorial on the Research Topic

ICT for Assessment and Rehabilitation in Alzheimer's Disease and Related Disorders

As depicted by the cover image, this special issue unites seemingly disparate items and objects. However, importantly, all these items are related to the theme, "ICT for Assessment and Rehabilitation in Alzheimer's Disease and Related Disorders." Under this rubric, our special issue addresses four subtopics: assessment, rehabilitation, virtual reality (VR), and education.

In the last decade, there has been a growing interest in employing information and communication technologies (ICTs) with the aging population, as well as with people living with Alzheimer's disease (AD) and related disorders. This interest has manifested in several ways. For example, there has been a notable increase in the amount of research funding dedicated to projects related to the theme of ICT and aging at the level of private, national, and international funding agencies. Furthermore, there has been a significant growth in the number of academic journals and publications dedicated to the topic with a resulting explosion in the number and quality of research, policy, and clinically related publications. Finally, there has been a welcome proliferation of national and international conferences/workshops themed on ICT and aging, as well as strong representation in the topics and themes of the most important AD- and dementia-related conferences.

One of the peculiarities, and indeed fascinating aspects, of this domain is that it is intrinsically interdisciplinary and is dependent on the tight collaboration among professionals from diverse backgrounds, including researchers, clinicians, engineers, and business people. Those involved are driven by the thrill of innovation and the potential to apply exciting new technologies to some of the most basic aspects of older people's daily lives. The ultimate aim of these endeavors is to improve quality of life, enhance independence, and promote healthy living in the older population. Yet this work can be accompanied by complications, snags and hitches, not the least of which is the necessity for all the players to develop a common language. The need to span the boundaries among disciplines has resulted in some unique professional pairings, such as is exemplified by the recently launched team of CoBTek, the Cognition, Behavior and Technology Unit of the University of Nice Sophia Antipolis, which has arisen from the collaboration of the Nice Memory Clinic and INRIA. CoBTek is now working with "Innovation Alzheimer" Association in France to host and deliver annual interdisciplinary workshops devoted to developing recommendations for the use of ICT in people with AD and related disorders (Robert et al., 2013; Robert et al.). The inspiration behind the present research topic was one of the successful outputs of the workshops and was intended to bring together international researchers and professionals working in this new field to provide new insights into the current use of ICT in healthy and pathological aging. The aim also included

Edited and Reviewed by:
Rodrigo Orlando Kuljiš, University of Miami School of Medicine, USA

****Correspondence:***
Valeria Manera
valeria.manera@unice.fr

Received: *01 October 2015*
Accepted: *07 January 2016*
Published: *20 January 2016*

Citation:
Robert P, Leroi I and Manera V (2016) Editorial: ICT for Assessment and Rehabilitation in Alzheimer's Disease and Related Disorders. Front. Aging Neurosci. 8:6. doi: 10.3389/fnagi.2016.00006

the need to identify challenges and new perspectives in the field, gather recommendations for the application of ICT in AD and related disorders in clinical practice, and showcase cutting edge clinical research.

ICT FOR ASSESSMENT

As summarized by König et al., ICT can help in the assessment and evaluation of patients' behavioral and functional impairments, and thus should be more consistently employed in clinical trials. ICT allow the development of non-invasive methods to facilitate an early patient diagnosis and to evaluate more objectively behavioral and functional deficits and their evolution over time. Importantly, this assessment and evaluation can take place in a more realistic, "ecologically"-valid setting, and thus enhance the validity of the findings. Along the same theme, Lyons et al. described an innovative in-home system for continuous evaluation employing pervasive computing technologies (including passive motion sensors, contact sensors, monitoring of computer use, and phone monitors). The system was designed to prospectively and continuously detect and record health-related parameters, such as gait and mobility, sleep and activity patterns, and medication adherence in older people, with the aim of detecting early signs of cognitive and physical decline. Similarly, König et al. presented a study in the context of the FP7 Dem@Care project where they employed video-analysis methods to automatically recognize performance in activities of daily living in elderly people with MCI and early AD. Results confirmed that automated video-analysis can provide objective and quantitative measures of autonomy and functional impairment in ADLs. Other ICT-based methods that can be applied in the assessment of people with AD and related disorders include actigraphy, computerized-testing, automated audio-analysis techniques, and instruments able to quantify objectively specific biological markers, such as eye movements and EEG signals. Crawford et al. offer a good example of how eye tracking can be used to monitor saccadic eye movements of people with AD, throwing light on the importance of monitoring the evolution of participants' performance over time. Finally, Wen et al. reviewed the coupling and synchronization EEG analysis methods for the evaluation and early diagnosis of MCI, and outlined differences between the two methods, underscoring their advantages and disadvantages.

ICT FOR TRAINING AND REHABILITATION

Information and communication technology is increasingly taking on the role of training and rehabilitation of physical and cognitive functions in people with dementia, as well as fostering social interactions and emotional well-being. In the present issue, Lancioni et al. demonstrated that a computer-mediated verbal reminiscence program could significantly improve reminiscence in people with moderate AD. In a similar vein, Valentí Soler et al. showed that robot-based therapeutic sessions in nursing homes and daycare centers reduced apathy and irritability in residents with dementia.

Another growing domain is exemplified by serious games (SGs). Manera et al. presented a new SG developed within the FP7 VERVE program, which trains executive functions in people with MCI and AD. The feasibility study showed the overall acceptability of the game among those with MCI and early AD, as well its potential role in training. Despite the increased interest in the field and the promising results, SG must be validated in larger and better controlled clinical trials, as suggested by Muscio et al. Specifically, it would be important to define standard SGs parameters and to combine and harmonize different outcome measures, including recognized and validated biomarkers.

VIRTUAL REALITY

Virtual reality is another emerging field that is successfully seeping into clinical settings. VR has been applied and adapted by researchers and clinicians working with elderly people for assessment as well as training and rehabilitation. The usefulness of VR tasks for the early assessment of cognitive impairment is elegantly illustrated by Tarnanas et al., who employed a VR-based SG targeting spatial navigation and executive functions combined with a dual-task walking measurement. Interestingly, they were able to establish that the combination of motor and cognitive performance parameters was more reliable than cognitive performance alone for the early characterization of amnesic MCI, a state which in some cases may be a prodrome of AD. In a similar vein, Serino et al. used a VR-navigation task requiring the encoding and memorization of spatial representations, and found that participants had a specific deficit in the ability to encode and store allocentric (viewpoint-independent) representation.

Despite these promising examples, more work needs to be done to exploit the full potential of VR. In their mini-review, García-Betances et al. demonstrated that only a handful of studies, thus far, have utilized fully immersive VR systems, which use 3D displays that virtually place the person inside the virtual environment. In contrast, the majority of VR-based studies used non-immersive or semi-immersive VR, with lower levels of immersion and interaction. This is unfortunate, as immersion and interaction are features that may strongly have impact on the quality of the assessment and the effectiveness of training in clinical populations. For instance, Jebara et al. showed that in healthy older adults, the possibility to choose the itinerary to follow in a VR-navigation task improved episodic memory encoding compared to a passive navigation condition.

ICT FOR EDUCATION, COMMUNICATION, AND CAREGIVER SUPPORT IN DEMENTIA

Several clinical trials are starting to investigate the potential of the Internet and online tools to create interactive educational programs to support caregivers of people with dementia. The aim here is to minimize caregiver burden and stress and improving quality of life. Internet-based approaches may also facilitate communication among the different stakeholders involved in a dementia care network. For example, Span et al. tested an interactive web tool developed to enhance shared decision-making among people with dementia, caregivers, and health-care professionals. They found that all the stakeholders found the tool useful for decision making and fostering communication.

Finally, another, and seemingly "space-age," approach to supporting caregivers is outlined in the paper by Pino et al. Here, the advantages of ICT are being exploited in an attempt to reduce caregiver burden by using socially assistive robots (SAR). The authors explored the opinions and attitudes toward SAR of healthy elderly persons those with MCI, as well as caregivers of people with dementia. They found that although SAR are perceived as useful solutions, especially by participants experiencing current needs (MCI and caregivers), it is clear that the field has a still a long way to progress.

As editors, we would like to extend our sincere gratitude to all our authors who have contributed to this exciting and groundbreaking special issue of Frontiers.

AUTHOR CONTRIBUTIONS

PR, VM, and IL edited the papers and wrote the manuscript.

REFERENCE

Robert, P., Konig, A., Andrieu, S., Bremond, F., Chemin, I., Chung, P. C., et al. (2013). Recommendations for ICT use in Alzheimer's disease assessment: Monaco CTAD Expert Meeting. *J Nutr Health Aging* 17, 653–660. doi:10.1007/s12603-013-0046-3

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

OPINION
published: 09 June 2015
doi: 10.3389/fnagi.2015.00110

The role of information and communication technologies in clinical trials with patients with Alzheimer's disease and related disorders

*Alexandra König[1,2], Guillaume Sacco[1,3,4], Gregory Bensadoun[1], Francois Bremond[5], Renaud David[1,6], Frans Verhey[2], Pauline Aalten[2], Philippe Robert[1,4,6] and Valeria Manera[1]**

[1] CoBTeK Cognition Behaviour Technology EA 7276, Research Center Edmond and Lily Safra, University of Nice Sophia Antipolis, Nice, France, [2] School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University Medical Center, Maastricht, Netherlands, [3] Rehabilitation Unit, Department of Geriatrics, CHU de Nice, Nice, France, [4] Centre d'Innovation et d'Usages en Santé (CIU-S), Cimiez Hospital, University Hospital of Nice, Nice, France, [5] STARS, INRIA, Sophia Antipolis, France, [6] Centre Mémoire de Ressources et de Recherche, CHU de Nice, Nice, France

Keywords: clinical trials, Alzheimer's disease, mild cognitive impairment, Information and communication technologies (ICT), sensors, outcome measures, endpoints, assessment tools

OPEN ACCESS

Edited by:
P. Hemachandra Reddy, Texas Tech University, USA

Reviewed by:
Archana Mukhopadhyay, University of Kansas, USA
Magda Tsolaki, Aristotle University of Thessaloniki, Greece

***Correspondence:**
Valeria Manera
valeria.manera@unice.fr

Received: 12 March 2015
Accepted: 23 May 2015
Published: 09 June 2015

Citation:
König A, Sacco G, Bensadoun G, Bremond F, David R, Verhey F, Aalten P, Robert P and Manera V (2015) The role of information and communication technologies in clinical trials with patients with Alzheimer's disease and related disorders. Front. Aging Neurosci. 7:110. doi: 10.3389/fnagi.2015.00110

Introduction

In the last decades, many promising disease-modifying treatments for Alzheimer's disease (AD) have been proposed. However, clinical trials conducted on the treatments' efficacy have not lead to any important breakthroughs. There is a growing consensus that this can, at least partially, be explained by methodological difficulties, including the inclusion of participants who are already in the later stages of the disease progression, and the selection of outcome measures – such as dementia conversion rate – which are not sensitive enough (Aisen et al., 2011).

Most of the current assessment tools have been accused to be artificial and to lack ecological validity (Robert et al., 2013). Furthermore, test results can show variability depending on many factors, such as the patient's emotional state, and may therefore not always fully reflect a patient's capacities and the complexity of the disease, leading to delayed diagnosis (Sampaio, 2007).

Based on the Monaco CTAD expert meeting in 2012, Robert et al. (2013) highlighted that new Information and Communication Technologies (ICT) – such as video and audio analysis techniques, computerized testing and actigraphy – may represent promising new tools to improve the functional and cognitive assessment of patients with Alzheimer's disease (AD) and related disorders [see also Konig et al. (2014), for a recent review of studies employing ICT in this domain]. However, these new technologies are still not widely employed in clinical trials for assessment purposes. In November 2014, the association Innovation Alzheimer organized a workshop with stakeholders in the field (e.g., psychiatrist, neurologists, geriatricians, psychologists, researchers, engineers, and patients) with the aim of gathering recommendations for the use of ICT in the different stages of clinical trials. These recommendations are available online on the website of the Association Innovation Alzheimer[1].

Based on these recommendations, in the present opinion paper, we will highlight how ICT may be employed in clinical trials involving patients with AD and related disorders to improve patient's assessment and the admissibility to participate in clinical trials.

[1] http://www.innovation-alzheimer.fr/homepage/

The Current Use of ICT in Clinical Trials

Information and Communication Technologies is now widely employed in several stages of clinical trials. For instance, pharmaceutical companies and Contract Research Organizations routinely adopt E-trainings for investigators. Patients' recruitment can take advantage of the wide employ of Electronic Health Records storing health-related data (Hsiao and Hing, 2014), and E-recruitment methods employing social media and the Internet are also starting to emerge. Similarly, data entry is now facilitated by electronic Case Report Forms, employed in almost the totality of the clinical trials leaded by pharmaceutical companies (Kuchinke et al., 2010). However, ICT is still not consistently used in clinical trials at the assessment stage.

ClinicalTrials.gov – a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world – contains at present (January 2015) more than 2500 clinical trials involving participants with mild cognitive impairment (MCI), AD, or other dementia types. We performed a keyword-based[2] search on these trials focusing on automated audio and video analysis techniques, actigraphy, and computerized testing. Only 16 pharmaceutical trials employing ICT for assessment purposes were retrieved: 6 employing accelerometers and 10 employing computerized testing. No study employing automated audio or video analysis techniques was found. While it is certainly possible that these numbers represent an underestimate, they suggest that more work should be done to bring the clinical domain closer to the frontiers of the clinical research.

[2]Keywords : "audio analysis", "speech analysis", "audio recording", "voice recording", "voice recognition", "video recording", "video recognition", "video analysis", "3D recognition", "accelerometer", "actigraph" "actigraphy", "motion sensor", "computerized test/testing", "computer test/testing"

ICT for Assessment in Clinical Research

The design of ICT solutions for the health domain is a complex process, which requires the close collaboration of different stakeholders (see **Figure 1**). Recent evidence suggests that ICT can play a crucial role in the assessment of AD and related disorders, both in terms of providing additional information for an earlier and more accurate diagnosis, and in terms of monitoring of the disease progression (Robert et al., 2013). For instance, it has been shown that automatic speech analysis techniques – analyses of verbal communication through computerized speech recognition interfaces – can represent a non-invasive and cheap method to gather information about verbal communication impairments, which are very common in patients with MCI and in the early stages of AD (Satt et al., 2013). These techniques are useful for automating the analysis of clinical and neuropsychological tests employed to assess linguistic abilities (such as verbal fluency and sentence repetition tests). But even more importantly, they can provide additional information that cannot be gathered in a clinical setting, such as utterance duration, filler typology, and analysis of voiced and voiceless segments. Recently, we showed that the vocal markers extracted from speech signal processing techniques differed significantly among healthy elderly participants, MCI, and early AD patients with accuracy higher than 80% (König et al., 2015a,b).

Similar observations apply to automatic video analysis techniques (Romdhane et al., 2012; Sacco et al., 2012; Konig et al., 2015c). These techniques have proven to be useful for fall detection and to improve home safety (Robinovitch et al., 2013), but recently they started to be adopted also for assessment purposes. For instance, in the FP7 project Dem@Care[3] video analysis techniques are employed to provide objective measures to assess

[3]www.demcare.eu

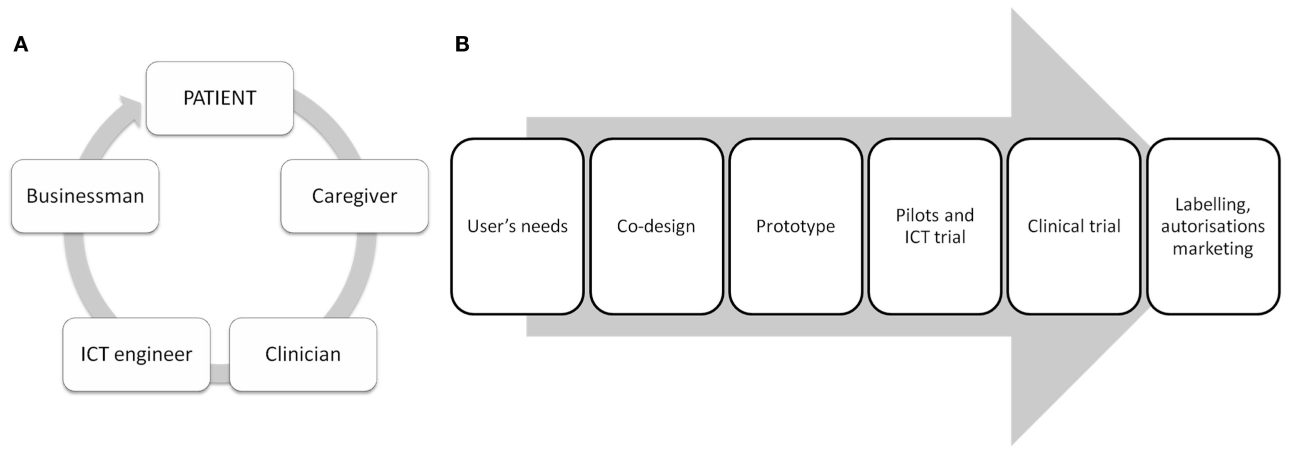

FIGURE 1 | Flowchart representing the different stakeholders (A) and the main steps involved in the design of ICT solutions for the health domain (B). **(B)** User's needs: finding and screening the patient's needs with patients, caregivers, and clinicians. Co-design: generating ideas and selecting viable ICT solutions with patients, caregivers, clinicians, and ICT engineers. Prototype development: developing a first ICT prototype with clinicians, ICT engineers, and businessmen. Pilot and ICT trial: initial tests on the usability/feasibility of the ICT solution, followed by prototype modifications. Clinical trial: study on a larger, well-defined patient's population in order to test the efficacy of the ICT solution in short and medium terms. Labeling, authorizations, marketing: leaded by ICT/business stakeholders with the help of clinicians, patients, and caregivers.

functional impairments in activities of daily living in elderly people and patients with MCI and AD. In the classical clinical settings, autonomy in activities such as taking medications, or handling finances are assessed through self-reports and informant-based questionnaires, which do not offer accurate, reproducible, objective, and ecological measures of functional performance. Using non-invasive 2D video recordings combined with video signal analysis, Konig et al. (2015c) showed that activities of daily living can be accurately detected and recognized by automated activity recognition algorithms, as suggested by results highly consistent with the clinician's evaluation. Furthermore, video analysis allowed obtaining finer-grade measures, such as the time spent on each activity, which could not be captured in the classical clinical evaluation. Siraly et al. (2015) investigated if early signs of cognitive decline could be monitored by computer memory games with the results that healthy elderly subjects achieving lower scores in the memory game have increased level of atrophy in the temporal brain structures and showed a decreased performance in the Paired Associates Learning (PAL) test. Thus, computer games may be useful tools in early screening for cognitive decline. Similarly, online questionnaires tapping risk and protective factors in different health domains (e.g., diet, physical and cognitive activity, social engagement), such as those developed in the FP7 project InMINDD[4], are starting to be employed to assess brain health and to screen for participants at risk of developing dementia.

A final example is represented by actigraphy, which is frequently used to monitor motor activity and rest-activity rhythms (Hatfield et al., 2004), and it has been proposed as an observer-independent evaluation method in different disorders, including dementia (Yakhia et al., 2014). Specifically, its utility as an assessment tool in AD and related disorders has been proven to assess neuropsychiatric symptoms such as agitation (Nagels et al., 2006; Mahlberg and Walther, 2007), depression (Volkers et al., 2003), and apathy (David et al., 2012). See Konig et al. (2014) for recent reviews on the use of actigraphy for assessment in patients with AD and related disorders.

Why Should ICT Be Employed More Consistently in Clinical Trials?

As detailed above, ICT-based techniques may represent non-invasive, objective, and inexpensive solutions to detect early cognitive and functional decline in patients with AD. Clinical interventional trials may take advantage of these solutions in several ways. First, ICT may contribute to determine the admissibility of participation in clinical trials at earlier stages of the disease, when treatment is supposed to be more effective. Patient's performance scores on one assessment may fluctuate as a function of daily rhythms, fatigue, emotion, stress, and many other state-dependent factors. Due to this variance, certain difficulties present in the earliest stages of AD and related disorders may be undetectable during the classical assessment. ICT may be of great interest in this respect, because they enable the patients' performance to be captured and accurately evaluated in real time and real life situations, even at the patient's home (Robert et al., 2013). Second, ICT may help in providing a more timely conversion diagnosis, thus improving the sensitivity of outcome measures based on conversion rate as end-point of the intervention. Similarly, by allowing easy and non-invasive continuous monitoring of the patient over time, ICT can help assessing subtle changes in behavioral, cognitive, and functional patterns, and thus contribute to the definition of outcome measures finer than dementia progression or neuropsychological test scores. Finally, ICT may provide an interesting solution for remote assessment and follow-up. One of the challenges faced by big cohort clinical studies is that there is a consistent drop-out rate, at least partially due to the fact that patients need to go to a clinic for the assessments and follow-ups. ICT solutions combined with safe data transfer methods may reduce drastically the number of required visits, thus reducing the drop-out rate and the costs/time associated with the clinical trial.

An interesting example of how ICT could be employed in clinical trials is represented by the assessment of agitation. Agitation represents one of the most frequent neuropsychiatric symptoms in patients with dementia, and one of the most challenging symptoms to manage for primary caregivers (Okura and Langa, 2011). Following the Agitation Definition Work Group provisional consensus definition (Cummings et al., 2015), agitation in patients with cognitive disorders is defined by (A) the presence of criteria for a cognitive impairment or dementia syndrome, and (B) the presence at least one of the following behaviors associated with observed or inferred evidence of emotional distress for a minimum of 2 weeks, which represent a change from the patient's usual behavior: (a) excessive motor activity; (b) verbal aggression; (c) physical aggression.

As for cognition, pharmacological solutions for agitation have given so far disappointing results (Soto et al., 2014). However, recently a new promising treatment has been released and tested, and showed preliminary efficacy evidence in larger cohort trials (Cummings et al., 2014; Siffert, 2014). ICT could play a key role in assessing agitation in patients with AD, and to test the new treatment efficacy. For instance, accelerometers could be employed to measure objectively the presence of abnormal motor activity. Speech analyses that extract automatically vocal features of recorded speech could be employed to assess verbal aggression in a more subtle and objective way. Finally, automated video analysis and activity-recognition techniques may be useful to quantify the appearance of certain activities and movement sequences that underline physical aggression.

Conclusion and Future Research Directions

In order to progress in the validation of the treatments for AD, better outcome measures for cognitive and functional changes are acutely needed in the earliest stages of the pathology (Snyder et al., 2014). The clinical assessment of cognitive and functional changes in AD has traditionally relied on cognitive screening tests

[4]http://www.inmindd.eu/

that are not always sensitive to the earliest cognitive, functional, and behavioral changes important to detect for effective preventive interventions (Snyder et al., 2014), are possibly subjected to variations in the clinical interpretation, and are not always good predictor of the progression from MCI to AD (Schmand et al., 2012). Furthermore, current diagnostic measures can be invasive (CSF analyses), expensive (neuroimaging), time-consuming (neuropsychological assessment), and are often available only in specialized clinics, which lead to reduced accessibility as frontline screening tool for AD and related disorders (Laske et al., 2014). Therefore, we face an increasing need for additional population-based screening and follow-up instruments with simpler and timelier adapted, non-invasive, and cost-effective tools allowing early identification of subjects in preclinical stages of AD.

Here, we highlighted how new tools involving ICT may represent an optimal solution to most of these challenges. However, in order to successfully integrate ICT measurements into clinical trials, some work has still to be done (Robert et al., 2013, 2014). Specifically, the use of such technologies should be validated in larger cohorts to demonstrate their clinical meaningfulness by correlating with available clinical diagnostics and biomarkers and thus receive recognition in the clinical scientific and medical world. Importantly, in addition, the use of ICT in clinical trials needs to be validated by Health authorities and policy makers. On the technological side, work in terms of system development and sensors integration has to be carried out to allow a reliable and complete assessment of a patient by merging information coming from different sensors into easily understandable feedback. The immediate and accurate visualization of the recorded data is of great importance to facilitate an easy use in clinical practice and to provide feedback to patients and their caregivers.

Acknowledgments

This article and the 2014 IA workshop were supported by grants from the FP7 Dem@care project (grant 288199), the FP7 VERVE project, the FP7 In-MINDD project (grant 304979), and the Innovation Alzheimer association.

References

Aisen, P. S., Gauthier, S., Ferris, S. H., Saumier, D., Haine, D., Garceau, D., et al. (2011). Tramiprosate in mild-to-moderate Alzheimer's disease – a randomized, double-blind, placebo-controlled, multi-centre study (the Alphase study). *Arch. Med. Sci.* 7, 102–111. doi:10.5114/aoms.2011.20612

Cummings, J., Lyketsos, C., Tariot, P., Peskind, E., Nguyen, U., Knowies, N., et al. (2014). "Dextromethorphan/quinidine (AVP-923) efficacy and safety for treatment of agitation in Alzheimer's disease (AD): results from a phase 2 study," in *Poster 2014 American Neurological Association (ANA) 139th Annual Meeting*. Baltimore, MA.

Cummings, J., Mintzer, J., Brodaty, H., Sano, M., Banerjee, S., Devanand, D. P., et al. (2015). Agitation in cognitive disorders: international psychogeriatric association provisional consensus clinical and research definition. *Int. Psychogeriatr.* 27, 7–17. doi:10.1017/S1041610214001963

David, R., Mulin, E., Friedman, L., Le Duff, F., Cygankiewicz, E., Deschaux, O., et al. (2012). Decreased daytime motor activity associated with apathy in Alzheimer disease: an actigraphic study. *Am. J. Geriatr. Psychiatry* 20, 806–814. doi:10.1097/JGP.0b013e31823038af

Hatfield, C. F., Herbert, J., van Someren, E. J., Hodges, J. R., and Hastings, M. H. (2004). Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. *Brain* 127(Pt 5), 1061–1074. doi:10.1093/brain/awh129awh129

Hsiao, C. J., and Hing, E. (2014). Use and characteristics of electronic health record systems among office-based physician practices: United States, 2001-2013. *NCHS Data Brief* 143, 1–8.

Konig, A., Aalten, P., Verhey, F., Bensadoun, G., Petit, P. D., Robert, P., et al. (2014). A review of current information and communication technologies: can they be used to assess apathy? *Int. J. Geriatr. Psychiatry* 29, 345–358. doi:10.1002/gps.4017

König, A., Crispim Junior, C., Gomez Uria Covella, A., Bremond, F., Derreumaux, A., Bensadoun, G., et al. (2015a). Ecological assessment of autonomy in instrumental activities of daily living in dementia patients by the means of an automatic video monitoring system. *Front. Aging Neurosci.* 7:98. doi:10.3389/fnagi.2015.00098

König, A., Satt, A., Sorin, A., Hoory, R., Derreumaux, A., Manera, V., et al. (2015b). Automatic speech analysis for the assessment of pre-demented and Alzheimer patients. *Alzheimer's Dementia: Diagnosis, Assessment & Disease Monitoring* 1, 112–124. doi:10.1016/j.dadm.2014.11.012

Konig, A., Crispim Junior, C. F., Derreumaux, A., Bensadoun, G., Petit, P. D., Bremond, F., et al. (2015c). Validation of an automatic video monitoring system for the detection of instrumental activities of daily living in dementia patients. *J. Alzheimers Dis.* 44, 675–685. doi:10.3233/JAD-141767

Kuchinke, W., Ohmann, C., Yang, Q., Salas, N., Lauritsen, J., Gueyffier, F., et al. (2010). Heterogeneity prevails: the state of clinical trial data management in Europe – results of a survey of ECRIN centres. *Trials* 11, 79. doi:10.1186/1745-6215-11-79

Laske, C., Sohrabi, H. R., Frost, S. M., Lopez-de-Ipina, K., Garrard, P., Buscema, M., et al. (2014). Innovative diagnostic tools for early detection of Alzheimer's disease. *Alzheimers Dement.* 11, 561–578. doi:10.1016/j.jalz.2014.06.004

Mahlberg, R., and Walther, S. (2007). Actigraphy in agitated patients with dementia. Monitoring treatment outcomes. *Z. Gerontol. Geriatr.* 40, 178–184. doi:10.1007/s00391-007-0420-z

Nagels, G., Engelborghs, S., Vloeberghs, E., Van Dam, D., Pickut, B. A., and De Deyn, P. P. (2006). Actigraphic measurement of agitated behaviour in dementia. *Int. J. Geriatr. Psychiatry* 21, 388–393. doi:10.1002/gps.1483

Okura, T., and Langa, K. M. (2011). Caregiver burden and neuropsychiatric symptoms in older adults with cognitive impairment: the aging, demographics, and memory study (ADAMS). *Alzheimer Dis. Assoc. Disord.* 25, 116–121. doi:10.1097/WAD.0b013e318203f208

Robert, P. H., Konig, A., Amieva, H., Andrieu, S., Bremond, F., Bullock, R., et al. (2014). Recommendations for the use of serious games in people with Alzheimer's disease, related disorders and frailty. *Front. Aging Neurosci.* 6:54. doi:10.3389/fnagi.2014.00054

Robert, P. H., Konig, A., Andrieu, S., Bremond, F., Chemin, I., Chung, P. C., et al. (2013). Recommendations for ICT Use in Alzheimer's disease assessment: Monaco CTAD expert meeting. *J. Nutr. Health Aging* 17, 653–660. doi:10.1007/s12603-013-0046-3

Robinovitch, S. N., Feldman, F., Yang, Y., Schonnop, R., Leung, P. M., Sarraf, T., et al. (2013). Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* 381, 47–54. doi:10.1016/S0140-6736(12)61263-X

Romdhane, R., Mulin, E., Derreumeaux, A., Zouba, N., Piano, J., Lee, L., et al. (2012). Automatic video monitoring system for assessment of Alzheimer's disease symptoms. *J. Nutr. Health Aging* 16, 213–218. doi:10.1007/s12603-012-0039-7

Sacco, G., Joumier, V., Darmon, N., Dechamps, A., Derreumaux, A., Lee, J. H., et al. (2012). Detection of activities of daily living impairment in Alzheimer's disease and mild cognitive impairment using information and communication technology. *Clin. Interv. Aging* 7, 539–549. doi:10.2147/CIA.S36297

Sampaio, C. (2007). Clinical relevance on Alzheimer's disease endpoints. *J. Nutr. Health Aging* 11, 316–317.

Satt, A., Sorin, A., Toledo-Ronen, O., Barkan, O., Kompatsiaris, I., Kokonozi, A., et al. (2013). "Evaluation of speech-based protocol for detection of early-stage dementia," in *Paper Presented at the INTERSPEECH*, Lyon.

Schmand, B., Eikelenboom, P., van Gool, W. A., and Alzheimer's Disease Neuroimaging, I. (2012). Value of diagnostic tests to predict conversion to Alzheimer's disease in young and old patients with amnestic mild cognitive impairment. *J. Alzheimers Dis.* 29, 641–648. doi:10.3233/JAD-2012-111703

Siffert, J. (2014). "Phase 2 of AVP-923 (dextromethorphan/quinidine) for treatment of agitation in Alzheimer's disease: topline results and considerations for future research," in *(Presentation) E.U./U.S. Task Force Meeting on Alzheimer's Trials: Outcome measures during the 7*th Annual Meeting of Clinical Trials in Alzheimer's Disease Meeting, Philadelphia, PA.

Siraly, E., Szabo, A., Szita, B., Kovacs, V., Fodor, Z., Marosi, C., et al. (2015). Monitoring the early signs of cognitive decline in elderly by computer games: an MRI study. *PLoS ONE* 10:e0117918. doi:10.1371/journal.pone.0117918

Snyder, P. J., Kahle-Wrobleski, K., Brannan, S., Miller, D. S., Schindler, R. J., DeSanti, S., et al. (2014). Assessing cognition and function in Alzheimer's disease clinical trials: do we have the right tools? *Alzheimers Dement.* 10, 853–860. doi:10.1016/j.jalz.2014.07.158

Soto, M., Andrieu, S., Nourhashemi, F., Ousset, P. J., Ballard, C., Robert, P., et al. (2014). Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design. *Int. Psychogeriatr.* 16, 1–17. doi:10.1017/S1041610214001720

Volkers, A. C., Tulen, J. H., van den Broek, W. W., Bruijn, J. A., Passchier, J., and Pepplinkhuizen, L. (2003). Motor activity and autonomic cardiac functioning in major depressive disorder. *J. Affect. Disord.* 76, 23–30. doi:10.1016/S0165-0327(02)00066-6

Yakhia, M., Konig, A., van der Flier, W. M., Friedman, L., Robert, P. H., and David, R. (2014). Actigraphic motor activity in mild cognitive impairment patients carrying out short functional activity tasks: comparison between mild cognitive impairment with and without depressive symptoms. *J. Alzheimers Dis.* 40, 869–875. doi:10.3233/JAD-131691

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

frontiers in Aging Neuroscience

METHODS
published: 10 June 2015
doi: 10.3389/fnagi.2015.00102

Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy

Bayard E. Lyons[1,2]*, *Daniel Austin*[1,3], *Adriana Seelye*[1,2], *Johanna Petersen*[1,3], *Jonathan Yeargers*[1], *Thomas Riley*[1], *Nicole Sharma*[1], *Nora Mattek*[1,2], *Katherine Wild*[1,2], *Hiroko Dodge*[1,2] and *Jeffrey A. Kaye*[1,2,3,4]

[1] Oregon Center for Aging and Technology, Oregon Health and Science University, Portland, OR, USA, [2] Department of Neurology, Oregon Health and Science University, Portland, OR, USA, [3] Department of Biomedical Engineering, Oregon Health and Science University, Portland, OR, USA, [4] Neurology Service, Portland Veteran Affairs Medical Center, Portland, OR, USA

OPEN ACCESS

Edited by:
*Philippe Robert,
University of Nice Sophia Antipolis, France*

Reviewed by:
*Auriane Gros,
Centre Hospitalier Universitaire de Nice, France
Carlos F. Crispim-Junior,
Institut National de Recherche en Informatique et Automatique, France*

***Correspondence:**
*Bayard E. Lyons,
Neurology, Oregon Center for Aging and Technology (ORCATECH), C. Rex and Ruth H. Layton Aging and Alzheimer's Disease Center, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
lyonsb@ohsu.edu*

Received: *24 February 2015*
Accepted: *13 May 2015*
Published: *10 June 2015*

Citation:
Lyons BE, Austin D, Seelye A, Petersen J, Yeargers J, Riley T, Sharma N, Mattek N, Wild K, Dodge H and Kaye JA (2015) Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy. Front. Aging Neurosci. 7:102. doi: 10.3389/fnagi.2015.00102

Traditionally, assessment of functional and cognitive status of individuals with dementia occurs in brief clinic visits during which time clinicians extract a snapshot of recent changes in individuals' health. Conventionally, this is done using various clinical assessment tools applied at the point of care and relies on patients' and caregivers' ability to accurately recall daily activity and trends in personal health. These practices suffer from the infrequency and generally short durations of visits. Since 2004, researchers at the Oregon Center for Aging and Technology (ORCATECH) at the Oregon Health and Science University have been working on developing technologies to transform this model. ORCATECH researchers have developed a system of continuous in-home monitoring using pervasive computing technologies that make it possible to more accurately track activities and behaviors and measure relevant intra-individual changes. We have installed a system of strategically placed sensors in over 480 homes and have been collecting data for up to 8 years. Using this continuous in-home monitoring system, ORCATECH researchers have collected data on multiple behaviors such as gait and mobility, sleep and activity patterns, medication adherence, and computer use. Patterns of intra-individual variation detected in each of these areas are used to predict outcomes such as low mood, loneliness, and cognitive function. These methods have the potential to improve the quality of patient health data and in turn patient care especially related to cognitive decline. Furthermore, the continuous real-world nature of the data may improve the efficiency and ecological validity of clinical intervention studies.

Keywords: in-home monitoring, technologies, smart home, sleep, gait, dementia, medication adherence, aging in place

Introduction

In the second half of the last century, medical practice became increasingly specialized. By the 1950s, the clinic or "doctor's office" visit largely replaced the traditional home visit (Kao et al., 2009). The office visit in some respects affords greater convenience and efficiency for providers. For example, more patients can be seen in a shorter amount of time and patients can have direct access to an array of medical technologies. However, in other respects, it has resulted in patient inconveniences, inefficiencies, and potential inaccuracies in the assessment itself. Clinic visits are episodic in nature, occurring potentially once or twice a year with occasional "off schedule" appointments for unanticipated concerns. Visits average approximately 22 min (Cherry et al., 2008) and often occur at the point of a health crisis rather than at early onset of an illness. This has led to a more reactive than proactive approach to treating patients.

Another significant challenge to assessing an individual's mental and functional status in the often annual office visit is that both patient self-report and collateral informant data are required, each of which might be biased or unreliable due to stress, worry, or forgetfulness (Wild et al., 2015). Given the implicit pressure to limit the duration of the visit, there is a high demand on patients to provide concise and well-organized health histories. This is a challenge particularly for individuals with Alzheimer's disease and related dementias. Even, cognitively intact individuals may have difficulty remembering potentially important events or trends such as dietary habits, minor falls, medication changes, or sleep habits.

Most neurodegenerative diseases evolve slowly and initially affect function subtly, at first imperceptible to the patient and family until symptoms emerge that disrupt daily function. Mild cognitive impairment (MCI) is often considered a prodromal stage for a variety of neurodegenerative disorders including Alzheimer's dementia and is used to describe individuals who have mild decline in their cognitive function but continue to engage independently in community and household affairs (Mariani et al., 2007). Subtle changes in a number of cognitively demanding daily activities (e.g., computer use, following a medication regimen) occur between normal cognitive aging, MCI, and dementia (Gold, 2012; Kaye et al., 2014; Schmitter-Edgecombe and Parsey, 2014). As these real-world functional changes are directly associated with cognitive changes, monitoring functional changes offers a means for early detection of incipient dementia. However, since the earliest changes are subtle and these individuals do not show frank impairments in these activities, these changes are often not brought to the attention of a patient's doctor until later in the disease process if at all. Clinic visits in turn often occur only after cognitive decline has had an obvious impact on an individual's functional abilities, rather than earlier in the disease course when interventions may delay decline.

Finally, clinic visits are inconvenient for many patients, requiring travel from their homes, sometimes over long distances. This may be especially challenging for elderly patients, particularly those who live in rural areas, have stopped driving, or have physical disabilities making it difficult to move around outside the home. Over 50% of all patients with dementia go undiagnosed by their primary care provider (Boise et al., 1999, 2004; Bradford et al., 2009; Kotagal et al., 2015), which may be due in part to the limitations of conventional approaches to cognitive and functional assessment noted above.

Researchers at Oregon Health and Science University (OHSU) Oregon Center for Aging and Technology (ORCATECH) have established an approach to transform the clinical assessment first in a research setting and then ultimately within the clinical enterprise. ORCATECH researchers have designed and are using a "smart home" system to carry out research. Interest in "smart home" research has grown over the last couple of decades as a means for improving patient health and independence. "Smart home" research covers an array of approaches for collecting data continuously on in-home activity. A number of technologies have been employed. These have included either smart home environmental sensors [video, passive infrared (IR), contact, pressure sensors] or the use of wearable technology (Cook and Krishnan, 2014). Continuous in-home monitoring and analysis of these data enable creation of better models of human behavior and prediction of changes in health. For example, researchers have used smart home data to give older adults feedback on their functional abilities (Lee and Dey, 2010), to correlate changes in how participants made coffee and changes in performance on neuropsychological tests (Hodges et al., 2010), to group participants into cognitive health categories (Dawadi et al., 2013), and to detect health status decline (Rantz et al., 2008, 2009).

The approach taken by ORCATECH has been to fully outfit homes with an unobtrusive platform of in-home sensors to be able to continuously collect daily activity data on hundreds of research volunteers. The activity data collected continuously over months and years enables the detection of changes in individual function around key behaviors relevant to change in cognitive status. These data provide the foundation for the development of predictive models relating changes in functional status to ongoing and future cognitive decline. Furthermore, this research has led to the development of new technologies to collect real-time data continuously and unobtrusively. All of this work has the potential to strengthen the ability of families and clinicians to be proactive in treating health in general – and cognitive decline in particular – without relying solely on the episodic or annual clinic visit. We present a review of the ORCATECH research initiative as it has developed over the last decade. After reviewing our research objectives, we describe the sensor platform installed in each home and provide an overview of exemplary studies that have benefited from ORCATECH's continuous data collection.

Research Objectives

ORCATECH's research is focused around several common goals. Our first goal has been to develop unobtrusive and continuous monitoring platforms, along with novel algorithms and assessment techniques for detecting motor and cognitive change. Second, we now seek to determine if these developed algorithms and techniques can be used to detect early or prodromal cognitive decline in older adults living in typical community settings. Third, we are focusing on identifying how these technologies might be best adapted for daily care practice to enhance the monitoring needs and optimize communication between patients and health care professionals. Finally, our goal is to make the system available for developing new interventions and conducting vitally needed clinical trials to advance dementia management and treatment.

Method

Volunteer Recruitment

Beginning in 2007, ORCATECH began scaled deployment of a simple home-based platform of ubiquitous sensors in hundreds of homes of older adults living independently in the community (see Kaye et al., 2011). Participants were all recruited from the Portland metropolitan area, including older adults living in retirement communities as well as free-standing single-family homes. Potential participant pools were created following formal community presentations. Participants were also recruited from lists of current OHSU Layton Aging and Alzheimer's Disease Center research participants who have been followed longitudinally in other projects.

All of the volunteers recruited met the following inclusion criteria: they were 70 years or older and living alone or with their spouse or partner (not as a caregiver). Volunteers with a Mini-Mental State Examination score >24, a Clinical Dementia Rating scale score ≤0.5 and a physical examination demonstrating average health for age were invited to participate. While these were the inclusion criteria used in the initial screening, changes in the participants' status after enrollment on any one of these criteria would not lead to exclusion from the study. The OHSU Institutional Review Board approved all of the research studies summarized below. All participants provided written informed consent.

Participation required filling out an initial comprehensive base line survey as well as a weekly brief online life events and health questionnaire. Participants also agreed to be continuously monitored through a platform of sensors to be installed in their homes. Older adults participating in the study were already computer literate or became computer literate through training provided by the Center. Computer literacy was defined as being able to reliably send and receive email. Computer literacy ensures that participants are able to complete a weekly health form and can communicate with research staff directly online. Participants who did not already have a personal computer were given a computer in order to be able to complete the weekly survey as well as Internet access if they did not have it. The provided computer could also be used at their leisure for general use as well.

ORCATECH Platform Design

Each participant's home was outfitted with several types of sensors – wireless passive IR motion sensors (MS16A; http://X10.com) strategically placed in each room and wireless magnetic contact sensors (DS10A, http://X10.com) placed on the outside doors and the refrigerator. Upgrades to this system have included IR sensors operating via the Zigbee wireless communication protocol (NYCE Control). The personal computer each participant received served as another type of sensor. General computer use (e.g., time on computer, mouse movements) comprised data collected via this activity. Based on specific research needs, some homes received additional sensors. These included medication trackers (Hayes et al., 2006), phone monitors (Shenzen Fiho Electronic, Fi3001B), and a wireless scale (Withings) capable of measuring body mass index, weight, pulse, temperature, and air quality.

Whenever they detect motion, the motion sensors send a signal wirelessly to a small computer (GlobalScale Dreamplug) placed out of the way in the participant's home. The contact sensors send event-based codes whenever a door is opened or closed (See **Figure 1** for a schematic depiction of how these sensors might be interconnected in a home.). Additionally, the contact sensors send a "heartbeat" every hour, which ensures proper functioning of the device. Data collected from the various sensors and the personal computer are sent nightly over a broadband connection and is stored in a SQL database on secure research servers and managed by custom software.

By fusing data from these various sensors, time series data are constructed regarding when and where activity is taking place in the home. Using these time series, profiles of fluctuations in-home activity including when a participant has exited and reentered the home are created. Because data are collected for a given individual over the course of months to years, accumulated data provide a longitudinal profile of changes in activity for analysis and interpretation. With these data, predictive tools for detecting cognitive and functional change are developed. In the following, we highlight examples of how these data have been used to identify meaningful activity and outcomes relevant to aging, cognition, and function.

Research Evidence

Through continuous in-home monitoring, the ORCATECH group has investigated a range of quantifiable activities that may reflect changes in cognitive status. These have included sleep, computer use, medication adherence, walking speed, overall activity patterns, and time out-of-home. Most of these overlap with and are not dissimilar from the type of activities assessed as either activities of daily living (ADLs) or instrumental activities of daily living (IADLs). The assessment of ADLs and IADLs has been used in geriatrics and dementia care as a tool for guiding decisions to move from independence to higher levels of care. There has also been recent interest in examining the frequency and types of IADL difficulties that occur in normal aging and MCI to inform development of targeted interventions for IADL impairment (Seelye et al., 2013). In the following sections, we offer examples of how we have collected and analyzed data in each of these functional domains through the technology platform installed in homes. In each case, we highlight the potential for continuous in-home monitoring to improve understanding of functional, motor, and cognitive status and to predict cognitive change.

Sleep

Disrupted sleep is a significant problem among older adults and is associated with a number of other health-related problems including cardiovascular and pulmonary co-morbidities, decreased quality of life, and increased fall risk. In addition, there is evidence demonstrating a correlation between sleep disturbance and Alzheimer's disease or MCI (Lyketsos et al., 2002; Tractenberg et al., 2005; Tworoger et al., 2006). Previous research has also demonstrated a correlation between disrupted sleep, sleep latency, and wake after sleep onset (WASO), with performance on memory tests the following day for individuals with amnestic MCI (aMCI) (Westerberg et al., 2010) as well as cognitively intact elderly (Seelye et al., 2015a). One of the goals of ORCATECH has been to better understand the relationship between sleep and cognitive decline

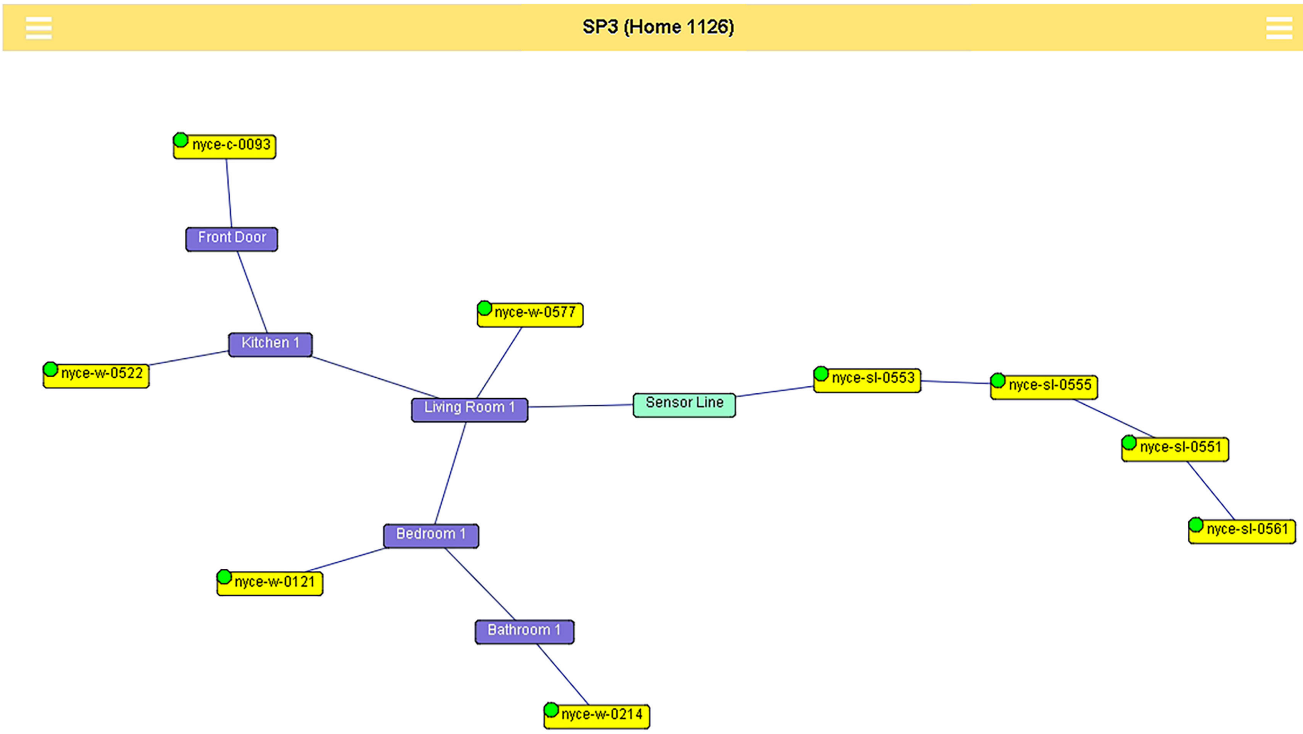

FIGURE 1 | Each room in a home is linked to the others based on valid room transitions. Passive infrared sensors are linked to the rooms in which they are located. The walking sensor line is an area, consisting of four restricted field passive infrared sensors linked together in the order in which they are placed. The walking sensor line links room(s) in which the sensors are located. Green or red dots on the sensor nodes indicate if the sensor is currently reporting in to the sensor network.

through continuous assessment of sleep behavior over an extended period of time.

In keeping with the goal of long-term, naturalistic assessment, the ORCATECH platform focuses on passive sensing of bed and bedroom activity to differentiate a number of relevant sleep parameters. The passive sensing approach has been validated to the ground truth of pressure mats in bed as well as showing favorable comparison to wrist worn actigraphy. As with all movement-based estimates of sleep measures (including actigraphy and bed mats), variables such as total sleep time (TST) must be inferred from periods of inactivity (Hayes et al., 2010). A validated algorithm was used to derive these measures against the ground truth measure of movement on the bed. Because data were obtained over a long-time span (26 weeks), this allowed for the data to be analyzed for central tendencies and variability while accounting for episodic activity outliers that may skew the data (e.g., up more frequently at night due to illness, increased restlessness due to unusual levels of day-time activity). These data, collected continuously over 6 months, provide information about an individual's "typical" night rather than a single night as in a polysomnography study, for example.

Using this approach, ORCATECH researchers collected objective sleep measures over an extended period of time comparing cognitively intact, aMCI, and non-amnestic MCI (naMCI) volunteers (Hayes et al., 2014). They found that aMCI volunteers had less disturbed sleep than both naMCI and cognitively intact volunteers, and in general, the naMCI volunteers showed a level of disturbed sleep that was intermediate to that of aMCI and intact volunteers. These differences contradicted self-report data that had suggested no differences in sleep behaviors across groups, underscoring the value of collecting frequent and objective in-home measurements. In contrast to some past studies (Geda et al., 2004), our findings suggest that aMCI volunteers typically experience less sleep disruption during the night than cognitively intact volunteers.

Another sleep study examined the relationship between episodes of poor sleep and cognitive test performance in cognitively intact older adults (Seelye et al., 2015a). Specifically, researchers examined the impact of sleep disturbance and sleep duration the *night prior*, the *week prior*, and the *month prior* to cognitive testing performance in the clinic. Results showed that more sustained periods of disturbed sleep, i.e., mildly disturbed sleep the week prior and month prior to cognitive testing was associated with reduced working memory on cognitive evaluation. On the other hand, one night of mild sleep disturbance was not associated with decreased cognitive performance the next day. Sleep duration was unrelated to cognitive test performance.

These findings suggest that in-home, unobtrusive sensor monitoring technologies provide a novel method for objective, long-term, and continuous assessment of sleep behavior and other lifestyle factors that might contribute to decreased or variable cognitive performance in healthy older adults. Future longitudinal studies of normal aging and MCI using sensor-based sleep assessment will explore whether mild sleep disturbance contributes to intra-individual variability in cognitive test scores over time.

Computer Use

Computer use is becoming increasingly ubiquitous among older adults. Currently, 59% of those 64 years or older go online and this number is increasing at a rapid pace (Smith, 2014). This is significant when considering cognitive health. Computers offer older adults the option of maintaining connections with a larger social network without leaving their homes. This has potential benefits to emotional and psychological health. Computers also provide a means for retrieving and storing important health information, and for exchanging health information directly with health care providers. All of these applications could help older adults remain independent in their homes longer or find help when cognition and function become a challenge. Finally, computer use is a complex task taxing multiple cognitive domains (attention, working memory, episodic memory, executive function, etc.) and an individual's use patterns – or changes in these patterns – may signal important cognitive changes. For example, the frequency and duration of computer use have the potential for offering insight into changes in cognitive function among the growing aging population.

An important part of the ORCATECH approach has been to ensure that when possible all research volunteers have access and could use a computer even at a very basic level. One of the volunteers' primary research tasks is to complete a weekly online survey using either their own computer or tablet or a laptop computer provided by the Center. The weekly online surveys have been important to the data collection as they provide information on activities that are difficult to infer by passive sensing alone (e.g., reports of pain, mood, falls, etc.). Additionally, the computer serves as an additional activity and behavior sensor, providing an opportunity to assess computer use on a specific task (completing the questionnaire) at a minimum of once a week in addition to the person's typical computer-based activity.

Custom-designed computer monitoring software (CMS) is installed on each of the computers. When participants use the computer, the CMS software requires them to log in, which in turn initiates computer use monitoring (Hatt et al., 2009; Kaye et al., 2014). Multiple types of events may be recorded from the participants' computers (general typing data, login events, login passwords, application focus change events, and mouse events). For example, keyboard typing is recorded in sets of three keystrokes, called *trigrams*, with the amount of time elapsed between the three key press events. The trigram is also time stamped with a 1 hour resolution, providing researchers with information about the approximate time of computer use and how fast the user was typing. Recording is done when a participant is typing a document or an email. Using trigrams of general typing data provides quantifiable information on typing strokes in terms of speed and duration while at the same time making it possible to respect individual privacy by restricting and obfuscating information about actual content (Hatt et al., 2009; Pavel et al., 2010).

ORCATECH researchers have used the above techniques to evaluate the relationship between computer use and cognitive decline. In one study, researchers collected data on 230,000 computer sessions over an average of 36 months from 113 computer users (mean age, 85 years; 38 with MCI) (Kaye et al., 2014). These data were assessed to compare computer use over time between individuals with and without MCI. Computer sessions were described by mouse movement data. Each mouse movement of more than five pixels generated a Windows event that was saved and time-stamped. In order to remove slow drifts in mouse position during inactivity, the computer was considered to be in use only when there were more than 100 mouse events within a 5-min period. Additionally, days of computer use were counted as days when a 5-min period was recorded. Mean daily usage (in hours) was the sum of total time on the computer per month divided by total number of days with usage in the month. Consistency in day-to-day computer use was indexed using the coefficient of variation.

This study was the first unobtrusive in-home monitoring and analysis of computer use in an aging and MCI population. While at baseline, there were no differences in use metrics between the two groups (likely reflecting initial training), over time there was a decrease in number of days per month, mean daily use, and day to day variability of use among participants with MCI as compared to cognitively intact participants (Kaye et al., 2014). In a survey of attitudes and beliefs about their computer use, MCI volunteers reported less confidence and more anxiety over time while using their computer relative to cognitively intact older adults, who gained confidence over time (Wild et al., 2012). These studies suggest that continuous assessment of computer use may be an efficient and sensitive method to evaluate early decline among individuals with MCI.

Another computer-based study (Austin et al., 2011c) investigated the relationship between motor speed and typing speed on a computer keyboard during computer login events. These login events consisted of typing a user name and password at the beginning of each participant's regular computer use session. The speed of typing was measured by inter keystroke intervals (IKI), which is the time in between consecutive keystrokes calculated from the trigrams. Motor speed was assessed by the Halstead–Reitan Finger Tapping Test (FTT) (Strauss et al., 2006). Data were analyzed from 22 participants who used their computer frequently in the 28-day period surrounding an annual neuropsychological exam. This study found a high correlation between tapping speed and typing with the dominant ($r = 0.7$, $p < 0.0002$) and non-dominant ($r = 0.77$, $p < 0.0001$) hand. One conclusion from this study is that monitoring speed of typing over time during regular computer use could unobtrusively detect motor decline known to precede cognitive impairment (Camicioli et al., 1998).

Ongoing studies are examining how other aspects of remotely monitored home computer use might be related to early cognitive changes in older adults. For example, preliminary work suggests that aspects of responding to the weekly online health questionnaire differ among cognitively intact older adults and those with MCI over 1 year (Seelye et al., 2015b). Computer mouse movements obtained during routine, everyday home computer use are also being examined as a novel method to identify real-world cognitive changes that are associated with MCI in older adults.

This research suggests that computers provide an additional sensor environment for investigating the relationship between functional change and cognitive change. Successful computer engagement not only requires intact complex motor and cognitive skills but also facilitates social connections. In the final section, we will discuss how computers used for online video chat may help us better understand the relationship between functional changes in social interaction and cognitive decline.

Medication Adherence

One of the greatest challenges facing persons with AD and other dementias is adherence to medication regimens. More than 76% of Americans aged 60 years and older take two or more prescription medications (Gu et al., 2010). Forgetful patients are inconsistent in their adherence and tend to be poor historians of when and how often they are taking their medications. Medication non-adherence leads to increased risk of hospitalization and mortality among the older population and in those with chronic diseases (Col et al., 1990; Ho et al., 2006).

Medication adherence relies on a set of cognitive skills, including prospective memory and executive functioning. Activities dependent on memory and executive function tend to be most difficult for older adults with MCI (Brooks, 2006; Allaire et al., 2009; Schmitter-Edgecombe et al., 2009; Griffith et al., 2010). Thus, adherence to a medication regimen can be an everyday task that if monitored can act as a bellwether of changes in cognitive function. Additionally, a system that independently monitors medication adherence can alert health care providers and informal care providers in real time. ORCATECH researchers have used medication-taking behavior and adherence data to develop systems to facilitate improved patient adherence and medication usage (Lundell et al., 2007; Hayes et al., 2009a,b; Pavel et al., 2010).

Insel and colleagues reported that a composite of executive function and working memory was a significant predictor of reduced medication adherence in a population of older adults (Insel et al., 2006). Building on this observation, ORCATECH researchers examined whether objective evidence of an individual's difficulty with medication adherence could identify those with early cognitive impairment. Using a 7-day electronic pillbox called the MedTracker, which records the time of day when a day's compartment is opened (Hayes et al., 2006), a 5-week drug adherence trial using vitamin C supplements was conducted. Participants took this supplement from the MedTracker twice daily at pre-specified times approximately 12 h apart ensuring that each person faced the same daily challenge. Adherence was calculated in two ways. First, there was overall adherence calculated as the percentage of days when both pills were taken. Second, regimen adherence was calculated by the percentage of times the volunteer took their medication within a window of 1 h before to 2 h after the prescribed times. An individual was considered to have poor adherence to the regimen if their adherence to one of the two measures was <80% (Hayes et al., 2009a).

Participants, who were all deemed cognitively intact at the time of the study, were divided into a relatively lower cognitively performing group compared to a higher performing group (HPG) based on their total score at entry on the Alzheimer's Disease Assessment Scale Cognitive Subtest (ADAS-cog). The cognitive differences between the groups were slight [mean ADAS-cog score in the lower performing group (LPG) was 10/40 vs. 6/40 in the HPG; lower score indicating better performance]. Despite this subtle distinction, there was a significant difference observed in medication adherence between the two groups with the LPG having significantly poorer total adherence than the HPG (LPG: 63.9 ± 11.2% adherence, HPG: 86.8 ± 4.3%). There was a 4.1 relative risk of non-adherence in the LPG as compared to the HPG. This study provides strong evidence that even very MCI in healthy older individuals has a detrimental impact on medication adherence and has important implications for clinical trials with MCI patients (Hayes et al., 2009a,b).

Movement Patterns and Walking

Almost two decades ago, motor slowing was demonstrated to precede the diagnosis of dementia shown by conventional in-person timed tests (e.g., using a stop-watch) (Camicioli et al., 1998). It is based on this research and others that ORCATECH researchers have sought to study both movement patterns and variation in walking speeds using continuous in-home measurement.

Mobility and Walking Speed

Walking speed is typically measured during a clinic visit. Some of the methods used to assess walking speed include using a stop-watch and counting steps, using a gait mat or by wearing an accelerometer. However, with the traditionally episodic nature of clinical evaluations and gait measurement, it is difficult to distinguish between abrupt changes in function and changes that occur more slowly over time. Body-worn accelerometers, which typically assess gait speed by identifying footfalls, are an alternative to clinic assessments as they can be used to continuously assess walking speed wherever a participant goes. However, remembering to wear or charge such devices can be challenging, especially among a memory impaired, older adult population. In addition, current accelerometry approaches do not provide location of the detected activity within a home. Furthermore, walking in the home environment is generally of low velocity and rarely linear or sustained, making the algorithms used to detect "walking" with accelerometry difficult to interpret. Among older adults in particular, it is therefore important to apply ecologically valid techniques to *unobtrusively* assess important metrics such as walking speed. The ability to continuously assess walking speed in the home provides a better understanding of the variability and change in walking speed of an individual over time.

To that end, we developed a method to assess walking speed using an array of in-home sensors. With careful in-series placement of wireless IR sensors in the home, walking data can be passively captured that identifies how quickly and frequently participants are passing by this sensor line on a daily basis (Hayes et al., 2008; Hagler et al., 2010; Austin et al., 2011b; Kaye et al., 2012). Algorithms estimating the speed of walking from the in-home sensor data have been validated against a "gold standard" gait mat (Hagler et al., 2010). This provides a more dynamic result than can be gained from a single assessment in the clinic or the home.

To examine how total activity during the day and walking speed more specifically might differentiate older adults with MCI compared to those with intact cognitive function, we captured over 108,000 person-hours of continuous activity data for up to 418 days (mean 315 $\pm$ 82 days) using the unobtrusive sensor system in the homes of 14 elderly volunteers (Hayes et al., 2008). In addition to mean or median measures of walking speed and amount of activity in the home, wavelet analysis was used to examine variance in activity at multiple timescales. The coefficient of variation in the median walking speed was twice as high in the MCI group as compared to the healthy group. Furthermore, the 24-h wavelet variance was greater in the MCI group (MCI: 4.07 $\pm$ 0.14, healthy elderly: 3.79 $\pm$ 0.23; $p = <0.008$) indicating that the day-to-day pattern of activity of subjects in the MCI group was more variable than that of the cognitively healthy older adults (Hayes et al., 2008).

In a study of 76 older adult volunteers living alone, measurements of walking speed were taken throughout the day for a 1-month period. These subjects generated a total of 39,474 walking episodes, which equated to 500 walks per subject per month. Holding constant age, sex, education, and Geriatric Depression Scale score, we found that a 1 SD increase in the global cognition z-score was associated with a 10.1 cm/s increase in mean in-home walking speed. Similarly, a 1 SD increase in attention z-score corresponded to a 7.7 cm/s increase in walking speed (Kaye et al., 2012).

In another ORCATECH study (Dodge et al., 2012), walking speeds were evaluated in 54 participants with intact cognition, 31 participants with naMCI, and 8 participants with aMCI at baseline, with a mean follow-up period of 3 years. Latent trajectory models identified three distinct trajectories (fast, moderate, and slow) of mean weekly walking speed. Participants with naMCI were significantly more likely to be in the slow speed group than in the fast or moderate speed groups. Further, there were four distinct trajectories of change with regard to variability in walking speed over time (measured by the coefficient of variation, COV): group 1, the highest baseline speed with increasing COV followed by a sharply declining COV; groups 2 and 3, relatively stable speeds and COV; and group 4, the lowest baseline and decreasing COV. Participants with naMCI were significantly more likely to be members of either highest or lowest baseline COV groups (groups 1 or 4), possibly representing the trajectory of walking speed variability for early- and late-stage MCI, respectively. Thus, walking speed and its daily variability may be taken as an early marker of the development of MCI. Patterns of movement and mobility turn out to be another.

Patterns of Movement and Mobility

Interpretation of data from remote monitoring of activity relies on the assumption that an individual's activities fall into patterns of varying predictability and once measured and documented, deviations from their established patterns provide the opportunity to detect meaningful change. However, it should be noted this does not assume that the opposite is necessarily true, i.e., that a person with no changes in routine patterns of activities is not experiencing cognitive decline. It may be that an individual with AD or another dementia may engage in very stereotyped behaviors to hide or compensate for cognitive decline. An important goal of ORCATECH research has been to better understand the relationship between activity patterns and cognitive decline.

Both establishing individual activity patterns and measuring meaningful change in these patterns pose a significant challenge. Traditionally, data gathered on mobility have focused on out of home mobility, such as for the purpose of tracking epidemics or planning transportation, and have demonstrated predictable patterns of mobility using time-independent universal scaling laws. Studying a data set of almost 15 million observations from 19 adults spanning up to 5 years of unobtrusive longitudinal home activity monitoring, we found two main results. We first found that the universal scaling laws shown to describe mobility outside of the home (González et al., 2008) did not hold for mobility in the home. Second, we found that there was substantial predictability and regularity in in-home mobility when accounting for the context of the individual movements (Austin et al., 2014a). This investigation focused on the temporal regularity and predictability of the number of times an individual moves between different rooms in their home. We found that like out of home mobility, in-home mobility is also highly stereotyped, albeit in a different way, which may have applications for predicting individual human health (Campbell et al., 2011) and functional status (Evans et al., 2011; Kaye et al., 2012) by detecting adverse events or trends (Candia et al., 2008) and in conducting more meaningful clinical trials (Carlsson, 2008; Kaye, 2008).

Social Engagement

Research has demonstrated that higher levels of social engagement can be protective against cognitive decline (Fratiglioni et al., 2000; Scarmeas et al., 2001; Wang et al., 2002; Wilson et al., 2002; Akbaraly et al., 2009). Individuals who are more socially active generally exhibit numerous positive health benefits including higher self-rated health (Cornwell and Waite, 2009) and lower all-cause mortality (House et al., 1988; Glass et al., 1999; Berkman et al., 2000; Holt-Lunstad et al., 2010). Additionally, there has been research to demonstrate that even brief social interactions lasting a few minutes can lead to increases in performance on subsequent tests of executive function (Ybarra et al., 2008).

Better understanding of the relationship between social engagement and cognitive decline opens the possibility for both early identification of those at risk of cognitive decline and development of prevention strategies using social engagement as a tool to improve cognitive function. Research in this area has begun using the in-home technologies described above as well as developing new data collection methods (Dodge et al., 2014; Petersen et al., 2014a). Several aspects of social engagement may be assessed passively. These include time out of the home (time with the "outside" world), amount of telephone use, frequency and duration of visitors to the home, and time on the Internet spent in certain activities (e.g., email, video chat). In the following, we highlight some of these preliminary investigations related to both identification and intervention of cognitive decline including evaluations of time spent out of house, telephone usage, use of Internet-based video chat, and the contribution of social engagement to risk of being placed in a long-term care (LTC) facility.

Time Out of Home

Spending time outside the home is a complex activity, requiring navigation, wayfinding, and physical capability (Wahl et al., 2013). Individuals with MCI have been shown to not only spend less overall time out of the home (Suzuki and Murase, 2010) but also do not travel as far from the home compared to healthy controls (Crowe et al., 2008; James et al., 2011; Shoval et al., 2011; Wettstein et al., 2015). These differences may be due to the cognitive demands involved in leaving the home. Additionally, leaving the home is important for maintaining quality of life, independence, and health in older adults (Gagliardi et al., 2010). Given that typical healthy older adults spend an average of about 20 h in their home per day (Kaye et al., 2011), the amount of time out of the home becomes particularly salient in evaluating reduced direct social engagement. Most of the techniques to assess time out-of-home to date depend on subjective self-report, for example, life space analysis (Crowe et al., 2008; James et al., 2011). However, such techniques tend to suffer from bias by recency effects, and cannot be maintained long-term.

Recently, Global Positioning Systems (GPS) have been employed to assess not only total time spent outside the home but also locations visited and walking speed while out (Shoval et al., 2011; Wahl et al., 2013; Wettstein et al., 2015). However, much like accelerometers to assess walking speed, this approach does not work well for older adults, especially those with memory complaints, as it depends on the adult to remember to carry or wear the device. To mitigate these shortcomings, we developed a technique to assess time out-of-home unobtrusively and continuously. In this technique, time out of the home was identified using a logistic regression classifier that takes into account firing of sensors within specific home locations as well as at the exit door(s). This approach was both sensitive (0.939) and specific (0.975) in detecting time out-of-home across over 41,000 epochs of data collected from four subjects monitored for at least 30 days each in their own homes. The method has the advantage of not only detecting the total daily hours spent outside the home but also the time of day the participant was out of the home. By being able to track not only the duration of time spent outside the home each day but also the time of day participants were out of the home, general behavioral patterns of older people could be documented. We found on average that half of the participants were outside their homes at noon and 6:00 p.m., likely corresponding to lunch and dinner hours. Additionally, we were able to show that higher time out-of-home is associated with lower levels of loneliness, as measured using the UCLA Loneliness Scale (Russell et al., 1980), and with higher levels of self-reported physical activity, using the physical activity component of the Berkman Social Disengagement Index (Petersen et al., 2014a).

Time out of home has also been shown to relate to relevant behavioral and psychological changes that may be commonly experienced by MCI or dementia patients such as low mood. Thus, using 18,960 weekly observations of online reported mood ratings over a period of 120 weeks, it was found that during weeks of low mood, participants spent less time out of residence, but did not show changes in walking speed or movement about their home measured by room transitions (Thielke et al., 2014).

Telephone Usage

Because people use the phone to call their network of friends, family, and acquaintances, monitoring phone use could give a picture of the size of the network (by monitoring numbers dialed) and the frequency of contact with the network (by monitoring total number of calls). An extensive body of literature has used mobile phone apps to detect and analyze the social network characteristics of younger individuals (Eagle and (Sandy) Pentland, 2006; Palla et al., 2007). However, older adults, especially the oldest old (85 and older) who are most susceptible to cognitive decline, have been slow to adopt mobile phone technologies. This means that landline use must be accounted for in this population.

Using phone monitors (Shenzen Fiho Electronic, Fi3001B) installed in the home, we have developed a technique to monitor landline phone use. These monitors work by detecting signals on the phone corresponding to phone events including "on-hook," "off-hook," number dialed, and "ring start." Using data from the monitors installed in the homes of 26 older adults for 6 months, we have shown that overall phone use is negatively associated with cognition (Petersen et al., 2014b).

Recording telephone conversations and analyzing their content have been another avenue of exploration carried out by ORCATECH collaborators (Stark et al., 2014). In this study by using standard natural language processing techniques to analyze incoming and outgoing calls from a few homes, researchers were able to differentiate business from personal calls, family from non-family calls, familiar from unfamiliar calls, and family from other personal calls ranging from 74 to 88% accuracy. Other groups have experimented with recording and analyzing facial expressions through video monitoring to infer emotional status (Hosseini and Krechowec, 2004). One limitation to this approach, however, is that it can be considered intrusive given the video data that are collected. ORCATECH researchers and collaborators are continuing to explore ways that social relationships and changes in mood may be inferred remotely and unobtrusively by analyzing speech and activity patterns.

Visitors

Another important aspect of evaluating social engagement is visitors to the home. When striving to be completely unobtrusive (not requiring subjects to wear any devices) and anonymous (contain no information about who is causing the sensors to fire), the presence of a visitor in the home cannot be directly extracted from in-home sensor data. As a first approach to identifying visitors using this anonymous sensor data, we developed a classifier to distinguish times when visitors were present in the home from times when they were absent using key features from the in-home motion sensor data (Petersen et al., 2012). For each 15-min interval, we calculated the dwell time in key living spaces (living room, dining room, kitchen, and bathroom), total number of sensor firings, and number of transitions between the major living spaces. Then, using twice daily diary-based (over 6 weeks) self-report from two subjects as ground truth, ORCATECH researchers trained and tested a Support Vector Machine classifier, which was able to detect the presence of visitors in the home with a sensitivity and specificity of 0.90 and 0.89 for subject 1 (with 31.8 h with visitors), and sensitivity and specificity of 0.67 and 0.78 for subject 2 (with

89.5 h with visitors). These preliminary data not only demonstrate the feasibility of detecting visitors with anonymous in-home sensor data but also highlight the need for more advanced modeling techniques, so the model performs well for all subjects and all types of visitors.

Online Video Chat

ORCATECH researchers have also investigated changes in the quantity of social interaction and its effects on cognitive function in a randomized controlled clinical trial (RCT). This proof of concept RCT examined whether stimulation through social interaction using contemporary communication technologies (PC, webcams, and Internet) could improve cognitive function (Dodge et al., 2014). The RCT participants with normal cognition or MCI were engaged daily by trained interviewers or "conversationalists" via the Internet and PC webcams to facilitate participating in 30–40 min of standardized, semi-structured conversations for 6 weeks. The control group received only a weekly phone call to monitor the amount of social interaction. In addition to measuring cognitive function by traditional and computerized cognitive tests, the trial assessed whether an increase in daily conversation leads to changes in emotional well-being (secondary outcome) and speech characteristics (exploratory outcome) such as word counts, characteristics of words used, proportion of filler words, and sentence complexity.

Several methodological innovations for delivering social interactions were tested in this trial. Specific software was developed, so older adults who may not have had any experience with computers could answer calls by simply touching the screen of the monitor instead of using a mouse or keyboard. The daily interview sessions were automatically recorded. Automated speech-recognition algorithms were refined to examine the speech characteristics associated with cognitive status and their changes over time. Additionally, participants wore small digital micro-recorders to track the time and duration of conversations occurring outside of the online chat session. In the RCT, the 83 participants (mean age 81 years) who met the study inclusion criteria and were randomized to the trial showed exceptional adherence to the protocol. There was no dropout and the mean percent of days completed out of the total possible sessions was 89. The intervention group improved on an executive/verbal fluency cognitive measure ($p = 0.02$) (Dodge et al., 2015).

Also examined was whether speech characteristics differ by cognitive status (MCI vs. intact cognition). Using the recorded conversation during intervention sessions, MCI participants were found to speak more words (i.e., had a higher proportion of words generated out of total word counts) compared with those with intact cognition (Kaye et al., 2014) There are several possible explanations for this finding: first, MCI participants may be more likely to need to substitute words in the conversation to convey their thoughts, especially in the early stage of MCI when phonemic fluency is still preserved, leading to an increased proportion of speech duration in timed conversations. Second, individuals with MCI may have subtle difficulties with executive and self-monitoring aspects of conversation including reduced passage-of-time estimation abilities relative to those with normal cognitive function. Third, individuals with MCI may acquire deficits in social cognition, i.e., misreading of social cues and intent during social exchanges that could result in more discursive conversation among MCI participants. Importantly, this metric appeared to discriminate participants with MCI from intact participants better than the traditional cognitive tests of Animal Fluency and CERAD Word List Delayed Recall.

A Multi-Domain Approach

In conventional model building a relatively restricted range of factors (e.g., demographics, baseline clinical measures) have been used to predict salient outcomes for individuals at risk for dementia. In order to build more accurate and meaningful models for assessment and intervention in MCI and dementia, integration of multiple data types and streams captured from the ubiquitous in-home computing platforms is needed.

Toward this end, an initial study using the conventional clinical measures typically used to predict a high value outcome – being placed into LTC was developed. In this study, ORCATECH researchers used a multi-factorial analysis combining data on risk factors for cognitive decline (social activity, sleep disturbances, and depressive symptoms) and the role they played in the risk of an older adult being placed in LTC (Miller et al., 2014). Controlling for cognitive and functional impairment, age, and medical conditions, each unit increase in social activity was associated with a 24% decrease in the risk of placement [odds ratio (OR) = 0.763, $p = 0.001$, 95% confidence interval (CI) (0.65, 0.89)]. While cognitive impairment, medical conditions, and age were also significant individual predictors of placement, many of these risk factors for placement are not readily modifiable. However, older adults who engage in more social activity outside the home may be able to delay transition from independent living (Miller et al., 2014).

Using the same cohort, but applying a fusion of variables from multiple assessment domains including the continuous sensed data, it was found that this approach could dramatically improve the prediction of care transitions to higher levels of care within 6 months. This study included 108 participants living alone who were followed longitudinally between July 2011 and March 2014. The mean age at study enrollment was 81.5 years (SD = 6.6 years); 89 participants were female (82%), and 81 were white (75%) (Austin et al., 2014a). During the monitoring period, 12 participants (11%) transitioned out of independence. In-home monitoring variables sampled at 1 min intervals were combined with clinical assessment, weekly self-report, and demographics/co-morbidities in a longitudinal logistic regression (Austin et al., 2014b). There were a total of 66,172,380 total samples collected during the monitoring period on a total of 34 covariates including the model constant. Thirty-six variables may seem high for only 108 participants, but only five of the variables – age, number of rooms in the home, years of education, socioeconomic status, and residence – were constant during the monitoring period. The remaining variables changed over time and were hypothesized to be predictive of a future transition to a higher level of care.

The results indicated that transitions to an advanced level of care were highly predictable and the model was a good fit for the data (McFadden's $R^2 = 0.71$; $p < 0.00001$). There was a clear pattern of in-home measured activity and behavior – a *behavioral signature* – associated with increased risk of transition to higher care.

Figure 2 illustrates this graphically with a spider plot and **Figure 3** shows the receiver operating curve (ROC). From **Figure 2**, it can be seen that in-home measured computer use and sleep latency are especially important for predicting whether an individual is likely to need additional care. In a sensitivity analysis, the area under the curve of the ROC was 0.947. These results are somewhat optimistic because no unseen data were used to test out-of-sample model predictions. However, the expected modest reduction in performance due to out-of-sample generalization would still allow precise predictions of who is likely to need additional care. Overall, these results suggest that fusing data collected in-home with more traditional assessments has the potential to improve diagnostic precision and efficiency. Future work will compare the predictive accuracy of different measurement domains (e.g., in-home assessment, clinical assessment, self-report, etc.) and to identify the optimally fused model that has the fewest and most predictive variables.

Perceptions and Acceptance of Continuous In-Home Monitoring

ORCATECH research has been guided by the principal that technologies, which are not overly obtrusive or threatening to an individual's sense of privacy or security, have a greater chance to be widely adopted by volunteers. In a focus group study of potential volunteers, acceptance of the in-home monitoring system was tied closely to perceived utility of the data gathered. If volunteers felt that their data would be useful in promoting research, they were more accepting of the in-home monitoring technology. Privacy was less of a concern to participants than anticipated (Wild et al., 2012). These results were reinforced in a survey of volunteers during the initial year of living with ORCATECH technology platform installed in their homes; almost 75% reported acceptance of in-home monitoring. However, in this initial survey, concerns for privacy and security were shared among more than half (60%) of those surveyed and these concerns increased after 1 year of participation. Nevertheless, participants were generally accepting of in-home monitoring, balancing their concerns over privacy and security with their desire to contribute to research that could potentially assist older individuals maintain independence (Boise et al., 2013).

Limitations

To date ORCATECH's data collection has predominantly employed wireless passive IR motion sensors, contact sensors, bed pressure sensors, and some non-content specific quantitative measures of computer use (typing speed, mouse use, duration of use, etc.). One limitation of using largely passive IR and contact sensors is the difficulty of distinguishing between individuals if there is more than one person in the home. In a recently published study, ORCATECH researchers explored using Gaussian mixture models (GMMs) combined with infrequent clinical assessments of gait velocity to model in-home walking speeds of two or more

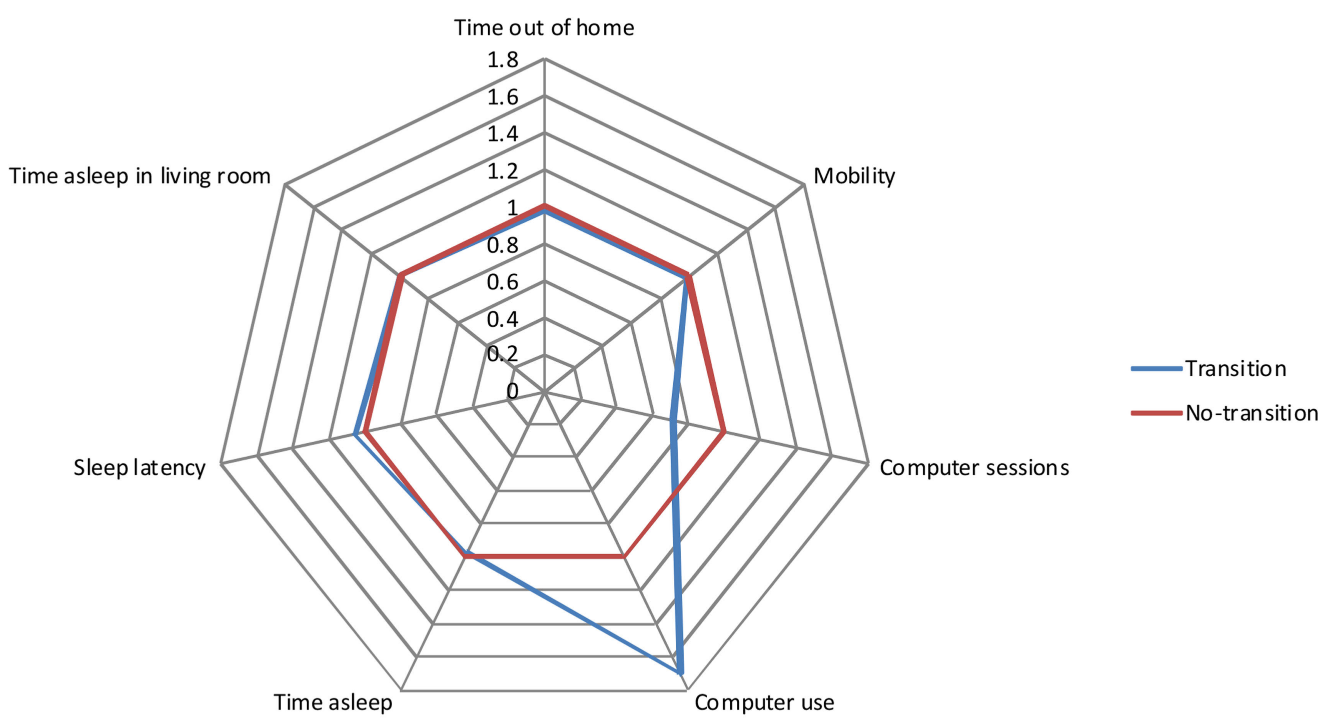

FIGURE 2 | Spider plot comparing the change in the odds ratio of transitioning (blue) compared to not transitioning (red) for several in-home measured variables. This shows that computer use and sleep are especially important in predicting an advanced care transition.

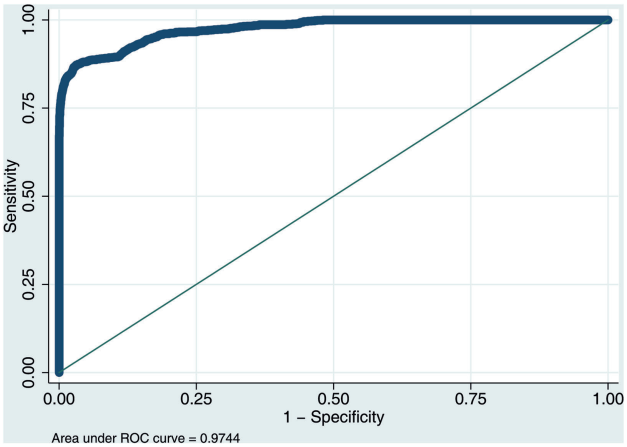

FIGURE 3 | ROC curve for a subset of 1,000,000 randomly selected data points comparing the trade-off between sensitivity and specificity of the logistic regression model's performance for predicting transitions to a higher level of care.

residents. These researchers were able to show that if the clinically measured gait velocities of residents are separated by at least 15 cm/s, a GMM can be accurately fit to the in-home gait velocity data (Austin et al., 2011a).

Other groups have experimented with solving the problem of user identification in a "smart home" using data approaches or augmenting the home or residents with additional devices. For example, Crandall and Cook (2011) proposed an algorithmic approach for tracking data from multiple residents in a single home. Srinivasan et al. (2010) used a height sensor installed in the home for resident identification and other groups have used wearables or video cameras (Wang et al., 2011; Banerjee et al., 2012; Ferdous et al., 2012). ORCATECH researchers are exploring using wearable technologies in several pilot studies. One such pilot study involves recording conversations during a specified segment of time. This requires participants to wear a digital recorder. Until it is possible to reliably distinguish between individuals in multiple person homes, one approach we have taken when analyzing our data is to limit our analyses to single-person homes only.

Another limitation is the low fidelity of recognizing and distinguishing between activities recorded. Currently, the data collected cannot distinguish between when someone is in the kitchen making a pot of coffee, unloading the dishwasher or surfing the internet on an ipad. Again there is a balance being drawn between respecting volunteer privacy and data collection.

Finally, "smart home" data collection can provide a wealth of information on what goes on in the home. Research would benefit from information that could be gathered on activities external for the home. With this in mind, ORCATECH researchers are currently exploring to expand data collection outside the home in tracking driving behavior and patterns and use of smartphones.

Conclusion

Traditionally, individuals with increasing cognitive impairment experience functional decline. As individuals' cognition becomes more impaired, they exhibit multiple behavioral changes, for example, difficulties in performing complicated tasks, limitations in engaging in meaningful social interactions, and challenges in maintaining mobility and efficiency of motor function. During a clinic visit, clinicians are only able to screen or "spot-check" changes in these functions during the short time period that the patient is in the examining room.

Continuous unobtrusive monitoring using pervasive in-home technology has allowed the capture of a wealth of data on individual daily activities previously not possible. As we and others continue to collect data and expand the participant pools, we are iteratively refining our understanding of how daily activities such as changes in night-time behaviors, mobility, computer use, medication adherence, and social engagement may track cognitive and functional changes and predict future cognitive impairment. This approach has clear application as an objective and sensitive tool for assessment in clinical trials. Given the density and frequency of the data, the precision of the estimates of change is orders of magnitude higher than current approaches. The possibility to collect a wealth of data through continuous monitoring reduces needed sample sizes and duration of studies and provides intra-individual predictions of change, while directly embodying the principle of personalized medicine.

While ORCATECH's model applies widely to health assessment and intervention, it fits particularly well for meeting the current public health challenge posed by Alzheimer's disease and related disorders. Home-based monitoring, in its ability to assess meaningful change, provides a method for tackling one of the greatest challenges across the spectrum of dementing diseases from pre-symptomatic to manifest disease.

Unobtrusive continuous in-home monitoring has the potential for revolutionizing how we conduct research in medicine and transforming clinical practice. The hope is that the wide adoption of continuous in-home monitoring will provide physicians and patients with the tools to predict and detect changes in health as they begin to occur – prior to detection with current tools. This would enable intervention to improve health outcomes, ultimately reducing the emotional and financial costs of disease.

References

Akbaraly, T. N., Portet, F., Fustinoni, S., Dartigues, J.-F., Artero, S., Rouaud, O., et al. (2009). Leisure activities and the risk of dementia in the elderly: results from the three-city study. *Neurology* **73**, 854–861. doi:10.1212/WNL.0b013e3181b7849b

Allaire, J. C., Gamaldo, A., Ayotte, B. J., Sims, R., and Whitfield, K. (2009). Mild cognitive impairment and objective instrumental everyday functioning: the everyday cognition battery memory test. *J. Am. Geriatr. Soc.* **57**, 120–125. doi:10.1111/j.1532-5415.2008.02054.x

Austin, D., Cross, R. M., Hayes, T., and Kaye, J. (2014a). *Regularity and Predictability of Human Mobility in Personal Space*. Available at: http://archive.org/details/pubmed-PMC3937357

Austin, D., Cross, R. M., Jacobs, P., Mattek, N. C., Petersen, J., Wild, K., et al. (2014b). *Predicting Transitions to Higher Levels of Care among Elderly: A Behavioral Approach*. Washington, DC: Gerontological Society of America Annual Conference.

Austin, D., Hayes, T. L., Kaye, J., Mattek, N., and Pavel, M. (2011a). On the disambiguation of passively measured in-home gait velocities from multi-person smart homes. *J. Ambient Intell. Smart Environ.* **3**, 165–174.

Austin, D., Hayes, T. L., Kaye, J., Mattek, N., and Pavel, M. (2011b). Unobtrusive monitoring of the longitudinal evolution of in-home gait velocity data with applications to elder care. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2011**, 6495–6498. doi:10.1109/IEMBS.2011.6091603

Austin, D., Jimison, H., Hayes, T., Mattek, N., Kaye, J., and Pavel, M. (2011c). Measuring motor speed through typing: a surrogate for the finger tapping test. *Behav. Res. Methods* **43**, 903–909. doi:10.3758/s13428-011-0100-1

Banerjee, T., Keller, J. M., and Skubic, M. (2012). *Resident Identification Using Kinect Depth Image Data and Fuzzy Clustering Techniques*. DeepDyve. Available at: https://www.deepdyve.com/lp/institute-of-electrical-and-electronics-engineers/resident-identification-using-kinect-depth-image-data-and-fuzzy-WN0s62RITr

Berkman, L. F., Glass, T., Brissette, I., and Seeman, T. (2000). From social integration to health: Durkheim in the new millennium. *Soc. Sci. Med.* **51**, 843–857. doi:10.1016/S0277-9536(00)00065-4

Boise, L., Morgan, D. L., Kaye, J., and Camicioli, R. (1999). Delays in the diagnosis of dementia: perspectives of family caregivers. *Am. J. Alzheimers Dis. Other Demen.* **14**, 20–26. doi:10.1177/153331759901400101

Boise, L., Neal, M. B., and Kaye, J. (2004). Dementia assessment in primary care: results from a study in three managed care systems. *J. Gerontol. A Biol. Sci. Med. Sci.* **59**, M621–M626. doi:10.1093/gerona/59.6.M621

Boise, L., Wild, K., Mattek, N., Ruhl, M., Dodge, H. H., and Kaye, J. (2013). Willingness of older adults to share data and privacy concerns after exposure to unobtrusive in-home monitoring. *Gerontechnology* **11**, 428–435. doi:10.4017/gt.2013.11.3.001.00

Bradford, A., Kunik, M. E., Schulz, P., Williams, S. P., and Singh, H. (2009). Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer Dis. Assoc. Disord.* **23**, 306–314. doi:10.1097/WAD.0b013e3181a6bebc

Brooks, B. L. (2006). *The Relationship Between Executive Functioning and Independent Living Skills in Mild Cognitive Impairment and Mild Dementia*. 8-B. Vol. 66. University of Calgary, Dissertation Abstracts International: Section B: The Sciences and Engineering, p. 4473.

Camicioli, R., Howieson, D., Oken, B., Sexton, G., and Kaye, J. (1998). Motor slowing precedes cognitive impairment in the oldest old. *Neurology* **50**, 1496–1498. doi:10.1212/WNL.50.5.1496

Campbell, I. H., Austin, D., Hayes, T. L., Pavel, M., Riley, T., Mattek, N., et al. (2011). Measuring changes in activity patterns during a norovirus epidemic at a retirement community. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2011**, 6793–6796. doi:10.1109/IEMBS.2011.6091675

Candia, J., González, M. C., Wang, P., Schoenharl, T., Madey, G., and Barabási, A.-L. (2008). Uncovering individual and collective human dynamics from mobile phone records. *J. Phys. Math. Theor.* **41**, 224015. doi:10.1088/1751-8113/41/22/224015

Carlsson, C. M. (2008). Lessons learned from failed and discontinued clinical trials for the treatment of Alzheimer's disease: future directions. *J. Alzheimers Dis.* **15**, 327–338.

Cherry, D. K., Hing, E., Woodwell, D. A., and Rechtsteiner, E. A. (2008). National ambulatory medical care survey: 2006 summary. *Natl. Health Stat. Report* **3**, 1–39.

Col, N., Fanale, J. E., and Kronholm, P. (1990). The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch. Intern. Med.* **150**, 841–845. doi:10.1001/archinte.150.4.841

Cook, D. J., and Krishnan, N. (2014). Mining the home environment. *J. Intell. Inf. Syst.* **43**, 503–519. doi:10.1007/s10844-014-0341-4

Cornwell, E. Y., and Waite, L. J. (2009). Social disconnectedness, perceived isolation, and health among older adults. *J. Health Soc. Behav.* **50**, 31–48. doi:10.1177/002214650905000103

Crandall, A. S., and Cook, D. J. (2011). Tracking systems for multiple smart home residents. *Human Behavior Recognition Technologies: Intelligent Applications Monitoring Security* 111–129.

Crowe, M., Andel, R., Wadley, V. G., Okonkwo, O. C., Sawyer, P., and Allman, R. M. (2008). Life-space and cognitive decline in a community-based sample of African American and Caucasian older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* **63**, 1241–1245. doi:10.1093/gerona/63.11.1241

Dawadi, P. N., Cook, D. J., and Schmitter-Edgecombe, M. (2013). Automated cognitive health assessment using smart home monitoring of complex tasks. *IEEE Trans. Syst. Man Cybern. Syst.* **43**, 1302–1313. doi:10.1109/TSMC.2013.2252338

Dodge, H. H., Mattek, N. C., Austin, D., Hayes, T. L., and Kaye, J. A. (2012). In-home walking speeds and variability trajectories associated with mild cognitive impairment. *Neurology* **78**, 1946–1952. doi:10.1212/WNL.0b013e318259e1de

Dodge, H. H., Ybarra, O., and Kaye, J. A. (2014). Tools for advancing research into social networks and cognitive function in older adults. *Int. Psychogeriatr* **26**, 533–539. doi:10.1017/S1041610213001750

Dodge, H. H., Zhu, J., Mattek, N. C., Bowman, M., Ybarra, O., Wild, K. V., et al. (2015). Web-enabled conversational interactions as a means to improve cognitive functions: results of a 6-week randomized controlled trial. *Alzheimers Dement. Transl. Res. Clin. Interv.* (in press).

Eagle, N., and (Sandy) Pentland, A. (2006). Reality mining: sensing complex social systems. *Pers. Ubiquitous Comput.* **10**, 255–268. doi:10.1007/s00779-005-0046-3

Evans, D. A., Grodstein, F., Loewenstein, D., Kaye, J., and Weintraub, S. (2011). Reducing case ascertainment costs in U.S. population studies of Alzheimer's disease, dementia, and cognitive impairment – part 2. *Alzheimers Dement. J. Alzheimers Assoc.* **7**, 110–123. doi:10.1016/j.jalz.2010.11.008

Ferdous, S., Vyas, K., and Makedon, F. (2012). "A survey on multi person identification and localization," in Proceedings of the 5th International Conference on PErvasive Technologies Related to Assistive Environments PETRA '12, Vol. **36** (New York, NY: ACM), 3.

Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M., and Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* **355**, 1315–1319. doi:10.1016/S0140-6736(00)02113-9

Gagliardi, C., Marcellini, F., Papa, R., Giuli, C., and Mollenkopf, H. (2010). Associations of personal and mobility resources with subjective well-being among older adults in Italy and Germany. *Arch. Gerontol. Geriatr.* **50**, 42–47. doi:10.1016/j.archger.2009.01.007

Geda, Y. E., Smith, G. E., Knopman, D. S., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., et al. (2004). De novo genesis of neuropsychiatric symptoms in mild cognitive impairment (MCI). *Int. Psychogeriatr.* **16**, 51–60. doi:10.1017/S1041610204000067

Glass, T. A., de Leon, C. M., Marottoli, R. A., and Berkman, L. F. (1999). Population based study of social and productive activities as predictors of survival among elderly Americans. *BMJ* **319**, 478–483. doi:10.1136/bmj.319.7208.478

Gold, D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *J. Clin. Exp. Neuropsychol.* **34**, 11–34. doi:10.1080/13803395.2011.614598

González, M. C., Hidalgo, C. A., and Barabási, A.-L. (2008). Understanding individual human mobility patterns. *Nature* **453**, 779–782. doi:10.1038/nature06958

Griffith, H. R., Stewart, C. C., Stoeckel, L. E., Okonkwo, O. C., den Hollander, J. A., Martin, R. C., et al. (2010). Magnetic resonance imaging volume of the angular gyri predicts financial skill deficits in people with amnestic mild cognitive impairment. *J. Am. Geriatr. Soc.* **58**, 265–274. doi:10.1111/j.1532-5415.2009.02679.x

Gu, Q., Dillon, C. F., and Burt, V. L. (2010). *Prescription Drug Use Continues to Increase: U.S. Prescription Drug data For 2007-2008*. Hyattsville, MD : NCHS Data Brief, 1–8.

Hagler, S., Austin, D., Hayes, T. L., Kaye, J., and Pavel, M. (2010). Unobtrusive and ubiquitous in-home monitoring: a methodology for continuous assessment of gait velocity in elders. *IEEE Trans. Biomed. Eng.* **57**, 813–820. doi:10.1109/TBME.2009.2036732

Hatt, W. J., Vanbaak, E. A., Jimison, H. B., Hagler, S., Hayes, T. L., Pavel, M., et al. (2009). The exploration & forensic analysis of computer usage data in the elderly. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2009**, 1216–1219.

Hayes, T. L., Abendroth, F., Adami, A., Pavel, M., Zitzelberger, T. A., and Kaye, J. A. (2008). Unobtrusive assessment of activity patterns associated with mild cognitive impairment. *Alzheimers Dement.* **4**, 395–405. doi:10.1016/j.jalz.2008.07.004

Hayes, T. L., Cobbinah, K., Dishongh, T., Kaye, J. A., Kimel, J., Labhard, M., et al. (2009a). A study of medication-taking and unobtrusive, intelligent reminding. *Telemed. J. E Health.* **15**, 770–776. doi:10.1089/tmj.2009.0033

Hayes, T. L., Larimer, N., Adami, A., and Kaye, J. A. (2009b). Medication adherence in healthy elders: small cognitive changes make a big difference. *J. Aging Health* **21**, 567–580. doi:10.1177/0898264309332836

Hayes, T. L., Hunt, J. M., Adami, A., and Kaye, J. A. (2006). An electronic pillbox for continuous monitoring of medication adherence. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **1**, 6400–6403. doi:10.1109/IEMBS.2006.260367

Hayes, T. L., Riley, T., Mattek, N., Pavel, M., and Kaye, J. A. (2014). Sleep habits in mild cognitive impairment. *Alzheimer Dis. Assoc. Disord.* **28**, 145–150. doi:10.1097/WAD.0000000000000010

Hayes, T. L., Riley, T., Pavel, M., and Kaye, J. A. (2010). Estimation of rest-activity patterns using motion sensors. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2010**, 2147–2150. doi:10.1109/IEMBS.2010.5628022

Ho, P., Rumsfeld, J. S., and Masoudi, F. A. (2006). EFfect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch. Intern. Med.* **166**, 1836–1841. doi:10.1001/archinte.166.17.1836

Hodges, M. R., Kirsch, N. L., Newman, M. W., and Pollack, M. E. (2010). "Automatic assessment of cognitive impairment through electronic observation of object usage," in *Pervasive Computing Lecture Notes in Computer Science*, eds Floréen P., Krüger A., and Spasojevic M. (Berlin: Springer), 192–209. Available at: http://link.springer.com/chapter/10.1007/978-3-642-12654-3_12

Holt-Lunstad, J., Smith, T. B., and Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS Med.* **7**:e1000316. doi:10.1371/journal.pmed.1000316

Hosseini, H. G., and Krechowec, Z. (2004). Facial expression analysis for estimating patient's emotional states in RPMS. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2**, 1517–1520. doi:10.1109/IEMBS.2004.1403465

House, J. S., Landis, K. R., and Umberson, D. (1988). Social relationships and health. *Science* **241**, 540–545. doi:10.1126/science.3399889

Insel, K., Morrow, D., Brewer, B., and Figueredo, A. (2006). Executive function, working memory, and medication adherence among older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **61**, 102–107. doi:10.1093/geronb/61.2.P102

James, B. D., Boyle, P. A., Buchman, A. S., Barnes, L. L., and Bennett, D. A. (2011). Life space and risk of Alzheimer disease, mild cognitive impairment, and cognitive decline in old age. *Am. J. Geriatr. Psychiatry* **19**, 961–969. doi:10.1097/JGP.0b013e318211c219

Kao, H., Conant, R., Soriano, T., and McCormick, W. (2009). The past, present, and future of house calls. *Clin. Geriatr. Med.* **25**, 19–34. doi:10.1016/j.cger.2008.10.005

Kaye, J. (2008). Home-based technologies: a new paradigm for conducting dementia prevention trials. *Alzheimers Dement.* **4**, S60–S66. doi:10.1016/j.jalz.2007.10.003

Kaye, J., Mattek, N., Dodge, H., Buracchio, T., Austin, D., Hagler, S., et al. (2012). One walk a year to 1000 within a year: continuous in-home unobtrusive gait assessment of older adults. *Gait Posture* **35**, 197–202. doi:10.1016/j.gaitpost.2011.09.006

Kaye, J., Mattek, N., Dodge, H. H., Campbell, I., Hayes, T., Austin, D., et al. (2014). Unobtrusive measurement of daily computer use to detect mild cognitive impairment. *Alzheimers Dement.* **10**, 10–17. doi:10.1016/j.jalz.2013.01.011

Kaye, J. A., Maxwell, S. A., Mattek, N., Hayes, T. L., Dodge, H., Pavel, M., et al. (2011). Intelligent systems for assessing aging changes: home-based, unobtrusive, and continuous assessment of aging. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **66B**, i180–i190. doi:10.1093/geronb/gbq095

Kotagal, V., Langa, K. M., Plassman, B. L., Fisher, G. G., Giordani, B. J., Wallace, R. B., et al. (2015). Factors associated with cognitive evaluations in the United States. *Neurology* **84**, 64–71. doi:10.1212/WNL.0000000000001096

Lee, M. L., and Dey, A. K. (2010). "Embedded assessment of aging adults: a concept validation with stakeholders," in *4th International Conference on-NO PERMISSIONS, Pervasive Computing Technologies for Healthcare (PervasiveHealth), 2010*, Munich, 1–8.

Lundell, J., Hayes, T. L., Vurgun, S., Ozertem, U., Kimel, J., Kaye, J., et al. (2007). Continuous activity monitoring and intelligent contextual prompting to improve medication adherence. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2007**, 6287–6290.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., and DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* **288**, 1475–1483. doi:10.1001/jama.288.12.1475

Mariani, E., Monastero, R., and Mecocci, P. (2007). Mild cognitive impairment: a systematic review. *J. Alzheimers Dis.* **12**, 23–35.

Miller, L. M., Dieckmann, N. F., Mattek, N. C., Lyons, K. S., and Kaye, J. A. (2014). Social activity decreases risk of placement in a long-term care facility for a prospective sample of community-dwelling older adults. *Res. Gerontol. Nurs.* **7**, 106–112. doi:10.3928/19404921-20140110-02

Palla, G., Barabási, A.-L., and Vicsek, T. (2007). Quantifying social group evolution. *Nature* **446**, 664–667. doi:10.1038/nature05670

Pavel, M., Jimison, H., Hayes, T., Larimer, N., Hagler, S., Vimegnon, Y., et al. (2010). Optimizing medication reminders using a decision-theoretic framework. *Stud. Health Technol. Inform.* **160**, 791–795.

Petersen, J., Austin, D., Kaye, J. A., Pavel, M., and Hayes, T. L. (2014a). Unobtrusive in-home detection of time spent out-of-home with applications to loneliness and physical activity. *IEEE J. Biomed. Health Inform.* **18**, 1590–1596. doi:10.1109/JBHI.2013.2294276

Petersen, J., Austin, D., Yeargers, J., and Kaye, J. (2014b). Unobtrusive phone monitoring as a novel measure of cognitive function. *Alzheimers Dement.* **10**, 366–367. doi:10.1016/j.jalz.2014.05.422

Petersen, J., Larimer, N., Kaye, J. A., Pavel, M., and Hayes, T. L. (2012). SVM to detect the presence of visitors in a smart home environment. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2012**, 5850–5853. doi:10.1109/EMBC.2012.6347324

Rantz, M., Skubic, M., Miller, S., and Krampe, J. (2008). "Using technology to enhance aging in place," in *Smart Homes and Health Telematics Lecture Notes in Computer Science*, eds Helal S., Mitra S., Wong J., Chang C. K., and Mokhtari M. (Berlin: Springer), 169–176. Available at: http://link.springer.com/chapter/10.1007/978-3-540-69916-3_20

Rantz, M. J., Skubic, M., and Miller, S. J. (2009). "Using sensor technology to augment traditional healthcare," in *Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2009*, Vol. **2009** (Minneapolis, MN: EMBC), 6159–6162.

Russell, D., Peplau, L. A., and Cutrona, C. E. (1980). The revised UCLA loneliness scale: concurrent and discriminant validity evidence. *J. Pers. Soc. Psychol.* **39**, 472–480. doi:10.1037/0022-3514.39.3.472

Scarmeas, N., Levy, G., Tang, M. X., Manly, J., and Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* **57**, 2236–2242. doi:10.1212/WNL.57.12.2236

Schmitter-Edgecombe, M., and Parsey, C. M. (2014). Assessment of functional change and cognitive correlates in the progression from healthy cognitive aging to dementia. *Neuropsychology* **28**, 881–893. doi:10.1037/neu0000109

Schmitter-Edgecombe, M., Woo, E., and Greeley, D. R. (2009). Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology* **23**, 168–177. doi:10.1037/a0014186

Seelye, A., Mattek, N., Howieson, D., Austin, D., Wild, K., Dodge, H., et al. (2015a). Embedded online questionnaire measures are sensitive to identifying mild cognitive impairment. *Alzheimer's Disease & Associated Dementias* (in press).

Seelye, A., Mattek, N., Howieson, D., Riley, T., Wild, K., and Kaye, J. (2015b). The impact of sleep on neuropsychological performance in cognitively intact older adults using a novel in-home sensor-based sleep assessment approach. *Clin. Neuropsychol* **29**, 53–66. doi:10.1080/13854046.2015.1005139

Seelye, A. M., Schmitter-Edgecombe, M., Cook, D. J., and Crandall, A. (2013). Naturalistic assessment of everyday activities and prompting technologies in mild cognitive impairment. *J. Int. Neuropsychol. Soc.* **19**, 442–452. doi:10.1017/S135561771200149X

Shoval, N., Wahl, H.-W., Auslander, G., Isaacson, M., Oswald, F., Edry, T., et al. (2011). Use of the global positioning system to measure the out-of-home mobility of older adults with differing cognitive functioning. *Ageing Soc.* **31**, 849–869. doi:10.1017/S0144686X10001455

Smith, A. (2014). *Older Adults and Technology Use*. Pew Res. Cent. Internet Am. Life Proj. Available at: http://www.pewinternet.org/2014/04/03/older-adults-and-technology-use/

Srinivasan, V., Stankovic, J., and Whitehouse, K. (2010). "Using height sensors for biometric identification in multi-resident homes," in *Pervasive Computing Lecture Notes in Computer Science*, eds Floréen P., Krüger A., and Spasojevic M. (Berlin: Springer), 337–354. Available at: http://link.springer.com/chapter/10.1007/978-3-642-12654-3_20

Stark, A., Shafran, I., and Kaye, J. (2014). Inferring social nature of conversations from words: experiments on a corpus of everyday telephone conversations. *Comput. Speech Lang.* **28**(1): 28. doi:10.1016/j.csl.2013.06.003

Strauss, E., Sherman, E. M. S., and Spreen, O. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, 3rd Edn. Oxford, NY: Oxford University Press.

Suzuki, T., and Murase, S. (2010). Influence of outdoor activity and indoor activity on cognition decline: use of an infrared sensor to measure activity. *Telemed. J. E Health* **16**, 686–690. doi:10.1089/tmj.2009.0175

Thielke, S. M., Mattek, N. C., Hayes, T. L., Dodge, H. H., Quiñones, A. R., Austin, D., et al. (2014). Associations between observed in-home behaviors and self-reported low mood in community-dwelling older adults. *J. Am. Geriatr. Soc.* **62**, 685–689. doi:10.1111/jgs.12744

Tractenberg, R. E., Singer, C. M., and Kaye, J. A. (2005). Symptoms of sleep disturbance in persons with Alzheimer's disease and normal elderly. *J. Sleep Res.* **14**, 177–185. doi:10.1111/j.1365-2869.2005.00445.x

Tworoger, S. S., Lee, S., Schernhammer, E. S., and Grodstein, F. (2006). The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. *Alzheimer Dis. Assoc. Disord.* **20**, 41–48. doi:10.1097/01.wad.0000201850.52707.80

Wahl, H.-W., Wettstein, M., Shoval, N., Oswald, F., Kaspar, R., Issacson, M., et al. (2013). Interplay of cognitive and motivational resources for out-of-home behavior in a sample of cognitively heterogeneous older adults: findings of the SenTra project. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **68**, 691–702. doi:10.1093/geronb/gbs106

Wang, H.-X., Karp, A., Winblad, B., and Fratiglioni, L. (2002). Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. *Am. J. Epidemiol.* **155**, 1081–1087. doi:10.1093/aje/155.12.1081

Wang, L., Gu, T., Tao, X., Chen, H., and Lu, J. (2011). Recognizing multi-user activities using wearable sensors in a smart home. *Pervasive Mob. Comput.* **7**, 287–298. doi:10.1016/j.pmcj.2010.11.008

Westerberg, C. E., Lundgren, E. M., Florczak, S. M., Mesulam, M.-M., Weintraub, S., Zee, P. C., et al. (2010). Sleep influences the severity of memory disruption in amnestic mild cognitive impairment: results from sleep self-assessment and continuous activity monitoring. *Alzheimer Dis. Assoc. Disord.* **24**, 325–333. doi:10.1097/WAD.0b013e3181e30846

Wettstein, M., Wahl, H.-W., Shoval, N., Oswald, F., Voss, E., Seidl, U., et al. (2015). Out-of-home behavior and cognitive impairment in older adults: findings of the SenTra project. *J. Appl. Gerontol.* **34**, 3–25. doi:10.1177/0733464812459373

Wild, K. V., Mattek, N. C., Austin, D., and Kaye, J. (2015). Are you sure?" Lapses in self-reported activities among healthy older adults reporting online. *J. Appl. Gerontol.* doi:10.1177/0733464815570667

Wild, K. V., Mattek, N. C., Maxwell, S. A., Dodge, H. H., Jimison, H. B., and Kaye, J. A. (2012). Computer-related self-efficacy and anxiety in older adults with and without mild cognitive impairment. *Alzheimers Dement.* **8**, 544–552. doi:10.1016/j.jalz.2011.12.008

Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., et al. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* **287**, 742–748. doi:10.1001/jama.287.6.742

Ybarra, O., Burnstein, E., Winkielman, P.,Keller, M. C., Manis, M., Chan, E.et al. (2008). Mental exercising through simple socializing: social interaction promotes general cognitive functioning. *Pers Soc Psychol Bull* **34**, 248–259. doi:10.1177/0146167207310454

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

CORRECTION
published: 11 December 2015
doi: 10.3389/fnagi.2015.00232

Corrigendum: Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy

Bayard E. Lyons[1,2]*, *Daniel Austin*[1,3], *Adriana Seelye*[1,2], *Johanna Petersen*[1,3], *Jonathan Yeargers*[1,3], *Thomas Riley*[1], *Nicole Sharma*[1], *Nora Mattek*[1,2], *Hiroko Dodge*[1,2], *Katherine Wild*[1,2] *and Jeffrey A. Kaye*[1,2,3,4]

[1] Oregon Center for Aging and Technology, Oregon Health and Science University, Portland, OR, USA, [2] Department of Neurology, Oregon Health and Science University, Portland, OR, USA, [3] Department of Biomedical Engineering, Oregon Health and Science University, Portland, OR, USA, [4] Neurology Service, Portland Veteran Affairs Medical Center, Portland, OR, USA

Keywords: Alzheimer's disease (AD), dementia, mild cognitive impairment (MCI), home monitoring, OHSU, ORCATECH, Layton Aging and Alzheimer's Disease Center

OPEN ACCESS

Edited and reviewed by:
Philippe Robert, University of Nice Sophia Antipolis, France

***Correspondence:**
Bayard E. Lyons
lyonsb@ohsu.edu

Received: *09 October 2015*
Accepted: *25 November 2015*
Published: *11 December 2015*

Citation:
Lyons BE, Austin D, Seelye A, Petersen J, Yeargers J, Riley T, Sharma N, Mattek N, Dodge H, Wild K and Kaye JA (2015) Corrigendum: Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy. Front. Aging Neurosci. 7:232. doi: 10.3389/fnagi.2015.00232

A corrigendum on

Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy
by Lyons, B. E., Austin, D., Seelye, A., Petersen, J., Yeargers, J., Riley, T., et al. (2015). Front. Aging Neurosci. 7:102. doi: 10.3389/fnagi.2015.00102

ACKNOWLEDGMENTS

This research is supported by National Institute of Health grants P30-AG008017, P30-AG024978, R01-AG024059, R01-AG042191, R01-AG033581, K01-AG23014, and Intel Corporation.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 02 June 2015
doi: 10.3389/fnagi.2015.00098

Ecological assessment of autonomy in instrumental activities of daily living in dementia patients by the means of an automatic video monitoring system

Alexandra König[1,2], Carlos Fernando Crispim-Junior[1,3], Alvaro Gomez Uria Covella[3], Francois Bremond[1,3], Alexandre Derreumaux[1], Gregory Bensadoun[1], Renaud David[1,4], Frans Verhey[2], Pauline Aalten[2] and Philippe Robert[1,4]*

[1] EA CoBTeK, Université Côte d'Azur (UCA), Nice, France, [2] Alzheimer Center Limburg, Maastricht University Medical Center, School for Mental Health and Neuroscience, Maastricht, Netherlands, [3] STARS, INRIA, Sophia Antipolis, France, [4] Centre Mémoire de Ressources et de Recherche, CHU de Nice, Nice, France

OPEN ACCESS

Edited by:
George E. Barreto, Pontificia Universidad Javeriana, Colombia

Reviewed by:
Elisabetta Ambron, Scuola Internazionale Superiore di Studi Avanzati (SISSA), Italy
Oscar L. López, University of Pittsburgh School of Medicine, USA

****Correspondence:***
Alexandra König, CoBTeK COgnition Behaviour Technology - Université de Nice Sophia Antipolis, Centre Mémoire de Ressources et de Recherche- CHU de Nice, Institut Claude Pompidou, Centre Edmond et Lily Safra 10, rue Moliére 06100, Nice, France
a.konig@maastrichtuniversity.nl

Received: *07 February 2015*
Accepted: *07 May 2015*
Published: *02 June 2015*

Citation:
König A, Crispim-Junior CF, Covella AGU, Bremond F, Derreumaux A, Bensadoun G, David R, Verhey F, Aalten P and Robert P (2015) Ecological assessment of autonomy in instrumental activities of daily living in dementia patients by the means of an automatic video monitoring system. Front. Aging Neurosci. 7:98. doi: 10.3389/fnagi.2015.00098

Currently, the assessment of autonomy and functional ability involves clinical rating scales. However, scales are often limited in their ability to provide objective and sensitive information. By contrast, information and communication technologies may overcome these limitations by capturing more fully functional as well as cognitive disturbances associated with Alzheimer disease (AD). We investigated the quantitative assessment of autonomy in dementia patients based not only on gait analysis but also on the participant performance on instrumental activities of daily living (IADL) automatically recognized by a video event monitoring system (EMS). Three groups of participants (healthy controls, mild cognitive impairment, and AD patients) had to carry out a standardized scenario consisting of physical tasks (single and dual task) and several IADL such as preparing a pillbox or making a phone call while being recorded. After, video sensor data were processed by an EMS that automatically extracts kinematic parameters of the participants' gait and recognizes their carried out activities. These parameters were then used for the assessment of the participants' performance levels, here referred as autonomy. Autonomy assessment was approached as classification task using artificial intelligence methods that takes as input the parameters extracted by the EMS, here referred as behavioral profile. Activities were accurately recognized by the EMS with high precision. The most accurately recognized activities were "prepare medication" with 93% and "using phone" with 89% precision. The diagnostic group classifier obtained a precision of 73.46% when combining the analyses of physical tasks with IADL. In a further analysis, the created autonomy group classifier which obtained a precision of 83.67% when combining physical tasks and IADL. Results suggest that it is possible to quantitatively assess IADL functioning supported by an EMS and that even based on the extracted data the groups could be classified with high accuracy. This means that the use of such technologies may provide clinicians with diagnostic relevant information to improve autonomy assessment in real time decreasing observer biases.

Keywords: dementia, Alzheimer, mild cognitive impairment, video analyses, assessment, information and communication technologies, autonomy, instrumental activities of daily living

Introduction

One of the key features of Alzheimer's disease (AD) is impairment in daily functioning as well as executive dysfunction due to global pathological changes in frontal and posterior areas (Marshall et al., 2006).

Studies show that in dementia patients, loss of functioning in instrumental activities of daily living (IADL) is strongly associated with faster cognitive decline (Arrighi et al., 2013) and, in particular, with poorer performances on executive function tasks (Razani et al., 2007; Karzmark et al., 2012) such as the frontal assessment battery (FAB) (Dubois et al., 2000) or the trail making test (version B) (Tombaugh, 2004). Hence, it represents an early predictor of cognitive deterioration and possibly even for conversion from mild cognitive impairment (MCI) to AD (Reppermund et al., 2013). This is in line with older findings that show that declines in IADL are influenced by cognitive functioning, and are affected relatively early in the course of dementia (Stern et al., 1990) and, in particular, the executive component in IADL tasks that requires higher frontal lobe activation (Baddeley et al., 1986).

The assessment of functioning in IADL has gradually attracted more attention in clinical research and should be included not only as a part of diagnostic evaluation in dementia but it would also be essential to evaluate efficacy in rehabilitation settings (Clare et al., 2003; Cotelli et al., 2006).

Characterizing impairment in IADL is controversial because no standard exists so far as to the practical or theoretical definition (DeBettignies et al., 1990). Furthermore, until now, the assessment of IADL has been mostly limited to questionnaires and relies often on informants' reports, such as the disability assessment for dementia scale (DAD) or the IADL scale of Lawton and Brody (1969), which suffer from biases and inaccuracies in informants' perceptions as well as the possibility that some older adults do not have an individual who can comment on their impact of cognitive impairment on routine activities. In general, existing functional assessments lack sufficient sensitivity to detect subtle functional changes or differences in behavior, and therefore, treatment effects (Gold, 2012). This leads to an urgent need for better measures of functional changes in people with the earliest changes associated with AD in clinical trials (Snyder et al., 2014).

Besides, just a few of the named tools capture the earliest functional deficits seen in preclinical AD.

Growing recognition of the need for a more objective and direct measurement has led to some attempts to improve the assessments of IADL in clinical practice by developing new extensive informant-based computerized IADL questionnaire (Sikkes et al., 2012) or direct performance-based measures (Moore et al., 2007), which differ from the traditional informant-based or self-report questionnaires, such as the IADL Lawton scale, by observing directly, in fact, an individual enacting an IADL, like making a phone call or managing money.

Farina et al. (2010) developed such direct performance-based measure of patients with dementia, e.g., the functional living skills assessment (FLSA) (Farina et al., 2010). This tool was conceived to detect functional impairment targeting high-order social abilities in everyday life and IADL by a clinician's direct observation of the patient carrying out practical tasks or being verbally stimulated.

Nevertheless, those methods can be criticized as well, first, for being still strongly dependent on a human observer, and second, for removing the individual's chosen routine and environmental cues that typically facilitate IADL. Finally, performance-based assessment can be often time-consuming (Sikkes et al., 2009) and represents a single evaluation data point compared with the multiple observations afforded by a questionnaire that comments on an individual's overall behavior through the past weeks.

Information and communication technology (ICT) and, in particular, automatic video analyses of patients carrying out various IADL could be an innovative assessment method (Robert et al., 2013) to help overcome those limitations in reducing the inter/intra-rater variability due to human interpretation and increase ecological value by removing completely the human observer from the assessment site. Such techniques, and thus further, our proposed automatized video-based IADL assessment differs from these current tools by enabling the patients' performances and actions to be captured in real time and real life situations and being accurately evaluated in order to provide the clinician with objective performance measures and a «second opinion»regarding the overall state of functionality of the patient.

In previous work, the use of such video sensor technology has already been demonstrated by Konig et al. (2014) by showing significant correlations between manually and automatically extracted parameters and neuropsychological test scores as well as high-accuracy rates for the detected activities (up to 89.47%). In a next step, we would like to investigate the use of video analyses for a completely automatized autonomy assessment based on the extracted video features.

In this line, the objective of this study is to investigate the use of ICT and, in particular, video analyses in clinical practice for the assessment of autonomy in IADL in healthy elderly MCI and AD patients by demonstrating an accurate automatized autonomy assessment based simply on automatically extracted video features from gait and IADL performances.

Materials and Methods

Study Participants and Clinical Assessment

Participants aged 65 or older were recruited within the Dem@care protocol at the Nice Memory Research Center located at the Geriatric department of the University Hospital.

The study was approved by the local Nice ethics committee and only participants with the capacity to consent to the study were included. Each participant gave informed consent before the first assessment. It was a non-randomized study involving three diagnosis groups of participants.

The video data of 49 participants were exploitable from which 12 patients were diagnosed with AD, 23 patients diagnosed with MCI, and 14 healthy controls (HC). All diagnoses were made by a medical doctor from the Geriatric University Hospital.

For the AD group, the diagnosis was determined using the proposed diagnostic criteria from Dubois et al. (2007) requiring the presence of a progressive episodic memory impairment and biomarker evidence. For the MCI group, patients were diagnosed using the Petersen clinical criteria (Petersen et al., 1999) and only included with a mini-mental state examination (MMSE) (Folstein et al., 1975) score higher than 24. Subjects were not included if they had a history of head trauma with loss of consciousness, psychotic, or aberrant motor activity (tremor, rigidity, Parkinsonism) as defined by the movement disorder society unified Parkinson disease rating scale (Fahn and Elton, 1987) in order to control for any possible motor disorders influencing the ability to carry out IADL. Furthermore, participants with a MMSE score below 16 were excluded in order to avoid that the participant suffers from experiencing this assessment as a major failure.

Each participant underwent a standardized neuropsychological assessment with a psychologist. In addition, medical, clinical, and demographical information were collected. Global cognitive functioning was assessed using the MMSE (Folstein et al., 1975). Other cognitive functions were assessed, among others, with the FAB (Dubois et al., 2000) and the free and cued selective reminding test (Buschke, 1984; Grober and Buschke, 1987). Neuropsychiatric symptoms were assessed using the neuropsychiatric inventory (Cummings, 1997) and functional abilities were assessed using the IADL scale (IADL-E) (Lawton and Brody, 1969) during a clinical interview with the caregiver if there was one available.

Clinical Protocol

The clinical protocol asked the participants to undertake first a set of physical tasks (Scenario 1) and second a set of typical IADL (Scenario 2) followed by a free discussion period while being recorded by a set of sensors. Scenario 1 consisted of a single walking task and a dual task. The dual task involves walking while counting backwards from "305." These tasks intend to assess kinematic parameters of the participant via gait analysis (e.g., duration, number of steps, cadence, stride length). Scenario 2, also called the "ecological assessment of IADL," consisted of carrying out a set of daily living activities such as preparing a pillbox or writing a check within a timeframe of 15 min (see **Table 1**) followed by a short discussion. The defined activities were based on commonly used IADL questionnaires and represent at once activities with high- or low-cognitive demand [in accordance with the Bayer activities of daily living (ADL) scale] (Hindmarch et al., 1998; Erzigkeit et al., 2001). The protocol was conducted in an observation room located in the Nice Research Memory Center, which was equipped with everyday objects for use in ADLs and IADL, e.g., an armchair, a table, a tea corner, a television, a personal computer, and a library. Color-depth sensors (Kinect®, Microsoft©) were installed to capture the activity of the participants during the assessment. The aim of this protocol is an ecological assessment based on a "real time" performance that determines to which extent the participant could undertake independently a list of daily activities within a timeframe of 15 min. All assessments were performed at the same time of the day, between 2 and 3 p.m.

A clinician verified the performance of each participant in terms of the amount of initiated activities and correctly carried out activities as well as repetitions and omissions in order to define the quality of each task execution. Accordingly to this performance verification and based on previous work (Romdhane et al., 2012; Sacco et al., 2012; Konig et al., 2014), participants were grouped (independently from their diagnosis group) into either "good," "intermediate," or "poor" performer.

TABLE 1 | Design of ecological assessment.

Part 1 **Guided activities (5 min)**	**Part 2** **Semi guided activities (30 min)**
TASK TO PERFORM	
Mono/dual directed tasks – Walking – Counting backwards – Both walking and counting backwards **Vocal directed tasks** – Sentence repeating task – Articulation control task	**List of ADLs/IADL to organize and perform within 15 mn** – Watering plant – Preparing tea – Medication preparation – Managing finance (establishing account balance, writing a check) – Watching TV – Using phone (answering, calling) – Reading article and answering to questions
CLINICAL TARGETS	
• Motor abilities: balance disorders • Cognitive abilities: flexibility, shared attention, psychomotricity coordination, answer time to a stimulus, working memory	• Cognitive abilities: flexibility, planification, shared attention, psychomotricity coordination, work memory, time estimation, answer time to a stimulus • ADL/IADL performance

Data Collection and Processing

Participants had their activity recorded using a color-depth sensor placed close to the ceiling of the ecological room to maximize its coverage of the room. Recorded data were posteriorly analyzed by an event monitoring system (EMS, see **Figure 1**) to automatically extract fine- to coarse-grained information about patient's performance (e.g., feet position, number of steps, the IADL carried out). Using the automatically extracted information, we estimate gait- and IADL-related parameters to describe the participant performance in the clinical protocol.

The estimated parameters were then used as input features for Naïve Bayes model to classify the participant's performance into the autonomy and dementia classes investigated in this work. Targeted autonomy classes were good, intermediate, and poor; and targeted cognitive status classes were Alzheimer's, MCI, and healthy.

Event Monitoring System

The EMS is composed of four main modules: people detection, people tracking, gait analysis, and event recognition. People detection step is performed by the background-subtraction algorithm proposed by Nghiem and Bremond (2014). The set of people detected in the scene is then tracked over the space and time by the algorithm of Chau et al. (2011). The output of these two modules is used as input for gait analysis and event recognition. The latter module is based on the work of Crispim-Junior et al. (2013), where a constraint-based ontology language is employed to model daily living activities in terms of posture, motion, and location patterns of the participant in the scene.

An IADL model is generally defined based on a set of physical objects (e.g., detected people, room furniture, and objects), a set of sub-events that model specific aspects of the targeted IADL, and constraints that establish rules sub-events and physical objects need to satisfy. **Figure 2** presents an example of event model "Prepare Drink" using the ontology language. "Prepare Drink" event model is based on two sub-events (components): one event that verifies whether the person global

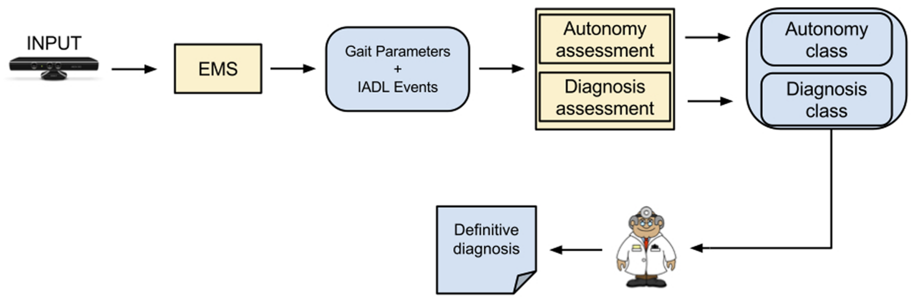

FIGURE 1 | System architecture; this figure shows the different steps from the system receiving the video input to the definitive clinical diagnosis. The event monitoring system (EMS) consists of four modules that will lead to the correct assessment based on automatically extracted video features: people detection, people tracking, gait analysis and event recognition. The main outcome is based on the fusion of "Gait Parameters" and "Instrumental Activities of Daily Living Events," which are processed with a feature selection method and a classifier for the autonomy and diagnosis assessment.

```
Composite Event (Prepare Drink),

Physical Objects (Person: p1) (Zone: zDrink) )

Components (

        (c1 : PrimitiveState Person_in_zone_Drink(p1,zDrink)

        (c2 : PrimitiveState Person_bending (p1) )

        )

Constraints( (c1->Interval AND c2->Interval

        (duration (c1) > 5 )

Alarm (URGENT )
```

FIGURE 2 | Presents an example of event model for the recognition of preparing drink event following the ontology language.

position is located where the drinking objects are generally placed (named Person_in_zone_Drink), and a second sub-event verifying whether the person displays the posture "bending" (named Person_bending). Given that both components are recognized by the system, to satisfy the first constraint in the IADL model the person must be performing both sub-events at the same time (c1- > Interval AND c2- > Interval). The second constraint establishes that the first sub-event must have being performed for at least 2 s already. Once both constraints are satisfied, the event starts to be recognized by the EMS. For more details on IADL modeling, please refer to the work of Crispim-Junior et al. (2013). **Figure 3** presents the monitored scene annotated with the semantic information used for event modeling and recognition. Left image displays the recognition of watering plant event.

The output of the EMS is the basis for the computation of the performance of the patients in the clinical protocol. From its output data (event report), we extract descriptors with different levels of granularity to appropriately describe the patient performance according to the complexity of the monitored activity. For gait analysis, we estimate fine-grained features like stride length, distance traveled, average speed, and cadence for the period of time of the physical task events (e.g., mono and dual task events).

For the IADL, we compute their frequency and duration, and the number of times the patient missed or repeated them. Activity repetition and omission are calculated with respect to the number of times the participants are expected to perform an activity given the instructions they received at the beginning of the experiment. The ensemble of data automatically computed by the system constituted the behavioral profile (or performance assessment) of the monitored participant.

Autonomy Assessment and Dementia Diagnosis Classification

Using the behavioral profile extracted by the EMS, two Naïve Bayes models were trained to classify participants into the targeted cognitive status and autonomy level classes according to their performance in the clinical protocol. To learn and validate the classifiers' performance, we employed a 20-fold cross-validation scheme, where we partitioned the data set into 20 equal parts, and then performed model learning and validation 20 times. At each iteration, the cross-validation scheme retained one of the 20 folds for validation and used the other 19 parts for model learning. The reported model performance corresponds to the averaged performance of the models in the 20 validation folds.

To determine the best combination of parameters for dementia and autonomy classification, we performed feature subset selection based on best first search and Naïve Bayes classifier (Kohavi and John, 1997; Hall and Holmes, 2003). Using the feature selection method, we downsized the patient behavioral profile to the most relevant parameters for the classification of dementia and autonomy. The feature selection for both classification tasks (autonomy and dementia diagnosis) started with the same global feature set, algorithms were free to choose the input-parameters that maximized the performance of the task at hand.

We have selected the Naïve Bayes classifiers due to its probabilistic nature, which quantifies the pertinence of a participant's performance for each class evaluated. Although this method assumes conditional independence among input parameters, an assumption that proves to be unrealistic for most practical application, it tends to perform reasonably well compared to more sophisticated methods, like support vector machines (John and Langley, 1995; Huang et al., 2003), with the advantage of having a much smaller running time and requiring very little training

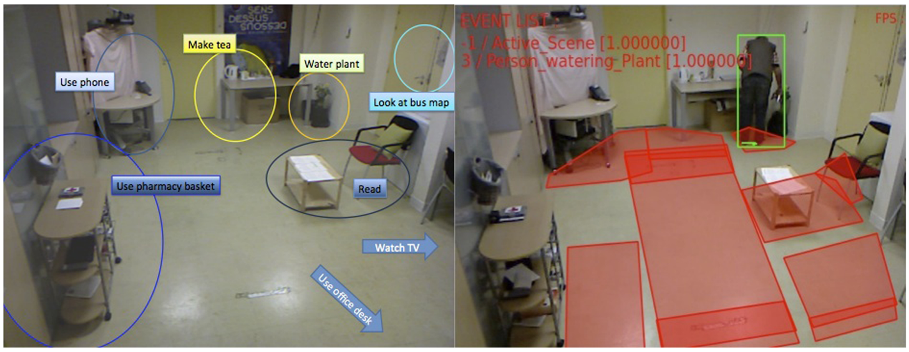

FIGURE 3 | Event recognition based on activity zones. The left image presents the contextual zones used to describe the scene semantics. The right image presents an example of output of the automatic video monitoring system.

data (Matwin and Sazonova, 2012). All classification experiments were performed using WEKA platform (Hall et al., 2009). The implementation of Naïve Bayes in WEKA is based on the work of John and Langley (1995).

Statistical Analyses

In a separate step, next to the video data extraction analyses, the characteristics of all participants as well as the annotated performance results of the ecological assessment were analyzed in order to determine the different autonomy levels. Comparisons between the groups (e.g., HC subjects, MCI patients, and AD group and good performer, intermediate, and poor performer) were performed with Mann-Whitney tests for each outcome variable of the automatic video analyses. Differences were reported as significant if $p < 0.05$. Spearman's correlations were further performed to determine the association between the extracted video parameters and established assessment tools, in particular, for executive functioning, e.g., the FAB.

Results

Population

Fourteen HC subjects (age = 74.1 ± 6.62), 23 MCI (age = 77.6 ± 6.17), and 12 AD subjects (age = 82.0 ± 8) were included. **Tables 2** and **3** show the clinical and demographic data of the participants. Significant intergroup differences in demographic factors were found for age between MCI and AD subjects as well as between HC and AD subjects ($p < 0.05$). Further, significant differences were found between all groups for the MMSE score, with a mean of 28.4 (±1.1) for the HC group, 25.5 (±2.1) for the MCI group, and 22.67 ± 3.6 for the AD group ($p < 0.05$). Significant differences were found for FAB results between HC subjects with 16.3 (±1.1) and MCI subjects with 14 (±2.4), as well as between HC subjects and AD subjects with 12.33 (±3.1) ($p < 0.05$). The mean IADL scores did not differ between groups, with a mean IADL score of 7 (±1.2) for the HC group, 6.33 (±1.7) for the MCI group, and (6 ± 1.8) for the AD group.

TABLE 2 | Characteristics and group comparisons for HC, MCI, and AD subjects.

Characteristics	All subject *N* = 49	Healthy control group *N* = 14	MCI group *N* = 23	AD group *N* = 12
Female, *n* (%)	26 (53.1%)	9 (64.3%)	10 (43.5%)	7 (58.33%)
Age, years mean ST	$77.7 \pm 7.3^{\dagger,\ddagger}$	74.1 ± 6.6	77.6 ± 6.2	82.0 ± 8
Level of education, *n* (%)				
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No formal education	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Elementary school	16 (32.6%)	2 (14.3%)	5 (21.7%)	9 (75%)
Middle school	9 (18.4%)	2 (14.3%)	6 (26.1%)	1 (8.3%)
High school	8 (16.3%)	4 (28.6%)	4 (17.4%)	0 (0%)
Post-secondary education	16 (32.6%)	6 (42.9%)	8 (34.8%)	2 (16.7%)
MMSE (mean ± SD)	$25.6 \pm 3.1^{*,\dagger,\ddagger}$	28.4 ± 1.1	25.5 ± 2.1	22.67 ± 3.6
FAB (mean ± SD)	$14.25 \pm 2.7^{*,\ddagger}$	16.3 ± 1.1	14 ± 2.4	12.33 ± 3.1
FCSR test ± SD	$39.2 \pm 9.9^{*,\ddagger}$	46.27 ± 1.9	38.19 ± 7.2	29.50 ± 16.7
IADL-E (mean ± SD)	6.4 ± 1.3	7 ± 1.2	6.33 ± 1.7	6 ± 1.8
NPI total (mean ± SD)	$6.89 \pm 8.1^{\dagger,\ddagger}$	3.54 ± 2.8	5.77 ± 7.1	12.6 ± 11
Ecological assessment results				
Single task time (in s)	$11.92 \pm 3.1^{\dagger,\ddagger}$	10.79 ± 1.31	11.43 ± 2.97	14.36 ± 3.83
Dual task time IADL	$18.53 \pm 8.19^{\dagger,\ddagger}$	14.79 ± 4.26	18.35 ± 8.78	23.25 ± 8.65
Activities initiated	$9.16 \pm 3.27^{*,\dagger,\ddagger}$	11.64 ± 1.15	9.39 ± 2.46	5.83 ± 3.61
Activities completed	$6.65 \pm 3.66^{*,\dagger,\ddagger}$	10.00 ± 1.47	6.57 ± 3.27	2.92 ± 2.27

*MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, mini mental state examination; FAB, frontal assessment battery; FCSR, free and cued selective reminding test; IADL-E, instrumental activities of daily living for elderly; NPI, neuropsychiatric inventory. All values represent means and SD (except n, gender, education and the classification results) *$p < 0.05$ for HC vs. MCI, $^{\dagger}p < 0.05$ for MCI vs. AD, $^{\ddagger}p < 0.05$ for HC vs. AD. Group comparisons were made using Mann–Whitney U test ($p < 0.05$).*

Ecological Assessment Results

The participants performed differently on the IADL scenario in terms of initiated and successfully completed activities in accordance with their cognitive status. **Tables 2** and **3** present results of the intergroup comparison of the performance results in the ecological assessment. Significant group differences were found for the single and dual task between MCI and AD ($p < 0.05$) and for HC and AD ($p < 0.05$). The amount of "activities initiated"

TABLE 3 | Intergroup comparison of scores and performance results from the ecological assessment (Mann–Whitney *U* test).

Comparison	Age *Z/p*	MMSE *Z/p*	FAB *Z/p*	FCSR *Z/p*	IADL *Z/p*	NPI *Z/p*	Single task	Dual task	AI	AC
HC vs. MCI	−1.695/ 0.090	−4.080/ 0.000	−3.024/ 0.002	−3.469/ 0.001	−1.603/ 0.109	−0.258/ 0.797	−0.286/ 0.775	−1.196/ 0.232	−3.067/ 0.002	−3.328/ 0.001
MCI vs. AD	−2.036/ 0.042	−2.432/ 0.015	−1.363/ 0.173	−1.024/ 0.306	−0.656/ 0.512	−2.228/ 0.026	−2.134/ 0.033	−2.003/ 0.045	−2.837/ 0.005	−3.093/ 0.002
HC vs. AD	0.023/ −2.267	−4.261/ 0.000	−3.838/ 0.000	−2.654/ 0.008	−1.476/ 0.140	−2.433/ 0.015	−2.492/ 0.013	−2968/ 0.003	−4.121/ 0.000	−4.326/ 0.000

MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE; mini mental state examination; FAB, frontal assessment battery; FCSR, free and cued selective reminding test; IADL-E, instrumental activities of daily living for elderly; NPI, neuropsychiatric inventory; AI, activities initiated; AC, activities completed.
p and Z values are presented for each group comparison.

TABLE 4 | Correlation between IADL scenario performance and conventional cognitive assessments (Spearman's correlation coefficient).

Video analyses data Spearman correlation coefficient (*r*)/*p*-values	MMSE	FAB	FCSR	NPI	IADL-E
Activities initiated	0.650** $p = 0.000$	0.519** $p = 0.000$	0.380* $p = 0.019$	−0.177 $p = 0.234$	0.324* $p = 0.030$
Activities completed	0.685** $p = 0.000$	0.620** $p = 0.000$	0.356* $p = 0.028$	−0.266 $p = 0.071$	0.334* $p = 0.025$

**p < 0.05 and **p < 0.01*

and "activities completed" differed significantly between all three groups ($p < 0.05$).

The parameter "activities initiated" correlated significantly with neuropsychological test results, namely, the MMSE ($p < 0.01$), FAB score ($p < 0.01$), FCSR ($p < 0.05$), and the IADL-E score ($p < 0.05$). In the same line, the parameter "activity completed" correlated significantly with the test results, MMSE ($p < 0.01$), FAB score ($p < 0.01$), FCSR ($p < 0.05$), and the IADL-E score ($p < 0.05$). The obtained correlation analyses results are presented in **Table 4**. None of the extracted parameters correlated with the NPI total scores.

After the performance analyses, the participants were classified based on their IADL performance. The cut-off scores between the classes have been based on the observation of the analyses of the participant's performances in terms of completely carried out activities, and on the cumulative frequencies of the completely carried out activities. These were divided into equal parts as homogeneously as possible in terms of data coverage following the frequency curve as presented in **Figure 4**. This division into three equal classes resulted in the following cut-off scores.

From 13 to 8 completed activities was a good performance, meaning highly independent; from 7 to 4 completed activities was an intermediate performance; and below 4 completed activities was a poor performance, representing highly dependent in daily living activities. The grouping of the participants was done blinded from their diagnosis group in order to avoid classification bases, i.e., more likely to classify a HC as a "good" performer. A HC subject could sometimes show a mediocre IADL performance on the assessment and in turn a MCI subject could show a good IADL performance. Taking into consideration that the

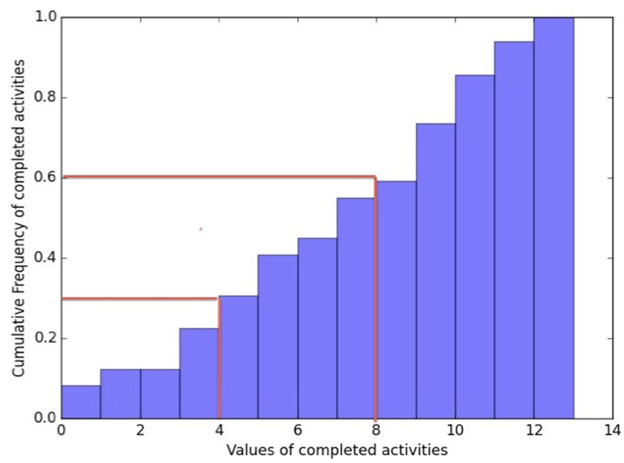

FIGURE 4 | Cumulative frequency curve of completed carried out activities. The red lines indicate the cut-off scores between the autonomy classes which have been based on the analyses of the participant's performances in terms of completely carried out activities, and on the cumulative frequencies of the completely carried out activities. These were divided in equal parts, as homogeneously as possible in terms of data coverage following the frequency curve.

objective of the assessment was to stage autonomy levels and not necessarily disease progression, even though they are associated, it was important to make that differentiation. **Table 5** shows the classification results based on the participants IADL scenario performances with their diagnosis group, as well as their average amount of completely carried out activities. Twenty-two participants from which 13 HC and 9 MCI subjects with an average of 10.04 correctly carried out activities were classified as good performer, 16 participants from which 1 HC, 10 MCI, and 5 AD subjects with an average of 5.5 correctly carried out activities were classified as intermediate performer and 11 participants from which 4 MCI and 7 AD patients with an average of 1.5 correctly carried out activities were classified as poor performer.

Validation of the Event Recognition System

Table 6 presents the results of the evaluation of the event video monitoring system (EMS) with respect to its precision at detecting correctly the events of the clinical protocol (scenario 1: single and

TABLE 5 | Ecological assessment results.

	N	HC	MCI	AD	Activities completed (in mean ± SD)
Good performance	22	13	9	–	10.04 ± 1.4
Intermediate performance	16	1	10	5	5.5 ± 1.2
Poor performance	11	–	4	7	1.54 ± 1.4

TABLE 6 | Activity/event detection performance.

Events	Recall (%)	Precision (%)
Scenario 01		
Mono task	100.0	88.0
Dual task	100.0	98.0
Scenario 02		
Searching bus line	58.0	62.5
Medication preparation	87.0	93.0
Watering plant	80.0	63.0
Reading article	60.0	88.0
Preparing drink	90.0	68.0
Talk on phone	89.0	89.0

dual task and scenario 2: the number of activities of daily living) annotated by domain experts while watching the experiment video.

Scenario 1, the single and dual task obtained the precision rates of 88 and 98%. From all proposed activities, "Medication preparation" was detected with the highest precision of 93% followed by "Using the phone" with 89% and "Reading an article" with 88%.

Classification of Participant Cognitive Status

Table 7 presents the classification results for autonomy assessment and dementia diagnosis. The classification procedure was intrinsically based on the features automatically extracted from the physical tasks and IADL performed by the participant during the clinical protocol. For comparison purposes, we have also learned two classifiers based only on behavioral data of the physical task or IADL-derived data. We hypothesized that combining the information from the two scenarios of the protocol increases the accuracy of the classification since they provide different but complementary information about a participant performance at daily living activities, e.g., motor and cognitive performances. For the three classifiers, the data set is the same and contains 49 patients in total. The overall activities were automatically detected with high sensitivity and precision results as previously described.

In the Autonomy classification task the following features were employed:

- Single Task Total Duration,
- Single Task Gap Duration,
- Single Task Standard Deviation Steps,
- Dual Task Gap Duration,
- Dual Task Max Steps,
- Person using PharmacyBasket Frequency of Event (frequency),
- Person using PharmacyBasket Duration of Event (seconds).

TABLE 7 | Classification results.

Performance	Input data		
	Scenario 01	Scenario 02	Both scenarios
Autonomy assessment			
Correctly classified instances	37 (75.5102%)	38 (77.551%)	41 (83.6735%)
Incorrectly classified instances	12 (24.4898%)	11 (22.449%)	8 (16.3265%)
Diagnosis assessment			
Correctly classified instances	36 (73.4694%)	30 (61.2245%)	36 (73.4694%)
Incorrectly classified instances	13 (26.5306%)	19 (38.7755%)	13 (26.5306%)

For the Diagnosis classification, the set of features was:

- Age,
- Single Task Average Steps,
- Single Task Speed Average from Centroid Information,
- Dual Task Max Steps,
- Dual Task Min Steps,
- Person reading inChairReadingTable Duration of Event (Frames).

The classifier for dementia diagnosis task obtained an accuracy of 61.22% when using only features based on IADL (Scenario 2), and of 75.51% when just extracting features from physical tasks (Scenario 1). The accuracy rate increased up to 73.46% when combining features from both scenarios. However, the higher recognition rates were found for the classifier learned for autonomy classification; based on simply the automatically extracted video features from Scenario 2, 77.55% accuracy was obtained and 75% accuracy for Scenario 1. The highest accuracy rate of 83.67% was obtained when combining directed tasks and IADL.

Discussion

The present study suggests that it is possible to assess autonomy in IADL functioning with the help of an EMS and that simply based on the extracted video features different autonomy levels can be classified highly accurately. The results obtained are significantly high not only for a correct assessment of autonomy but also cognitive status in terms of diagnosis. This means that "the proposed system" may become a very useful tool providing clinicians with diagnostic relevant information and improve autonomy assessment in AD or MCI patients in real time decreasing observer biases.

The results demonstrate further that gait analysis applied to IADL assessment may provide a reliable and precise methodology to assess patients functioning in daily life, which could be used at both diagnostic and rehabilitation levels. All extracted elements of the clinical protocol, the kinetic parameters from the single and dual tasks as well as the selected features from the IADL task are important and should be taken into consideration in the automatized analyses in order to assess and further predict accurately autonomy performances of patients. This means that in extractable gait features such as "single task standard deviation steps" and "dual task gap duration" lies relevant information about a patient's capacity to perform IADL, and therefore, his or her autonomy level. These features added up to the automatically detected lengths and frequencies to carry out activities result in a highly accurate autonomy classification rate of almost 84%, allowing soon an almost fully automatized functional assessment in clinical practice.

The work of Gillain et al. (2009) illustrates in the same manner that it may be possible to determine different cognitive profiles, and hence autonomy levels, by the measurement of gait parameters. This confirms previous research findings that gait ability and cognitive functions are interrelated, and, in particular, executive functions and gait speed (Montero-Odasso et al., 2009; Beauchet et al., 2013; Doi et al., 2013, 2014). Gait impairment is already known to be a common characteristic of patients with MCI (Allan et al., 2005) and represents a risk factor for conversion to AD (Verghese et al., 2007; Buracchio et al., 2010). Therefore, changes in these motor functions may be useful in the early detection of dementia during preclinical stages and easily measurable by sensor technologies.

Furthermore, significant correlations were found between the parameters of initiated and completed activities and most neuropsychological test results, particularly with MMSE and FAB scores showing that group differences even with just a small sample size could be detected when using such techniques, and this when regular assessment tools such as the IADL-E questionnaire lacked sensitivity to detect these group differences.

Finally, high-single activity detection rates, up to 93% for the "Medication preparation" activity, could be achieved validating further the use of EMS for evaluation and monitoring purposes.

The study's results were consistent with previous work where with a sensitivity of 85.31% and a precision of 75.90%, the overall activities were correctly automatically detected (Konig et al., 2015) although the present study was with a larger cohort and included AD patients as well.

Similar work, hence quantitative assessments of IADL performance, has been done using a different technique by Wadley et al. (2008) with the results that across timed IADL domains, MCI participants demonstrated accuracy comparable with cognitively normal participants but took significantly longer to complete the functional activities.

This suggests that slower speed in task execution could explain the differences found in the extracted features and thus, represents an important component and early marker of functional change already in the MCI patient, a component that would not be clearly identified using traditional measurements of daily function, but could be easily spotted using the quantitative and unbiased EMS data.

Likewise, Stucki et al. (2014) proved feasibility and reliability of a non-intrusive web-based sensor system for the recognition of ADL and the estimation of a patient's self-dependency with high classification precision rates (up to 90%). Bang et al. (2008) used multiple sensor fusion (pressure sensors, passive infrared sensors, and worn accelerometers) for automatized ADL detection with achieved accuracy rates of up to 90%. Nevertheless, these studies were carried out with a very small group sample of healthy, and in average, younger participants.

Until now, the clinical assessment of functional changes in AD and MCI patients has traditionally relied on scales and questionnaires that are not always sensitive to the earliest functional changes. This leads to an important need to develop improved methods to measures these changes, ideally at the earliest stages. Therefore, recently research efforts have been placed on studies finding new innovative and more objective ways to measure functional and cognitive changes associated with AD (Vestal et al., 2006; Goldberg et al., 2010; López-de-Ipiña et al., 2012; Zola et al., 2013; Yakhia et al., 2014).

The main interest of the present study was to demonstrate the practical application of the use of such a video monitoring system in clinical practice. Now, once the systems' use has been validated by significant correlation with neuropsychological test scores, particularly for executive functioning, and highly accurate detection rates, it can be employed as a supportive assessment tool within clinical routine check-ups also on a rehabilitation level and even move on to more naturalistic environments such as nursing homes.

The system's extracted information can provide the clinician with direct measurements (see the list of features) indicating, once interpreted, a certain level of autonomy performance, as well as with information about possible underlying mechanisms caused by decline in certain cognitive functioning, namely, executive functions, which are highly associated (Marshall et al., 2011). This technique has the advantage of leaving out the clinician, who represents often in assessments a potential stress factor, completely from the evaluation site, and thus increasing ecological validity by leaving the patient alone in a more naturalistic "living-room alike" setting. The use of sensors for the measurement of behavioral patterns reduces important assessment biases often present in clinical practice and adds objectiveness to the assessment procedure.

The objective on a long term is to provide a stable system that allows monitoring patients and their autonomy at home over a longer period. The parameters validated within this study can serve as indicators for illness progression, decline in IADL performance and hence, executive functions detectable with the help of new technologies much earlier, before somebody in the family would notice and send the patient to a specialist.

The limitation of this study resides first in the age and education differences among the groups; the AD population was older than the other groups, and the HC and MCI group had higher levels of education. This can be partly explained by the recruitment process and that generally in clinical practice it is quite difficult to recruit young AD patients. However, age and education level differences could have had an impact on the IADL and gait performances and should therefore being taken into consideration.

Therefore, in future studies, it would be important to also focus on recruiting younger AD patients and participants with equal education levels in order to control for this variability. Second, the HC subjects were recruited through the Memory Center, which means that most of the HC participants came to the center with a memory complaint even though in their neuropsychological tests they performed within normal ranges. It has to be taken into consideration that those participants may not be completely healthy and suffer from a higher risk to convert to MCI than people that do not consult the center for a memory complaint (Jacinto et al., 2014).

It has to be further underlined that even if participants were alone during the IADL assessment, the simple fact of knowing that they were recorded could have had an impact on their stress level and thus, their performance.

Finally, it cannot be denied that the development of such a system and its analysis program was time-consuming and expensive. Engineers worked within the European FP7 Research Program Dem@care several years on improving the system's efficacy and detection precision. However, once its usability in clinical practice has been further demonstrated by validation studies, its integration in routine assessment procedures is feasible; installation of such a system is affordable (Kinect camera and a computer) for Memory Clinics and analyses can be provided in real time. Nevertheless, more efforts in performance evaluation of such ICTs are needed to help the industry meet user needs and researchers in considering the available technologies for clinical practice. A solid economic model is a major issue: who will pay for assistive technology? Who will install and maintain ICTs at AD patients' homes? The cost–effectiveness balance for assistive technology remains a matter of debate.

To conclude, according to the recently published review of Snyder et al. (2014), research efforts have launched large prevention trials in AD and these efforts have further clearly demonstrated a need for better and more accurate measures of cognitive and functional changes in people already in the earliest stages of AD. In the same line, the US Food and Drug Administration elevated the importance of cognitive and functional assessments in early stage clinical trials by proposing that even in the pre-symptomatic stages of the disease, approval will be contingent on demonstrating clinical meaningfulness.

Similiarly, Laske et al. (2014) argued that there is an increasing need for additional non-invasive and/or cost-effective tools, allowing identification of subjects in the preclinical or early clinical stages of AD who could be suitable for further cognitive evaluation and dementia diagnostics. Once examined in ongoing large trials, the implementation of such tools may facilitate early, and potentially more effective therapeutic and preventative strategies, for AD.

All this points out, the need for improved cognitive and functional outcome measures for clinical studies of participants with preclinical AD and those diagnosed with MCI due to AD. With our study, we propose a new method of measuring objectively and accurately functional decline in patients from the earliest stages on with the support of the vision sensor technologies; a reliable method that could potentially, once validated through larger scale cohort studies, serve within clinical trial of new drug interventions as an endpoint measure to prove their effects on ADL function. Finally, the use of such systems could facilitate and support aging-in-place and improve medical care in general for these patients.

Acknowledgments

This study was supported by grants from the FP7 Dem@care project (grant 288199), and by the Innovation Alzheimer association. The study was realized at the Cimiez hospital CIU-S platform and at the Institut Claude Pompidou, research center Edmond & Lily Safra.

References

Allan, L. M., Ballard, C. G., Burn, D. J., and Kenny, R. A. (2005). Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. *J. Am. Geriatr. Soc.* 53, 1681–1687. doi:10.1111/j.1532-5415.2005.53552.x

Arrighi, H. M., Gelinas, I., McLaughlin, T. P., Buchanan, J., and Gauthier, S. (2013). Longitudinal changes in functional disability in Alzheimer's disease patients. *Int. Psychogeriatr.* 25, 929–937. doi:10.1017/S1041610212002360

Baddeley, A., Logie, R., Bressi, S., Della Sala, S., and Spinnler, H. (1986). Dementia and working memory. *Q. J. Exp. Psychol. A* 38, 603–618.

Bang, S., Kim, M., Song, S. K., and Park, S. J. (2008). Toward real time detection of the basic living activity in home using a wearable sensor and smart home sensors. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2008, 5200–5203. doi:10.1109/IEMBS.2008.4650386

Beauchet, O., Allali, G., Launay, C., Herrmann, F. R., and Annweiler, C. (2013). Gait variability at fast-pace walking speed: a biomarker of mild cognitive impairment? *J. Nutr. Health Aging* 17, 235–239. doi:10.1007/s12603-012-0394-4

Buracchio, T., Dodge, H. H., Howieson, D., Wasserman, D., and Kaye, J. (2010). The trajectory of gait speed preceding mild cognitive impairment. *Arch. Neurol.* 67, 980–986. doi:10.1001/archneurol.2010.159

Buschke, H. (1984). Cued recall in amnesia. *J. Clin. Neuropsychol.* 6, 433–440.

Chau, D. P., Bremond, F., and Thonnat, M. (2011). "A multi-feature tracking algorithm enabling adaptation to context variations," in *Paper Presented at the International Conference on Imaging for Crime Detection and Prevention* (London: ICDP).

Clare, L., Woods, R. T., Moniz Cook, E. D., Orrell, M., and Spector, A. (2003). Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. [Review]. *Cochrane Database Syst. Rev.* 4, CD003260. doi:10.1002/14651858.CD003260

Cotelli, M., Calabria, M., and Zanetti, O. (2006). Cognitive rehabilitation in Alzheimer's disease. [Review]. *Aging Clin. Exp. Res.* 18, 141–143.

Crispim-Junior, C., Bathrinarayanan, V., Fosty, B., Konig, A., Romdhane, R., Thonnat, M., et al. (2013). "Evaluation of a monitoring system for event recognition of older people," in *Paper Presented at the 10th IEEE International Conference on Advanced Video and Signal-Based Surveillance* (Krakow: AVSS).

Cummings, J. (1997). The neuropsychiatric inventory: assessing psychopathology in dementia patients. *Neurology* 48, 10–16.

DeBettignies, B. H., Mahurin, R. K., and Pirozzolo, F. J. (1990). Insight for impairment in independent living skills in Alzheimer's disease and multi-infarct dementia. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *J. Clin. Exp. Neuropsychol.* 12, 355–363.

Doi, T., Makizako, H., Shimada, H., Park, H., Tsutsumimoto, K., Uemura, K., et al. (2013). Brain activation during dual-task walking and executive function among older adults with mild cognitive impairment: a fNIRS study. *Aging Clin. Exp. Res.* 25, 539–544. doi:10.1007/s40520-013-0119-5

Doi, T., Shimada, H., Makizako, H., Tsutsumimoto, K., Uemura, K., Anan, Y., et al. (2014). Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment. *BMC Neurol.* 14:67. doi:10.1186/1471-2377-14-67

Dubois, B., Feldman, H. H., Jacova, C., Dekosky, S. T., Barberger-Gateau, P., Cummings, J., et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 6, 734–746. doi:10.1016/S1474-4422(07)70178-3

Dubois, B., Slachevsky, A., Litvan, I., and Pillon, B. (2000). The FAB: a frontal assessment battery at bedside. [Comment Research Support, Non-U.S. Gov't]. *Neurology* 55, 1621–1626. doi:10.1212/WNL.55.11.1621

Erzigkeit, H., Lehfeld, H., Pena-Casanova, J., Bieber, F., Yekrangi-Hartmann, C., Rupp, M., et al. (2001). The Bayer-activities of daily living scale (B-ADL): results from a validation study in three European countries. *Dement. Geriatr. Cogn. Disord.* 12, 348–358. doi:10.1159/000051280

Fahn, S., and Elton, R. L. (1987). "UPDRS program members. Unified Parkinsons disease rating scale," in *Recent Developments in Parkinsons*

Disease, eds S. Fahn, M. Goldstein, and D. B. Calne (Florham Park, NJ), 153–163.

Farina, E., Fioravanti, R., Pignatti, R., Alberoni, M., Mantovani, F., Manzoni, G., et al. (2010). Functional living skills assessment: a standardized measure of high-order activities of daily living in patients with dementia. [validation studies]. *Eur. J. Phys. Rehabil. Med.* 46, 73–80.

Folstein, M., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 121, 189–198.

Gillain, S., Warzee, E., Lekeu, F., Wojtasik, V., Maquet, D., Croisier, J.-L., et al. (2009). The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Ann. Phys. Rehabil. Med.* 52, 453–474. doi:10.1016/j.rehab.2008.10.004

Gold, D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. [Research Support, Non-U.S. Gov't Review]. *J. Clin. Exp. Neuropsychol.* 34, 11–34. doi:10.1080/13803395.2011.614598

Goldberg, T. E., Koppel, J., Keehlisen, L., Christen, E., Dreses-Werringloer, U., Conejero-Goldberg, C., et al. (2010). Performance-based measures of everyday function in mild cognitive impairment. *Am. J. Psychiatry* 167, 845–853. doi:10.1176/appi.ajp.2010.09050692

Grober, E., and Buschke, H. (1987). Genuine memory deficits in dementia. *Dev. Neuropsychol* 3, 13–36.

Hall, M., Frank, E., Holmes, G., Pfahringer, B., Reutemann, P., and Witten, I. (2009). "The WEKA data mining software: an update," in *ACM SIGKDD Explorations Newsletter table of contents archive, vol. 11. Sponsor SIGKDD ACM Special Interest Group on Knowledge Discovery in Data*. eds M. A. Hall and G. Holmes (New York, NY: ACM), 10–18.

Hall, M. A., and Holmes, G. (2003). "Benchmarking attribute selection techniques for discrete class data mining," in *Paper Presented at the IEEE Transactions on Knowledge and Data Engineering*, 15, 1437–1447.

Hindmarch, I., Lehfeld, H., de Jongh, P., and Erzigkeit, H. (1998). The bayer activities of daily living scale (B-ADL). *Dement. Geriatr. Cogn. Disord.* 9(Suppl. 2), 20–26.

Huang, J., Lu, J., and Ling, C. X. (2003). "Comparing naive Bayes, decision trees, and SVM with AUC and accuracy," in *Paper Presented at the Third IEEE International Conference on Data Mining ICDM 2003*, 553–556.

Jacinto, A. F., Brucki, S. M., Porto, C. S., Arruda Martins, M., and Nitrini, R. (2014). Subjective memory complaints in the elderly: a sign of cognitive impairment? *Clinics (Sao Paulo)* 69, 194–197. doi:10.6061/clinics/2014(03)09

John, G. H., and Langley, P. (1995). "Estimating continuous distributions in bayesian classifiers," in *Paper Presented at the Eleventh Conference on Uncertainty in Artificial Intelligence* (San Mateo, CA).

Karzmark, P., Llanes, S., Tan, S., Deutsch, G., and Zeifert, P. (2012). Comparison of the frontal systems behavior scale and neuropsychological tests of executive functioning in predicting instrumental activities of daily living. *Appl. Neuropsychol. Adult* 19, 81–85. doi:10.1080/09084282.2011.643942

Kohavi, R., and John, G. H. (1997). *Wrappers for Feature Subset Selection*. Mountain View, CA: Silicon Graphics, Inc.

Konig, A., Crispim Junior, C. F., Derreumaux, A., Bensadoun, G., Petit, P. D., Bremond, F., et al. (2014). Validation of an automatic video monitoring system for the detection of instrumental activities of daily living in dementia patients. *J. Alzheimers Dis.* 44, p. 675–685.doi:10.3233/JAD-141767

Konig, A., Crispim Junior, C. F., Derreumaux, A., Bensadoun, G., Petit, P. D., Bremond, F., et al. (2015). Validation of an automatic video monitoring system for the detection of instrumental activities of daily living in dementia patients. *J. Alzheimers Dis.* 44, 675–685. doi:10.3233/JAD-141767

Laske, C., Sohrabi, H. R., Frost, S. M., Lopez-de-Ipina, K., Garrard, P., Buscema, M., et al. (2014). Innovative diagnostic tools for early detection of Alzheimer's disease. *Alzheimers Dement.* 11, 561–578. doi:10.1016/j.jalz.2014.06.004

Lawton, M. P., and Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 9, 179–186.

López-de-Ipiña, K., Alonso, J. B., Barroso, N., Faundez-Zanuy, M., Ecay, M., Solé-Casals, J., et al. (2012). New approaches for Alzheimer's disease diagnosis based on automatic spontaneous speech analysis and emotional temperature. *Ambient Assist. Living Home Care Lecture Notes in Computer Science* 7657, 407–414. doi:10.1007/978-3-642-35395-6_55

Marshall, G. A., Fairbanks, L. A., Tekin, S., Vinters, H. V., and Cummings, J. L. (2006). Neuropathologic correlates of activities of daily living in Alzheimer disease. [Research Support, N.I.H., Extramural]. *Alzheimer Dis. Assoc. Disord.* 20, 56–59.

Marshall, G. A., Rentz, D. M., Frey, M. T., Locascio, J. J., Johnson, K. A., Sperling, R. A., et al. (2011). Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement.* 7, 300–308. doi:10.1016/j.jalz.2010.04.005

Matwin, S., and Sazonova, V. (2012). Direct comparison between support vector machine and multinomial naive bayes algorithms for medical abstract classification. *J. Am. Med. Inform. Assoc.* 19, 917. doi:10.1136/amiajnl-2012-001072

Montero-Odasso, M., Bergman, H., Phillips, N. A., Wong, C. H., Sourial, N., and Chertkow, H. (2009). Dual-tasking and gait in people with mild cognitive impairment. The effect of working memory. *BMC Geriatr.* 9:41. doi:10.1186/1471-2318-9-41

Moore, D. J., Palmer, B. W., Patterson, T. L., and Jeste, D. V. (2007). A review of performance-based measures of functional living skills. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.Review]. *J. Psychiatr. Res.* 41, 97–118. doi:10.1016/j.jpsychires.2005.10.008

Nghiem, A. T., and Bremond, F. (2014). "Background subtraction in people detection framework for RGB-D cameras," in *Paper Presented at the 11th IEEE International Conference on Advanced Video and Signal-Based Surveillance* (Seoul: AVSS).

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.* 56, 303–308.

Razani, J., Casas, R., Wong, J. T., Lu, P., Alessi, C., and Josephson, K. (2007). Relationship between executive functioning and activities of daily living in patients with relatively mild dementia. [Research Support, N.I.H., Extramural]. *Appl. Neuropsychol.* 14, 208–214. doi:10.1080/09084280701509125

Reppermund, S., Brodaty, H., Crawford, J. D., Kochan, N. A., Draper, B., Slavin, M. J., et al. (2013). Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. *Psychol. Med.* 43, 2437–2445. doi:10.1017/S003329171200308X

Robert, P. H., Konig, A., Andrieu, S., Bremond, F., Chemin, I., Chung, P. C., et al. (2013). Recommendations for ICT use in Alzheimer's disease assessment: monaco CTAD expert meeting. *J. Nutr. Health Aging* 17, 653–660. doi:10.1007/s12603-013-0046-3

Romdhane, R., Mulin, E., Derreumeaux, A., Zouba, N., Piano, J., Lee, L., et al. (2012). Automatic video monitoring system for assessment of Alzheimer's disease symptoms. *J. Nutr. Health Aging* 16, 213–218. doi:10.1007/s12603-011-0154-x

Sacco, G., Joumier, V., Darmon, N., Dechamps, A., Derreumaux, A., Lee, J. H., et al. (2012). Detection of activities of daily living impairment in Alzheimer's disease and mild cognitive impairment using information and communication technology. *Clin. Interv. Aging* 7, 539–549. doi:10.2147/CIA.S36297

Sikkes, S. A., de Lange-de Klerk, E. S., Pijnenburg, Y. A., Gillissen, F., Romkes, R., Knol, D. L., et al. (2012). A new informant-based questionnaire for instrumental activities of daily living in dementia. [Research Support, Non-U.S. Gov't]. *Alzheimers Dement.* 8, 536–543. doi:10.1016/j.jalz.2011.08.006

Sikkes, S. A., de Lange-de Klerk, E. S., Pijnenburg, Y. A., Scheltens, P., and Uitdehaag, B. M. (2009). A systematic review of instrumental activities of daily living scales in dementia: room for improvement. [Research Support, Non-U.S. Gov't Review]. *J. Neurol. Neurosurg. Psychiatr.* 80, 7–12. doi:10.1136/jnnp.2008.155838

Snyder, P. J., Kahle-Wrobleski, K., Brannan, S., Miller, D. S., Schindler, R. J., DeSanti, S., et al. (2014). Assessing cognition and function in Alzheimer's disease clinical trials: do we have the right tools? *Alzheimers Dement.* 10, 853–860. doi:10.1016/j.jalz.2014.07.158

Stern, Y., Hesdorffer, D., Sano, M., and Mayeux, R. (1990). Measurement and prediction of functional capacity in Alzheimer's disease. *Neurology* 40, 8–14.

Stucki, R. A., Urwyler, P., Rampa, L., Muri, R., Mosimann, U. P., and Nef, T. (2014). A web-based non-intrusive ambient system to measure and classify activities of daily living. *J. Med. Internet Res.* 16, e175. doi:10.2196/jmir.3465

Tombaugh, T. N. (2004). Trail making test A and B: normative data stratified by age and education. *Arch. Clin. Neuropsychol.* 19, 203–214. doi:10.1016/S0887-6177(03)00039-8

Verghese, J., Wang, C., Lipton, R. B., Holtzer, R., and Xue, X. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *J. Neurol. Neurosurg. Psychiatr.* 78, 929–935. doi:10.1136/jnnp.2006.106914

Vestal, L., Smith-Olinde, L., Hicks, G., Hutton, T., and Hart, J. Jr. (2006). Efficacy of language assessment in Alzheimer's disease: comparing in-person examination and telemedicine. *Clin. Interv. Aging* 1, 467–471. doi:10.2147/ciia.2006.1.4.467

Wadley, V. G., Okonkwo, O., Crowe, M., and Ross-Meadows, L. A. (2008). Mild cognitive impairment and everyday function: evidence of reduced speed in performing instrumental activities of daily living. *Am. J. Geriatr. Psychiatry* 16, 416–424. doi:10.1097/JGP.0b013e31816b7303

Yakhia, M., Konig, A., van der Flier, W. M., Friedman, L., Robert, P. H., and David, R. (2014). Actigraphic motor activity in mild cognitive impairment patients carrying out short functional activity tasks: comparison between mild cognitive impairment with and without depressive symptoms. *J. Alzheimers Dis.* 40, 869–875. doi:10.3233/JAD-131691

Zola, S. M., Manzanares, C. M., Clopton, P., Lah, J. J., and Levey, A. I. (2013). A behavioral task predicts conversion to mild cognitive impairment and Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen.* 28, 179–184. doi:10.1177/1533317512470484

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 23 June 2015
doi: 10.3389/fnagi.2015.00118

The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study

*Trevor J. Crawford**, *Alex Devereaux*, *Steve Higham* and *Claire Kelly*

Dementia Research and Eye Tracking Lab, Department of Psychology, Centre of Aging Research, Centre for Learning and Human Development, Lancaster University, Lancaster, UK

Introduction: Eye tracking provides a convenient and promising biological marker of cognitive impairment in patients with neurodegenerative disease. Here we report a longitudinal study of saccadic eye movements in a sample of patients with Alzheimer's disease and elderly control participants who were assessed at the start of the study and followed up 12-months later.

Methods: Eye movements were measured in the standard gap and overlap paradigms, to examine the longitudinal trends in the ability to disengage attention from a visual target.

Results: Overall patients with Alzheimer's disease had slower reaction times than the control group. However, after 12-months, both groups showed faster and comparable reductions in reaction times to the gap, compared to the overlap stimulus. Interestingly, there was a general improvement for both groups with more accurately directed saccades and speeding of reaction times after 12-months.

Conclusions: These findings point to the value of longer-term studies and follow-up assessment to ascertain the effects of dementia on oculomotor control.

Keywords: dementia, eye-tracking, Alzheimer's disease, attention, cognition

OPEN ACCESS

Edited by:
Philippe Robert, University of Nice Sophia Antipolis, France

Reviewed by:
Valeria Manera, University of Nice Sophia Antipolis, France
Renaud David, Nice Memory Clinic, France

Correspondence:
Trevor J. Crawford, Department of Psychology, Centre of Aging Research, Centre for Learning and Human Development, Lancaster University, Fylde College, Lancaster, Lancashire LA1 4YF, UK
t.crawford@lancaster.ac.uk

Received: *16 January 2015*
Accepted: *02 June 2015*
Published: *23 June 2015*

Citation:
Crawford TJ, Devereaux A, Higham S and Kelly C (2015) The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study. Front. Aging Neurosci. 7:118. doi: 10.3389/fnagi.2015.00118

Introduction

Alzheimer's Disease (AD) is a major cognitive disorder of older adults that blights the lives of millions of people and their families across the globe (Stokes, 2013). Many sufferers are undiagnosed due to the lengthy clinical and psychometric procedures that are often used by local and national health services. Eye tracking provides a convenient and promising biological marker of cognitive impairment in patients with neurodegenerative disease (Crawford et al., 2013), and is likely to enhance the current procedures for early diagnosis and long-term monitoring of disease progression. Comprehensive studies on the profile of eye movement control in dementia are essential in order to fully exploit its full potential.

Clinicians and researchers have tended to focus on the problems in memory retrieval, which may occur relatively late in the evolution of AD. However, there is increasing evidence that there are subtle impairments in visual attention and other cognitive domains that occur early in the course of the disease. Several studies have reported a dysfunction in the disengagement of attention in AD (Della Sala et al., 1992; Parasuraman et al., 1992; Parasuraman and Haxby, 1993; Scinto et al., 1994; Perry and Hodges, 1999; Baddeley et al., 2001; Solfrizzi et al., 2002; Tales et al., 2002) which appears to coincide with the progressive decline in working memory and executive function

(Awh and Jonides, 1998; Parasuraman and Greenwood, 1998). Parasuraman et al. (1992) reported that AD patients, of mild severity, displayed an attention-shifting or disengagement deficit in a letter-discrimination task, in a similar way to patients with hemi-neglect that was caused by a lesion in the parietal lobe (Posner et al., 1984). In AD, the speeding-up of response times to a "valid" cue (i.e., a cue that signaled the correct location of the target), did not differ from healthy controls. In contrast, the slowing-down of response times following an "invalid" cue (i.e., a cue that signaled an incorrect location of the target), was abnormally high, compared to healthy controls. This implied that attention to spatial locations was preserved in early AD, whereas the ability to disengage (or "unplug") attention was impaired. Using PET Parasuraman et al. (1992) also reported that the degrees of disengagement deficit was correlated with the level of hypo-metabolism in the superior parietal lobe.

The process of disengagement has also been widely investigated using the gap and overlap saccadic paradigms (Saslow, 1967; Fischer and Boch, 1983; Kalesnykas and Hallett, 1987; Braun and Breitmeyer, 1988; Fischer and Weber, 1993). These paradigms have also been explored in newborns (Farroni et al., 1999) and non-human species (Kano et al., 2011). In a traditional "Gap" paradigm (**Figure 1**) the onset of the peripheral target is preceded by a short period (usually 200 ms), when the current fixation point is switched-off, leaving a brief "gap" between the offset of the fixation point and the onset of the target for the saccade. In the "overlap" paradigm, the fixation point remains on for a period of time, when the peripheral target is presented. The gap paradigm facilitates the disengagement of attention from the fixation point and therefore yields faster saccadic response times, since there is no other visual stimulus to compete with the target. The overlap slows the disengagement of attention since the persistence of the fixation point continues to capture attention whilst the target is presented (see **Figure 2**, based on Crawford et al., 2013). The ability to "unplug" visual attention can be readily estimated by measuring the time it takes for the eye to begin a saccadic eye movement towards the gap stimulus, in relation to the overlap paradigm. According to one widely supported scheme (Findlay and Walker, 1999), the gap manipulation helps to resolve the competition that occurs between two mutually exclusive activities: the eye fixation and saccade initiation systems. One important physiological arena for this competition is the superior colliculus (Munoz and Wurtz, 1993a,b; Dorris and Munoz, 1995; Dorris et al., 1997). Top-down saccadic eye movement signals are also controlled by various cortical areas including the parietal and frontal cortex (Dias and Bruce, 1994; Hanes and Schall, 1996; Müri et al., 1998; Munoz and Everling, 2004).

Yang et al. (2013) found that the "gap" effect was increased in patients with mild cognitive impairment and mild to moderate Alzheimer's disease, suggesting a potential biological marker for AD. This implies that they have difficulty in unplugging, or transferring attention away from events. However, no study has yet examined the longitudinal effects of the disease on eye movements in these paradigms. Therefore, we examined the hypothesis that the magnitude of the "gap" effect will increase over time, due to a deterioration in the ability to disengage attention. An alternative outcome is that the magnitude of the "gap" effect will not increase, but that there will be a proportional change in saccade latency for both the gap and overlap paradigms. This would result in a "gap" effect that remains relatively stable across the disease, showing that this effect changes with age, rather than the disease (Crawford et al., 2013).

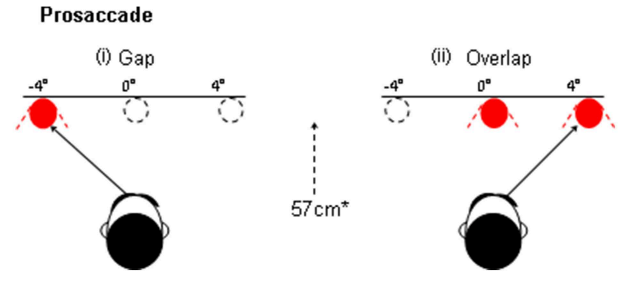

FIGURE 1 | An illustration of the "gap" and overlap paradigms. In the gap task the fixation point is withdrawn prior to the presentation of the peripheral target. In the Overlap paradigm the fixation remains on at the onset of the target.

Materials and Methods

Participants

Elderly control participants were volunteers from the local community ($N = 25$; age range = 62–80 years; mean = 70.6; $SD = 4.9$; male $n = 8$; female $n = 17$; see **Table 1**). The AD group comprised mild-to-moderate patients with Alzheimer's disease recruited from the Dementia Research Project at Lytham Hospital Memory Clinic, United Kingdom. All patients fulfilled the criteria for probable Alzheimer's disease according to the American Psychiatric Association's DSM IV (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) ($N = 11$; age range = 71–88; mean = 78; $SD = 4.94$; male $n = 6$; female $n = 5$, see **Table 2**). Three patients from the original sample with a diagnosis of vascular or mixed dementia were not included in these analyses. All patients underwent a detailed clinical history, physical/neurological examination and routine investigations: hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, blood glucose, thyroid function tests, serum vitamin B12, and folate, serology for syphilis and urinalysis. Cognitive impairment was assessed with the Standardized Mini Mental State Examination (SMMSE) (Folstein et al., 1975; Molloy et al., 1991) and the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (European version; EADAS-cog); (Rosen et al., 1984; Dahalke et al., 1992). Dementia severity was conducted at baseline using the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982). All participants underwent a detailed neuropsychological assessment (see Crawford et al., 2013), [National Adult Reading Test (NART) (Nelson, 1982), Verbal Fluency (Storandt et al., 1984), Trail Making Form A and B (Reitan, 1958), Digit Span from Wechsler Adult Intelligence Scale III (Wechsler, 1997a), Spatial Span from Wechsler Memory Scale III (Wechsler, 1997b) and the Gibson

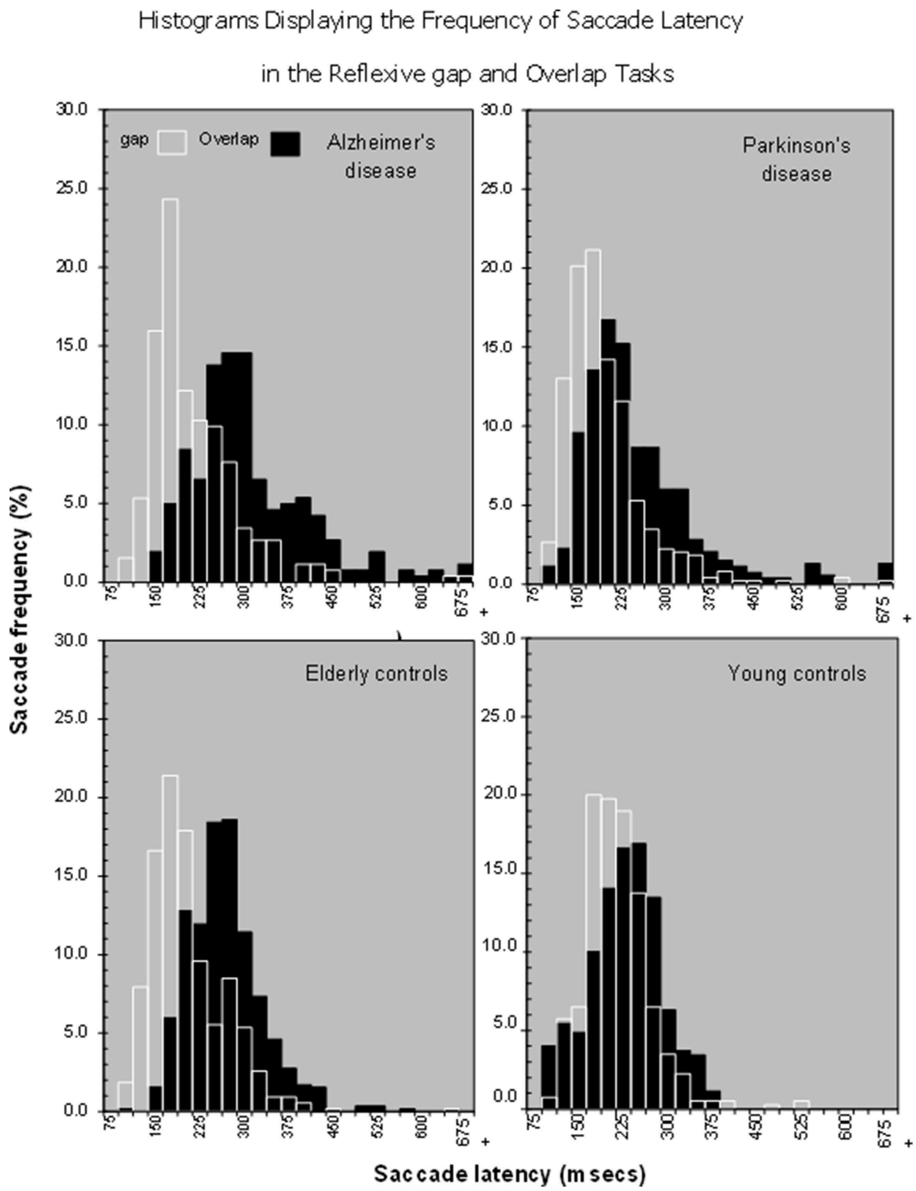

FIGURE 2 | Histograms showing that there is a shift in the distribution of saccade latencies in the overlap stimuli in comparison to the gap stimuli in various patient groups, Alzheimer's Disease, Parkinson's disease, Older and young controls.

Spiral Maze (Pattie and Gilleard, 1987)]. All participants were right-handed, with normal or corrected Snellen chart visual acuity. No participant demonstrated visual neglect on the line bisection task (Schenkenberg et al., 1980). Written informed consent was obtained from all participants after a detailed description of the study, which was approved by the Blackpool, Wyre, and Fylde Local Research Ethics Committee.

Assessment of Saccadic Eye Movements

Saccadic eye movements were recorded using an infra-red scleral reflection eye-tracker "ExpressEye" (Optom, Freiburg, Germany). The eyes were recorded monocularly with a temporal resolution of 1 ms and spatial resolution of 0.1°. The system is linear over a 15° visual field. The stimulus display presented a central fixation point within an unfilled 0.75 × 0.75° empty square marker; the target was a red 0.4° spot, which was projected left and right horizontally. The device projected these stimuli from a head-mounted laser onto a white tangential screen at 57 cm. The laser output was 0.2 mW, with a wavelength of 635 nm with a luminance of 66.37 cd/m^2. The three head-mounted lasers provided a simple way to compensate for lateral head motion.

Gap prosaccade paradigm

Each trial commenced with the central fixation point (see **Figure 1**) that was presented within a central square marker

TABLE 1 | Demographics and cognitive assessment at baseline and at the 12-month (12) follow-up in the control group.

Controls	Age	MMSE (12)	EADAS (12)	Years ED
1	65	30(29)	5(4)	12
2	67	29(28)	11(5)	14
3	65	30(29)	4(6)	10
4	65	27(29)	9(6)	10
5	62	29(30)	5(2)	13
6	78	30(29)	11(8)	15
7	71	30(29)	5(6)	12
8	65	29(29)	8(2)	13
9	68	30(30)	9(5)	20
10	76	28(30)	7(8)	12
11	63	30(30)	3(4)	12
12	73	30(30)	9(5)	12
13	69	28(29)	11(5)	17
14	68	30(30)	7(4)	12
15	76	30(30)	9(6)	12
16	71	29(30)	8(0)	12
17	71	30(27)	10(9)	9
18	74	29(29)	7(5)	14
19	76	30(28)	8(11)	11
20	77	27(28)	8(7)	9
21	68	30(30)	6(4)	17
22	71	28(30)	12(8)	10
23	80	30(27)	10(7)	10
24	73	30(30)	4(6)	12
25	73	30(30)	7(4)	9
Mean	70.60	29.3(29.4)	7.7((5)	12.4
SD	4.97	0.99(0.6)	2.5(1.8)	2.7

TABLE 2 | Demographics and cognitive assessment at baseline and at the 12-month (12) follow-up in the Alzheimer group.

Dementia	Age	MMSE(12)	EADAS(12)	Years ED
1	71	27(26)	11(10)	12
2	88	23(22)	22(23)	9
3	77	27(27)	17(21)	11
4	76	21(20)	21(25)	12
5	80	24(25)	23(19)	9
6	78	20(27)	16(19)	9
7	75	23(13)	26(28)	10
8	84	16(9)	39(44)	14
9	80	27(30)	12(12)	10
10	72	23(21)	22(18)	14
11	77	29(25)	10(11)	12
Mean	78.0	23.64(22.27)	19.91(20.09)	11.09
SD	4.94	3.78(6.34)	8.28(10.12)	1.87

for 1000 ms. The central square remained visible throughout all of the trials and provided a useful reference point for the stabilization of the head. The fixation point was then removed for a period of 200 ms (i.e., "gap") before the saccade target was presented at ±4° (randomized). The target was switched off for an interval of 1200 ms when only the central square was visible. The central fixation point was then presented at the start of the next trial.

Overlap prosaccade paradigm

An identical stimulus was used in the overlap display, where the procedure was similar to the gap display apart from the timing of the removal of the central fixation point. Here, the fixation point "overlapped" for 200 ms with the presentation of the pro-saccade target, whereas the fixation point was removed before the target was presented in the gap task described previously.

GO/NO–GO paradigm

At the start of each trial a central fixation light was illuminated for 1000 ms. This central light was then switched off, followed by a 200 ms "GAP." At the termination of the "GAP" period a target was presented at ±4° for 700 ms, while the central fixation point remained off. The next trial commenced after an interval of 1200 ms during which only the central square was presented. Three versions of this paradigm examined the ability to maintain central attention and to ignore a target that was presented in the left, right or both visual fields. (A) NO-GO: Participants were instructed to ignore the target light and to maintain fixation at the center of the screen for the duration of the trial. (B) GO-RIGHT/NO-GO-LEFT: Participants were instructed to "look" at the targets that were presented in the right visual field, but to suppress eye movements to all targets in the left field. (C) GO-LEFT/NO-GO-RIGHT: Participants were required to "look" at the targets that were presented in the left field but to suppress eye movements to all targets in the right field. Inhibitory control was assessed at the baseline assessment in a subset of patients and controls.

Measurement of Saccadic Parameters

The start and end of a saccade was initially detected at the point at which the eye velocity crossed 30°/s threshold. These measurements include: the amplitudes and reaction times of the primary saccade that was generated toward or away from the target, and proportion of correctly directed saccades toward the target. Tests for homogeneity of variance were conducted using IBM SPSS Statistics 21.

Results

Saccade Reaction Times

The present work investigated whether or not the magnitude of the reflexive "gap" effect changes longitudinally in patients with AD. AD were slower to generate a saccadic eye movement towards the target in comparison to the control group (mean = 226 ms, $SE = 4.97$); AD group {mean = 249 ms, $SE = 7.4$; [$F_{(1, 35)} = 6.43, p = 0.016$]}. There was also a significant effect of test session [$F_{(1, 35)} = 4.77, p = 0.036$] with a general reduction of mean saccadic reaction times (RTs) at the 12-month session (see **Figure 3**), but with no interaction with group [$F_{(1, 38)} = 0.739$, ns]. The size of the "gap" effect was measured as the

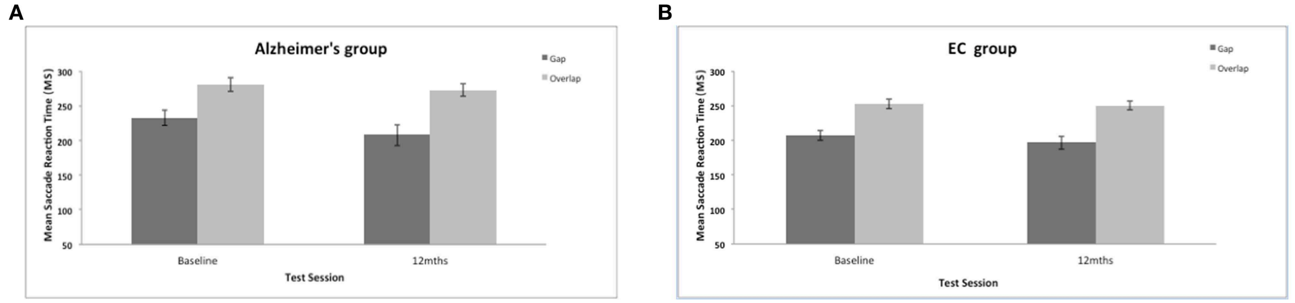

FIGURE 3 | (A,B) Figure shows the mean saccadic reaction times (in ms, with standard error bars) to the gap and overlap stimuli at baseline and 12-months for AD patients **(A)** and elderly controls **(B)**.

difference between the overlap and gap RTs. The "gap" effect was highly significant [$F_{(1, 35)} = 86.45$, $p = 0.001$]; overall both groups revealed slower reaction times in the overlap, compared to the gap task. Both groups benefited from the gap effect: At the baseline assessment the control group "gap" effect = 46 ms; whilst the "gap" effect for the AD patients = 48 ms; At 12-months the control group revealed a "gap" effect = 54 ms and the dementia patients showed a "gap" effect of 65 ms. There was no overall group difference in the magnitude of the "gap" effect [$F_{(1, 35)} = 0.37$, ns] and no change in the effect at 12-months [$F_{(1, 35)} = 2.7$, ns]. Clearly, the "gap" effect is relatively well preserved in patients with AD. Indeed, Yang et al. (2013) reported a large "gap" effect for AD patients (115 ms) and for the control group (88 ms). However, it is not clear whether the "gap" effect increases with age, disease progression or both (see Crawford et al., 2013).

Saccadic Amplitudes (Degrees)

There was a significant effect of the stimulus gap on saccadic amplitudes for both groups [$F_{(1, 34)} = 8.3$, $p = 0.007$]. Saccades were generally of larger amplitude and more accurate to the overlap stimulus (see **Figure 4**). There was no significant effect of group on the mean amplitude of the prosaccades [$F_{(1, 37)} = 1.008$, ns]; no effect of test session [$F_{(1, 37)} = 2.48$, ns], and no interaction between session and group status [$F_{(1, 34)} = 0.049$, ns]. In comparison to other eye movement features (see Crawford et al., 2005, 2013) the ability to modulate the amplitude of a saccade is clearly preserved well into the course of the disease.

Saccadic Direction (%correct)

Saccadic direction to the gap and overlap targets revealed a marginal trend of a group effect [$F_{(1, 35)} = 3.7$, $p = 0.062$]. **Figure 5** shows a high proportion of correctly directed saccades for the AD and control groups (overall mean = 86%, $SE = 2.1$; control mean = 91%, $SE = 1.44$). Patients did not have great difficulty aiming their eyes in the correct direction and were correct on most trials. There was a strong effect of test session [$F_{(1, 35)} = 18.5$, $p = 0.001$] with a general improvement in accuracy in both groups after 12-months. There was a strong effect of the stimulus gap [$F_{(1, 35)} = 20.72$, $p = 0.001$] for both patients and controls revealing more correctly directed eye movements towards the overlap target (**Figure 5**), but with no interaction with participant group or test session.

Z-score plots

From the perspective of clinical diagnosis it is important to supplement eye-tracking analyses that are based on group data with evidence from individual cases. Therefore, we examined the data for AD patients who were tested across the full range of oculomotor paradigms. Each saccadic parameter is expressed as a z-score ($z = \frac{(\bar{x} - x)}{SD}$) with reference to the equivalent mean score for the control group. **Figure 6** shows the chart of z-scores across the cognitive assessments, together with the eye-tracking z-scores. Unsurprisingly, AD patients revealed high z-scores for the EADAS Cog and MMSE cognitive assessments, which helped to inform the clinical diagnosis. Z-scores across the battery of neuropsychological measures were typically within ±1 standard deviation of the control group (0-score reference line). For the eye-tracking assessments the patients varied in their profile of z-scores across the saccadic features. ADs differed from the controls by 2 standard deviations or more for at least one of the oculomotor parameters. This implies that oculomotor assessment in AD will benefit from a comprehensive range of oculomotor tests with reference to a standardized z-score profile, as an alternative to the more common approach that employs limited measures from a specific oculomotor paradigm.

Cognitive Assessment (MMSE and EADAS); Years of Education and Age

A substantive level of cognitive impairment was revealed at the baseline assessment by the lower scores on the MMSE [$F_{(1, 35)} = 50.54$, $p < 0.01$] and the higher EADAS scores [$F_{(1, 35)} = 46.94$, $p < 0.01$] in the AD group. This cognitive impairment was also evident at the 12-month follow-up assessment [MMSE $F_{(1,35)} = 29.38$, $p < 0.01$; EADAS $F_{(1, 35)} = 47.83$, $p < 0.01$]. A strong correlation was revealed between the cognitive scores at baseline and at follow-up for the AD group (MMSE, $r = 0.698$, $p = 0.017$; EADAS Cog, $r = 0.942$, $p = 0.001$). At the 12-month follow-up the AD group revealed a decline in spatial memory [$t_{(10)} = 2.472$, $p = 0.03$] from the baseline assessment. There was no reliable change in the AD scores for MMSE [$t_{(10)} = 0.986$, ns], EADAS [$t_{(10)} = -0.666$, ns]. Similarly, NART errors, digit span, Trails A and B, verbal fluency, Gibson maze–all ns) all showed no

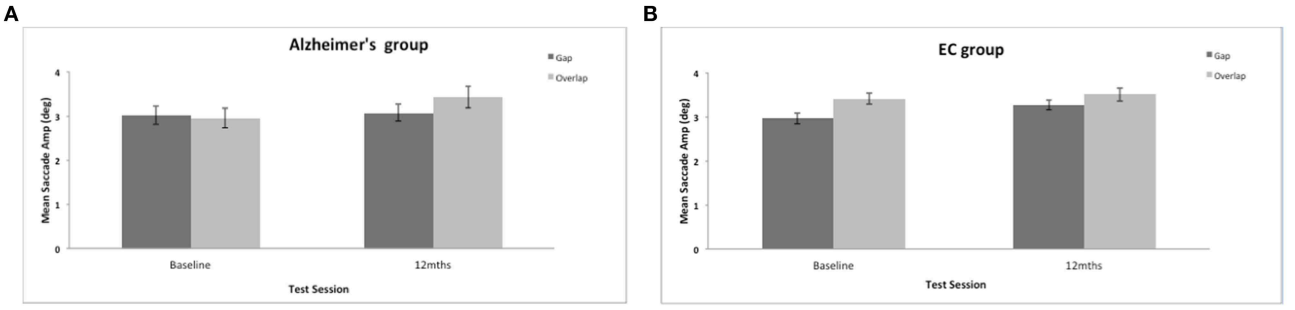

FIGURE 4 | (A,B) Figure shows the mean saccadic amplitudes (in degrees, with standard error bars) to the gap and overlap stimuli at baseline and 12-months for AD patients **(A)** and elderly controls **(B)**.

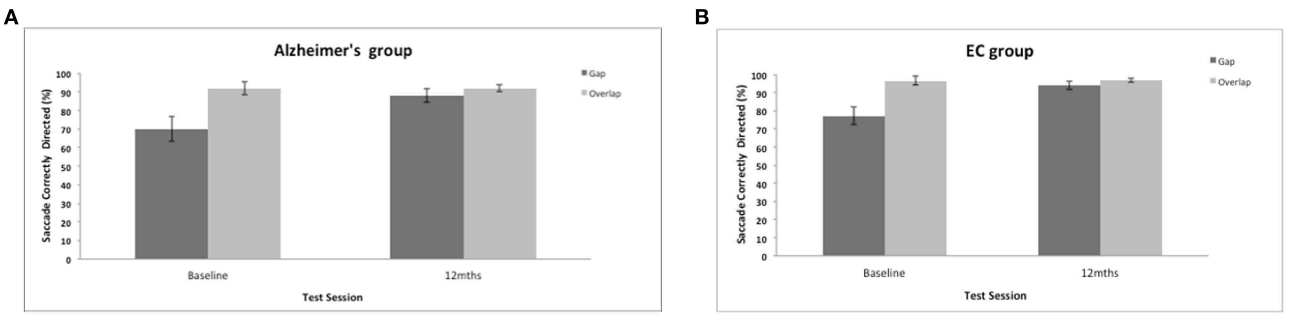

FIGURE 5 | (A,B) Figure shows the mean frequency of the correctly directed saccades (with standard error bars) to the gap and overlap stimuli at baseline and 12-months for AD patients **(A)** and elderly controls **(B)**.

change at the 12-month follow-up. Importantly, the groups were matched on years of education [$F_{(1,\ 35)} = 2.005$, ns]. The mean age of the control group (70.6 years), was lower than the AD group (78 years). However, there was no correlation of saccadic reaction times with age at baseline ($r = 0.119, p = 0.55$ ns) nor at the 12-month follow-up ($r = 0.134, p = 0.397$ ns). Thus, age did not predict saccadic reaction times within this cohort. To further confirm that neither age nor years of education were a predictor of performance, a further analysis of variance was conducted on a subgroup of AD patients and controls matched on mean age and years of education. The results confirmed clear effects of test session and saccade task (faster reaction times for the gap task for both groups).

Discussion

There have been relatively few longitudinal investigations of eye movements in dementia. To our knowledge there have been only two such studies (Hutton et al., 1984; Bylsma et al., 1995). Here we report a longitudinal study with assessments at baseline and a 12-month follow-up. Yang et al. (2013) reported a larger "gap" effect in patients with AD in comparison to the controls. These longitudinal data revealed that this robust "gap" effect in AD, was maintained at a 12-month follow-up. Crawford et al. (2013) reported that the "gap" effect was larger in older groups compared to younger participants, which suggests that the "gap" effect may provide a marker of aging, rather than neurodegenerative disease. Surprisingly, the AD reaction times were selectively decreased in the gap task over the course of the assessments. It is remarkable that both groups revealed a similar change in reaction times and saccade direction at the 12-month follow-up session. Why could this be? A number of non-specific factors are likely to have contributed to the overall improvement. Saccadic eye movements toward a target (i.e., prosaccades) are a low, level visuomotor behavior that we produce hundreds of times every day. It should not be surprising that this everyday activity can improve in a laboratory setting. Initial test anxiety, is likely to be reduced with increased task familiarity and less distractibility in the research environment. What is intriguing is that these factors may also be relevant to people with mild dementia. Although speculative, it may be possible that eye-tracking paradigms can tap into a reserved capacity to respond to implicit cues that has been previously reported in patients with dementia (Gabrieli et al., 1993; Verfaellie et al., 2000; Ballesteros and Reales, 2004; Debra and Fleischman, 2007). Future work will explore this further to determine whether implicit learning is corroborated with converging evidence from additional sources.

These findings revealed that the prosaccade tasks were able to discriminate AD patients from healthy controls at baseline assessment. Z-score eye-tracking charts revealed large standardized deviations at the level of individuals with reference

(Awh and Jonides, 1998; Parasuraman and Greenwood, 1998). Parasuraman et al. (1992) reported that AD patients, of mild severity, displayed an attention-shifting or disengagement deficit in a letter-discrimination task, in a similar way to patients with hemi-neglect that was caused by a lesion in the parietal lobe (Posner et al., 1984). In AD, the speeding-up of response times to a "valid" cue (i.e., a cue that signaled the correct location of the target), did not differ from healthy controls. In contrast, the slowing-down of response times following an "invalid" cue (i.e., a cue that signaled an incorrect location of the target), was abnormally high, compared to healthy controls. This implied that attention to spatial locations was preserved in early AD, whereas the ability to disengage (or "unplug") attention was impaired. Using PET Parasuraman et al. (1992) also reported that the degrees of disengagement deficit was correlated with the level of hypo-metabolism in the superior parietal lobe.

The process of disengagement has also been widely investigated using the gap and overlap saccadic paradigms (Saslow, 1967; Fischer and Boch, 1983; Kalesnykas and Hallett, 1987; Braun and Breitmeyer, 1988; Fischer and Weber, 1993). These paradigms have also been explored in newborns (Farroni et al., 1999) and non-human species (Kano et al., 2011). In a traditional "Gap" paradigm (**Figure 1**) the onset of the peripheral target is preceded by a short period (usually 200 ms), when the current fixation point is switched-off, leaving a brief "gap" between the offset of the fixation point and the onset of the target for the saccade. In the "overlap" paradigm, the fixation point remains on for a period of time, when the peripheral target is presented. The gap paradigm facilitates the disengagement of attention from the fixation point and therefore yields faster saccadic response times, since there is no other visual stimulus to compete with the target. The overlap slows the disengagement of attention since the persistence of the fixation point continues to capture attention whilst the target is presented (see **Figure 2**, based on Crawford et al., 2013). The ability to "unplug" visual attention can be readily estimated by measuring the time it takes for the eye to begin a saccadic eye movement towards the gap stimulus, in relation to the overlap paradigm. According to one widely supported scheme (Findlay and Walker, 1999), the gap manipulation helps to resolve the competition that occurs between two mutually exclusive activities: the eye fixation and saccade initiation systems. One important physiological arena for this competition is the superior colliculus (Munoz and Wurtz, 1993a,b; Dorris and Munoz, 1995; Dorris et al., 1997). Top-down saccadic eye movement signals are also controlled by various cortical areas including the parietal and frontal cortex (Dias and Bruce, 1994; Hanes and Schall, 1996; Müri et al., 1998; Munoz and Everling, 2004).

Yang et al. (2013) found that the "gap" effect was increased in patients with mild cognitive impairment and mild to moderate Alzheimer's disease, suggesting a potential biological marker for AD. This implies that they have difficulty in unplugging, or transferring attention away from events. However, no study has yet examined the longitudinal effects of the disease on eye movements in these paradigms. Therefore, we examined the hypothesis that the magnitude of the "gap" effect will increase over time, due to a deterioration in the ability to disengage attention. An alternative outcome is that the magnitude of the "gap" effect will not increase, but that there will be a proportional change in saccade latency for both the gap and overlap paradigms. This would result in a "gap" effect that remains relatively stable across the disease, showing that this effect changes with age, rather than the disease (Crawford et al., 2013).

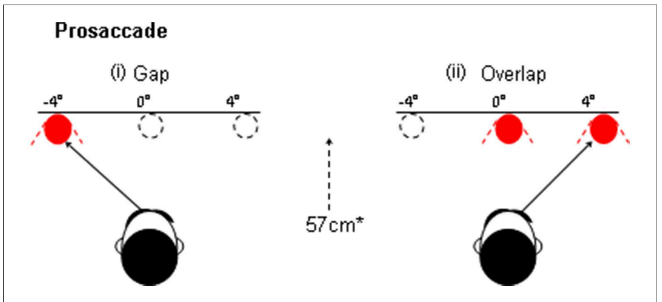

FIGURE 1 | An illustration of the "gap" and overlap paradigms. In the gap task the fixation point is withdrawn prior to the presentation of the peripheral target. In the Overlap paradigm the fixation remains on at the onset of the target.

Materials and Methods

Participants

Elderly control participants were volunteers from the local community ($N = 25$; age range = 62–80 years; mean = 70.6; $SD = 4.9$; male $n = 8$; female $n = 17$; see **Table 1**). The AD group comprised mild-to-moderate patients with Alzheimer's disease recruited from the Dementia Research Project at Lytham Hospital Memory Clinic, United Kingdom. All patients fulfilled the criteria for probable Alzheimer's disease according to the American Psychiatric Association's DSM IV (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) ($N = 11$; age range = 71–88; mean = 78; $SD = 4.94$; male $n = 6$; female $n = 5$, see **Table 2**). Three patients from the original sample with a diagnosis of vascular or mixed dementia were not included in these analyses. All patients underwent a detailed clinical history, physical/neurological examination and routine investigations: hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, blood glucose, thyroid function tests, serum vitamin B12, and folate, serology for syphilis and urinalysis. Cognitive impairment was assessed with the Standardized Mini Mental State Examination (SMMSE) (Folstein et al., 1975; Molloy et al., 1991) and the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (European version; EADAS-cog); (Rosen et al., 1984; Dahalke et al., 1992). Dementia severity was conducted at baseline using the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982). All participants underwent a detailed neuropsychological assessment (see Crawford et al., 2013), [National Adult Reading Test (NART) (Nelson, 1982), Verbal Fluency (Storandt et al., 1984), Trail Making Form A and B (Reitan, 1958), Digit Span from Wechsler Adult Intelligence Scale III (Wechsler, 1997a), Spatial Span from Wechsler Memory Scale III (Wechsler, 1997b) and the Gibson

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 23 June 2015
doi: 10.3389/fnagi.2015.00118

The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study

Trevor J. Crawford, Alex Devereaux, Steve Higham and Claire Kelly*

Dementia Research and Eye Tracking Lab, Department of Psychology, Centre of Aging Research, Centre for Learning and Human Development, Lancaster University, Lancaster, UK

Introduction: Eye tracking provides a convenient and promising biological marker of cognitive impairment in patients with neurodegenerative disease. Here we report a longitudinal study of saccadic eye movements in a sample of patients with Alzheimer's disease and elderly control participants who were assessed at the start of the study and followed up 12-months later.

Methods: Eye movements were measured in the standard gap and overlap paradigms, to examine the longitudinal trends in the ability to disengage attention from a visual target.

Results: Overall patients with Alzheimer's disease had slower reaction times than the control group. However, after 12-months, both groups showed faster and comparable reductions in reaction times to the gap, compared to the overlap stimulus. Interestingly, there was a general improvement for both groups with more accurately directed saccades and speeding of reaction times after 12-months.

Conclusions: These findings point to the value of longer-term studies and follow-up assessment to ascertain the effects of dementia on oculomotor control.

Keywords: dementia, eye-tracking, Alzheimer's disease, attention, cognition

Edited by:
Philippe Robert, University of Nice Sophia Antipolis, France

Reviewed by:
Valeria Manera, University of Nice Sophia Antipolis, France
Renaud David, Nice Memory Clinic, France

****Correspondence:***
Trevor J. Crawford, Department of Psychology, Centre of Aging Research, Centre for Learning and Human Development, Lancaster University, Fylde College, Lancaster, Lancashire LA1 4YF, UK
t.crawford@lancaster.ac.uk

Received: *16 January 2015*
Accepted: *02 June 2015*
Published: *23 June 2015*

Citation:
Crawford TJ, Devereaux A, Higham S and Kelly C (2015) The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study. Front. Aging Neurosci. 7:118. doi: 10.3389/fnagi.2015.00118

Introduction

Alzheimer's Disease (AD) is a major cognitive disorder of older adults that blights the lives of millions of people and their families across the globe (Stokes, 2013). Many sufferers are undiagnosed due to the lengthy clinical and psychometric procedures that are often used by local and national health services. Eye tracking provides a convenient and promising biological marker of cognitive impairment in patients with neurodegenerative disease (Crawford et al., 2013), and is likely to enhance the current procedures for early diagnosis and long-term monitoring of disease progression. Comprehensive studies on the profile of eye movement control in dementia are essential in order to fully exploit its full potential.

Clinicians and researchers have tended to focus on the problems in memory retrieval, which may occur relatively late in the evolution of AD. However, there is increasing evidence that there are subtle impairments in visual attention and other cognitive domains that occur early in the course of the disease. Several studies have reported a dysfunction in the disengagement of attention in AD (Della Sala et al., 1992; Parasuraman et al., 1992; Parasuraman and Haxby, 1993; Scinto et al., 1994; Perry and Hodges, 1999; Baddeley et al., 2001; Solfrizzi et al., 2002; Tales et al., 2002) which appears to coincide with the progressive decline in working memory and executive function

References

Abel, L. A., Unverzagt, F., and Yee, R. D. (2002). Effects of stimulus predictability and interstimulus gap on saccades in Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 13, 235–243. doi: 10.1159/000057702

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edn*. Washington, DC: American Psychiatric Association.

Awh, E., and Jonides, J. (1998). "Spatial Working Memory and Spatial Selective Attention," in *The Attentive Brain*, ed R. Parasuraman (Cambridge, MA: MIT Press), 353–380.

Baddeley, A., Baddeley, H. A., Bucks, R. S., and Wilcock, G. K. (2001). Attentional control in Alzheimer's disease. *Brain* 124, 1492–1508. doi: 10.1093/brain/124.8.1492

Ballesteros, S., and Reales, J. M. (2004). Intact haptic priming in normal aging and Alzheimer's disease: evidence for dissociable memory systems. *Neuropsychologia* 42, 1063–1070. doi: 10.1016/j.neuropsychologia.2003.12.008

Braun, D., and Breitmeyer, B. G. (1988). Relationship between directed visual attention and saccadic reaction times. *Exp. Brain Res*. 73, 546–552. doi: 10.1007/BF00406613

Broerse, A., Crawford, T. J., and Boer, J. A. (2001). Parsing of cognition in Schizophrenia using saccadic eye movement paradigms: a selective overview. *Neuropsychologia* 39, 742–756. doi: 10.1016/S0028-3932(00)00155-X

Bylsma, F. W., Rasmusson, D. X., Rebok, G. W., Keyl, P. M., Tune, L., and Brandt, J. (1995). Changes in visual fixation and saccadic eye movements in Alzheimer's disease. *Int. J. Psychophysiol.* 19, 33–40. doi: 10.1016/0167-8760(94)00060-R

Crawford, T. J., Higham, S., Mayes, J., Shaunak, S., and Lekwuwa, G. (2013). The role of working memory and attentional engagement in inhibitory control: effects of aging and Alzheimer's disease. *Age* 35, 1637–1650. doi: 10.1007/s11357-012-9466-y

Crawford, T. J., Higham, S., Renvoize, T., Patel, J., Dale, M., Suriya, A., et al. (2005). Inhibitory control of saccadic eye movements and cognitive impairment in Alzheimer's disease. *Biol. Psychiatry* 57, 1052–1060. doi: 10.1016/j.biopsych.2005.01.017

Csibra, G., Johnson, M. H., and Tucker, L. A. (1997). Attention and oculomotor control: a high-density ERP study of the gap effect. *Neuropsychologia* 35, 855–865. doi: 10.1016/S0028-3932(97)00016-X

Currie, J., Ramsden, B., McArther, C., and Maruff, P. (1991). Validation of a clinical antisaccade eye movement test in the assessment of dementia. *Arch. Neurol.* 48, 644–648. doi: 10.1001/archneur.1991.00530180102024

Dahalke, F., DeBerdt, W., Duka, T., Eich, F. X., Fischer, H. J., Hentschel, B., et al. (1992). *Manual for the European Version of the Alzheimer's Disease Assessment Scale (Euro-ADAS).* Berlin: Clinical Research Working Group from the Pharmaceutical Industry on Dementia.

Debra, A., and Fleischman, D. A. (2007). Repetition priming in aging and Alzheimer's Disease: an integrative review and future directions. *Cortex* 43, 889–897. doi: 10.1016/S0010-9452(08)70688-9

Della Sala, S., Laiacona, M., Spinnler, H., and Ubezio, C. A. (1992). A Cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease. *Psychol. Med.* 22, 885–901. doi: 10.1017/S0033291700038460

Dias, E. C., and Bruce, C. J. (1994). Physiological correlate of fixation disengagement in the primate's frontal eye field. *J. Neurophysiol*. 72, 2532–2537.

Dorris, M. C., and Munoz, D. P. (1995). A neural correlate for the 'gap' effect on saccadic reaction times in monkey. *J. Neurophysiol.* 73, 2558–2562.

Dorris, M. C., Pare, M., and Munoz, D. P. (1997). Neuronal activity in monkey superior colliculus related to the initiation of saccadic eye movements. *J. Neurosci.* 17, 8566–8579.

Farroni, T., Simion, F., Umilt, C., and Barba, B. D. (1999). The 'gap' effect in newborns. *Dev. Sci.* 2, 174–186. doi: 10.1111/1467-7687.00066

Findlay, J. M., and Walker, R. (1999). A model of saccade generation based on parallel processing and competitive inhibition. *Behav. Brain Sci.* 22, 661–674. doi: 10.1017/s0140525x99002150

Fischer, B., and Boch, R. (1983). Saccadic eye movements after extremely short reaction times in the monkey. *Brain Res.* 260, 21–26. doi: 10.1016/0006-8993(83)90760-6

Fischer, B., and Weber, H. (1993). Express saccades and visual attention. *Behav. Brain Sci.* 16, 553–567. doi: 10.1017/S0140525X00031575

Folstein, M., Folstein, S., and McHugh, P. (1975). Mini-mental state examination. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Gabrieli, J. D. E., Corkin, S., Mickel, S. F., and Growdon, J. H. (1993). Intact acquisition and long-term retention of mirror-tracing skill in Alzheimer's disease and in global amnesia. *Behav. Neurosci.* 107, 899–910. doi: 10.1037/0735-7044.107.6.899

Garbutt, S., Matlin, A., Hellmuth, J., Schenk, A. K., Johnson, J. K., Rosen, H., et al. (2008). Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. *Brain* 131, 1268–1281 doi: 10.1093/brain/awn047

Hanes, D. P., and Schall, J. D. (1996). Neural control of voluntary movement initiation. *Science* 274, 427–430. doi: 10.1126/science.274.5286.427

Hughes, C., Berg, L., Danziger, W., Coben, L., and Martin, R. (1982). A new clinical scale for the staging of dementia. *Br. J. Psychiatry* 140, 566–572. doi: 10.1192/bjp.140.6.566

Hutton, J. T., Nagel, J. A., and Loewenson, R. B. (1984). Eye tracking dysfunction in Alzheimer-type dementia. *Neurology* 34, 99–102. doi: 10.1212/WNL.34.1.99

Kalesnykas, R. P., and Hallett, P. E. (1987). The differentiation of visually guided and anticipatory saccades in gap and overlap paradigms. *Exp. Brain Res*. 68, 115–121. doi: 10.1007/bf00255238

Kano, F., Hirata, S., Call, J., and Tomonaga, M. (2011). The visual strategy specific to humans among hominids: a study using the gap–overlap paradigm. *Vision Res*. 51, 2348–2355. doi: 10.1016/j.visres.2011.09.006

Kaufman, L. D., Pratt, J., Levine, B., and Black, S. E. (2010). Antisaccades: a probe into the dorsolateral prefrontal cortex in Alzheimer's disease. A critical review. *J. Alzheimers Dis.* 19, 781–793. doi: 10.3233/JAD-2010-1275

Kaufman, L. D., Pratt, J., Levine, B., and Black, S. E. (2012). Executive deficits detected in mild Alzheimer's disease using the antisaccade task. *Brain Behav.* 2, 15–21 doi: 10.1002/brb3.28

Kawakubu, Y., Maekawa, H., Itoh, K., and Iwanami, A. (2002). The attentional disengagement processing reflected by ERPs and saccade reaction times during a gap task. *Int. Cong. Ser.* 1232, 91–95. doi: 10.1016/S0531-5131(01)00716-6

Molloy, D. W., Alemayehu, E., and Roberts, R. (1991). A standardized mini-mental state examination (SMMSE): its reliability compared to the traditional mini-mental state examination (MMSE). *Am. J. Psychiatry* 148, 102–105. doi: 10.1176/ajp.148.1.102

Munoz, D. P., and Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nat. Rev. Neurosci*. 5, 218–228. doi: 10.1038/nrn1345

Munoz, D. P., and Wurtz, R. H. (1993a). Fixation cells in monkey superior colliculus. I. Characteristics of cell discharge. *J. Neurophysiol.* 70, 559–575.

Munoz, D. P., and Wurtz, R. H. (1993b). Fixation cells in monkey superior colliculus.II. Reversible activation and deactivation. *J. Neurophysiol.* 70, 576–589.

Müri, R. M., Rivaud, S., Gaymard, B., Ploner, C. J., Vermersch, A. I., Hess, C. W., et al. (1998). Role of the prefrontal cortex in the control of express saccades. A transcranial magnetic stimulation study. *Neuropsychologia* 37, 199–206. doi: 10.1016/S0028-3932(98)00094-3

Nelson, H. E. (1982). *National Adult Reading Test (NART): Test Manual, 2nd Edn*. Windsor, ON: NFER-Nelson.

Parasuraman, R., and Greenwood, P. M. (1998). "Selective attention in aging and dementia," in *The Attentive Brain*, ed R. Parasuraman (Cambridge, MA: MIT Press), 461–487.

Parasuraman, R., Greenwood, P. M., Haxby, J. V., and Grady, C. L. (1992). Visuospatial attention in dementia of the Alzheimer type. *Brain* 115, 711–733. doi: 10.1093/brain/115.3.711

Parasuraman, R., and Haxby, J. V. (1993). Attention and brain function in Alzheimer's disease: a review. *Neuropsychology* 7, 242–272. doi: 10.1037/0894-4105.7.3.242

Pattie, A., and Gilleard, C. (1987). *Clifton Assessment Procedures for the Elderly (CAPE)*. Sevenoaks: Hodder and Stoughton Educational.

Perry, R. J., and Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's Disease; a critical review. *Brain* 122, 383–404. doi: 10.1093/brain/122.3.383

Pierrot-Deseilligny, C. (1991). Cortical control of saccades. *Neuroophthalmology* 11, 63–75. doi: 10.3109/01658109108997298

Pierrot-Deseilligny, C., Milea, D., and Müri, R. (2004). Eye movement control by the cerebral cortex. *Curr. Opin. Neurol.* 17, 17–25. doi: 10.1097/00019052-200402000-00005

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., and Agid, Y. (1991). Cortical control of memory-guided saccades in man. *Exp. Brain Res.* 83, 607–617. doi: 10.1007/bf00229839

Pierrot-Deseilligny, C., Rivaud, S., Penet, C., and Rigolet, M. H. (1987). Latencies of visually guided saccades in unilateral hemispheric cerebral lesions. *Ann. Neurol.* 21, 138–148. doi: 10.1002/ana.410210206

Posner, M. I., Walker, J. A., Friedrich, F. A., and Rafal, R. D. (1984). Effects of parietal injury covert orienting of attention. *J. Neurosci.* 4, 1863–1874.

Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Percept. Mot. Skills* 8, 271–276. doi: 10.2466/pms.1958.8.3.271

Rivaud, S., Müri, R. M., Gaymard, B., Vermersch, A. I., and Pierrot-Deseilligny, C. (1994). Eye movement disorders after frontal eye field lesions in humans. *Exp. Brain Res.* 102, 110–120. doi: 10.1007/BF00232443

Rosen, W. G., Mohs, R. C., and Davis, K. L. (1984). A new rating scale for Alzheimers disease. *Am. J. Psychiatry* 141, 1356–1364. doi: 10.1176/ajp.141.11.1356

Saslow, M. G. (1967). Effects of components of displacement-step stimuli upon latency for saccadic eye movement. *J. Opt. Soc. Am.* 57, 1024–1029. doi: 10.1364/JOSA.57.001024

Schenkenberg, T., Bradford, D. C., and Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology* 30, 509–517. doi: 10.1212/WNL.30.5.509

Scinto, L. F., Daffner, K. R., Castro, L., Weintraub, S., Vavrik, M., and Mesulam, M. M. (1994). Impairment of spatially directed attention in patients with probable Alzheimer's disease as measured by eye movements. *Arch. Neurol.* 51, 682–688. doi: 10.1001/archneur.1994.00540190062016

Shafiq-Antonacci, R., Maruff, P., Masters, C., and Currie, J. (2003). Spectrum of saccade system function in Alzheimer's disease. *Arch. Neurol.* 60, 1272–1278. doi: 10.1001/archneur.60.9.1272

Solfrizzi, V., Panza, F., Torres, F., Capurso, C., D'Intronio, A., Colaccio, A., et al. (2002). Selective attention skills in differentiating between Alzheimer's disease and normal aging. *J. Geriatr. Psychiatry Neurol.* 15, 99–109. doi: 10.1177/089198870201500209

Stokes, G. (2013). *And Still The Music Plays: Stories of People with Dementia*. London: Hawker Publications.

Storandt, M., Botwinick, J., Danziger, W. L., Berg, L., and Hughes, C. P. (1984). Psychometric differentiation of mild senile dementia of the Alzheimer type. *Arch. Neurol.* 41, 497–499. doi: 10.1001/archneur.1984.04050170043013

Tales, A., Muir, J. L., Bayer, A., and Snowden, R. J. (2002). Spatial shifts in visual attention in normal ageing and dementia of the Alzheimer type. *Neuropsychologia* 40, 2000–2012. doi: 10.1016/S0028-3932(02)00057-X

Verfaellie, M., Keane, M. M., and Johnson, G. (2000). Preserved priming in auditory perceptual identification in Alzheimer's disease. *Neuropsychologia* 38, 1581–1592. doi: 10.1016/S0028-3932(00)00073-7

Walker, R., and Findlay, J. M. (1996). Saccadic eye movement programming in unilateral neglect. *Neuropsychologia* 34, 493–508. doi: 10.1016/0028-3932(95)00156-5

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale, 3rd Edn*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale, 3rd Edn*. San Antonio, TX: The Psychological Corporation.

Yang, Q., Wang, T., Su, N., Xiao, S., and Kapoula, Z. (2013). Specific saccade deficits in patients with Alzheimer's disease at mild to moderate stage and in patients with amnestic mild cognitive impairment. *Age* 35, 1287–1298. doi: 10.1007/s11357-012-9420-z

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

MINI REVIEW
published: 20 April 2015
doi: 10.3389/fnagi.2015.00054

A critical review: coupling and synchronization analysis methods of EEG signal with mild cognitive impairment

*Dong Wen [1,2], Yanhong Zhou [3] and Xiaoli Li [4]**

[1] School of Information Science and Engineering, Yanshan University, Qinhuangdao, China, [2] The Key Laboratory for Computer Virtual Technology and System Integration of Hebei Province, Yanshan University, Qinhuangdao, China, [3] Institute of Mathematics and Information Technology, Hebei Normal University of Science and Technology, Qinhuangdao, China, [4] State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China

At present, the clinical diagnosis of mild cognitive impairment (MCI) patients becomes the important approach of evaluating early Alzheimer's disease. The methods of EEG signal coupling and synchronization act as a key role in evaluating and diagnosing MCI patients. Recently, these coupling and synchronization methods were used to analyze the EEG signals of MCI patients according to different angles, and many important discoveries have been achieved. However, considering that every method is single-faceted in solving problems, these methods have various deficiencies when analyzing EEG signals of MCI patients. This paper reviewed in detail the coupling and synchronization analysis methods, analyzed their advantages and disadvantages, and proposed a few research questions needed to solve in the future. Also, the principles and best performances of these methods were described. It is expected that the performance analysis of these methods can provide the theoretical basis for the method selection of analyzing EEG signals of MCI patients and the future research directions.

Keywords: coupling, synchronization, EEG, mild cognitive impairment, Alzheimer's disease

OPEN ACCESS

Edited by:
Philippe Robert, University of Nice Sophia-Antipolis, France

Reviewed by:
Archana Mukhopadhyay, University of Kansas, USA
Michel Benoit, Université de Nice Sophia-Antipolis, France

***Correspondence:**
Xiaoli Li, State Key Laboratory of Cognitive Neuroscience and Learning; and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, Beijing, China
xiaoli@bnu.edu.cn

Received: *28 January 2015*
Accepted: *30 March 2015*
Published: *20 April 2015*

Citation:
Wen D, Zhou Y and Li X (2015) A critical review: coupling and synchronization analysis methods of EEG signal with mild cognitive impairment. Front. Aging Neurosci. 7:54. doi: 10.3389/fnagi.2015.00054

Introduction

Mild cognitive impairment (MCI), which acts as the transitory stage between normal aging and Alzheimer's disease (AD), is often the main concern evaluating and diagnosing the early AD (Aarabi et al., 2008; Darvas et al., 2009; Knyazeva et al., 2010, 2013). As basic activity patterns between neurons or nerve clusters, coupling and synchronization become the important window through which people understand nervous system diseases including MCI and AD (Fell et al., 2001; Varela et al., 2001; Buzsáki and Draguhn, 2004). Relative to normal control (NC), the coupling and synchronization performance between different neurons or brain regions of MCI patients often show unusual behavior (Babiloni et al., 2006; Darvas et al., 2009; Vecchio and Babiloni, 2011; Knyazeva et al., 2013). EEG signals have the characteristic of coupling and synchronization, which make analyzing the abnormal state of MCI become possible from the angle of the EEG signals. The coupling pays close attention to the relationship between two EEG signals from different channels of single brain region or two brain regions, the synchronization more often appears in the relationship between two EEG signals from different brain regions or among multiple EEG signals from more brain regions (Fell et al., 2001; Womelsdorf et al., 2007).

Therefore, if we can calculate and analyze effectively the relationship of coupling and synchronization between different neurons or brain regions of MCI patients from EEG signal perspective, it will promote our understanding the predisposing mechanism of MCI and AD to a large extent. Many studies displayed the initial value of the coupling and synchronization analysis of EEG signals with application to evaluating MCI (Koenig et al., 2005; Babiloni et al., 2010; Dauwels et al., 2010b; Sweeney-Reed et al., 2012; Tóth et al., 2014). Therefore, the advantages and disadvantages of each coupling and synchronization method are the problems that at present we are in urgent need for understanding in-depth on diagnosis and evaluation of MCI. This paper reviewed in-depth, the various analysis methods of EEG signals of MCI patients from coupling and synchronization perspectives, and discussed the future research questions and trend.

The Research Situation of EEG Signal Analysis Methods Used for Mild Cognitive Impairment Patients

The Coupling Analysis Methods

Methods Description and Evaluation

At present, the coupling analysis has become the focus of most concern in studying biological systems (Rosenblum and Pikovsky, 2001). The coupling between two EEG signals from different brain regions or two different electrodes is the object of much researchers concern, including of EEG signal coupling of normal subjects (Mizuhara and Yamaguchi, 2007; Cantero et al., 2009; Darvas et al., 2009) and subjects with diseases (Uhlhaas and Singer, 2006; Amor et al., 2009). In addition, many methods were used to analyze the coupling character between two EEG signals from different brain regions or two dissimilar electrodes of MCI patients, such as coherence (Moretti et al., 2008), mutual information (Liu et al., 2012), synchronization likelihood (SL) (Babiloni et al., 2006), Granger causality (Babiloni et al., 2009), and permutation conditional mutual information (PCMI) (Wen et al., 2014a).

For the method of coherence, it quantifies the linear correlation between two time series on frequency domain. Brassen et al. (2004) studied the MCI patients with depression by using the method, and the results showed that the MCI patients with depression were different significantly the NC in coherence strength between frontal and temporal area. However, the method does not consider the owner non-linear properties of signals.

For the method of mutual information, it calculates the own and joint probability density distribution of two time series, and quantifies the statistical independence between two time series by computing various entropies. Liu et al. (2012) analyzed the change related to the task in neural oscillation and connection between cerebral cortex of MCI patients and NC, and found that MCI patients were significantly different from NC in the neural oscillation strength and connection between parietal and occipital on theta frequency band. However, the computation of mutual information requires longer data, and shorter data are not enough to make the result of calculation have statistical significance.

For the method of SL, it is employed to calculate the degree of dynamic interactions between certain time series and another or multiple time series. Many studies displayed that the SL could be used for analyzing EEG signals of MCI patients: SL strength between EEG signals from frontal–parietal of MCI was lesser than NC on alpha1 frequency band, the SL strength between EEG signals from frontal–parietal of MCI was lesser than NC on delta frequency band (Babiloni et al., 2006), and the SL strengths of EEG signals of MCI were greater than NC on low alpha frequency band (8–10 Hz) (Pijnenburg et al., 2004). On the method of SL, the likelihood extent of time series patterns is calculated with statistical method, and this method determines which time series pattern is similar with other time series patterns according to threshold; however, the similarity is not considered in the decision-making process (Ahmadlou and Adeli, 2011), and it will affect the reliability of the method on diagnosing MCI to some extent.

Above most of the methods quantified the strength of coupling or coherence, were contributed to the in-depth study in analyzing EEG signals of MCI to a certain extent. Recently, many studies were trying to estimate the coupling direction between two EEG signals from different electrodes besides focusing on the coupling or coherence strength, such as Granger causality (Lungarella and Sporns, 2006), transfer entropy (Schreiber, 2000), conditional mutual information (Vejmelka and Paluš, 2008), instantaneous phases of interacting oscillators (Rosenblum and Pikovsky, 2001) and state space and phase-dynamics (Smirnov and Andrzejak, 2005), and so on. However, at present only Granger causality and its directed transfer function (DTF) were used to analyze the coupling direction or information flow of EEG signals from two electrodes of different brain regions of MCI (Babiloni et al., 2009; Dauwels et al., 2010b).

The Granger causality quantifies the degree of linear interdependence between different signals, and was often used in analyzing the linear model of EEG signals. The linear methods of Granger causality include partial directed coherence (PDC) and DTF, they belong to parametric method in accordance with multivariate auto-regressive model (Baccalá and Sameshima, 2001), and may describe the causality between multi-dimensional EEG signals on certain frequency band. The Granger causality methods achieved some valid results preliminarily in analyzing the EEG signals of MCI: the all frequency DTF of MCI decreased significantly in comparison with NC (Dauwels et al., 2010b), the direction index of information flow from parietal to frontal of MCI and AD decreased relative to NC, and especially the decrease became significant on alpha and beta frequency bands (Babiloni et al., 2009). The selection of order of multivariate auto-regressive model is difficult during estimating the parameters of multivariate auto-regressive model. Because lesser order affects the accuracy in estimating model parameters, bigger order can improve the accuracy and needed longer EEG signals to involve the calculation.

Recently, PCMI is a non-linear method, is used to estimate the coupling strength and direction of two time series from neural mass model, and also used to calculate the coupling strength and direction of time series of epilepsy and spike potential series (Li and Ouyang, 2010; Li et al., 2011). The studies showed that PMCI was superior to Granger causality in recognizing the coupling direction of unidirectional and bi-directional neural group. Meanwhile, Wen et al. (2014a) found the superiority of PCMI in analyzing the EEG signals of MCI in T2DM, and the results displayed that there exist differences between coupling strength or direction of two different brain regions of aMCI and control in T2DM on Alpha frequency bands. However, it remains to be further studied whether the method can be utilized for analyzing EEG signals of other types of MCI.

Problems to be Solved in the Future

According to above research status that presented the coupling analysis methods of two-channel EEG signals of MCI, we find that there exist a few key questions for further study in the future.

(1) It is urgently needed that know how to extract more meaningful features of EEG signals of MCI patients and dissect in-depth the interaction relationship between different EEG signals of MCI, in order to improve the computational accuracy of coupling strength.
(2) The vast majority of methods used to analyze EEG signals of MCI did not consider the calculation of coupling direction. Therefore, in the future we will need to explore new methods in order to calculate simultaneously the coupling strength and direction between different EEG signals of MCI.
(3) We need to improve the validity of statistical methods about coupling direction in the future, and change the present situation that existing methods relied on visual inspection or simple statistical method to estimate the main direction of information flow.

The Synchronization Analysis Methods

Methods Description and Evaluation

Many methods were used to estimate the synchronization strength of two time series and multiple time series, including of phase synchronization (Tóth et al., 2014), S estimator (Dauwels et al., 2010b), global synchronization (Koenig et al., 2005), stochastic events synchronization (Dauwels et al., 2010b), global synchronization index (GSI) (Cui et al., 2010; Lee et al., 2010), and global coupling index (GCI) (Wen et al., 2014b). And these methods were often applied to the studies analyzing the EEG signals of MCI and AD.

Phase synchronization refers to the interdependent relationship between instantaneous phases of two signals. Many studies showed that the phase synchronization strength of EEG signals of MCI was significantly different with NC (Sweeney-Reed et al., 2012; Tóth et al., 2014). The change appeared in synchronization features of MCI patients on delta and theta frequency bands before and after a year: the connect between frontal and temporal, frontal, and parietal decreased significantly, the function disconnection between different brain regions that are far apart from each other acted as a major feature of MCI patients (Tóth et al., 2014). There were the significant difference between MCI and NC on the time points and the degree of phase synchronization on theta and alpha frequency bands (Sweeney-Reed et al., 2012). In these studies, two methods extracting phase often were used, including wavelet transform and Hilbert transform (Quiroga et al., 2002; Pikovsky et al., 2003). Hilbert transform will appear obvious errors when computing the correlation between the phases of shorter EEG signals, and need longer EEG signals in order to estimate accurately the synchronization strength. Meanwhile, the phase synchronization method only extracts the phase feature of EEG signals and ignores other features.

Recently, S estimator was put forward, and it is a synchronization method based on state space, namely, it calculates the synchronization strength by analyzing the interdependent relationship among multiple signals in state space reconstruction domain (Carmeli et al., 2005). The S estimator was used to analyze the signals embedding dimension and time delay (Carmeli et al., 2005). Meanwhile, S estimator was preliminarily used for analyzing the EEG signals of MCI patients (Dauwels et al., 2010b), the research results of Dauwels et al. showed that the S estimator values of MCI patients were lesser significantly NC, and the Omega complexity of MCI patients were more than NC. Many researches showed that S estimator own good robustness and reliability in analyzing the data of model and real EEG signals (Quiroga et al., 2002; Knyazeva et al., 2013). However, S estimator does not consider adequately the effect of random and artifact component to analysis, and the accuracy of calculation has yet to be improved.

Global field synchronization (GFS) is another method measuring function synchronization, and employed to analyze the synchronization of multi-channel time series (Koenig et al., 2001). The method often focusses to the processing of EEG signals in frequency domain, and can estimate functional connection among multiple brain regions on different frequency bands (Koenig et al., 2005). Many studies showed that GFS could distinguish the EEG signals of MCI patients and NC on a few frequency bands (Koenig et al., 2005; Dauwels et al., 2010b). GFS belongs to a simple calculation between two normalized eigenvalues of the covariance matrix, and does not estimate accurately specific global synchronization strength. Meanwhile, GFS method acts as a simple multivariate method with quantifying synchronization of multiple signals, and first needs to calculate the synchronization correlation between two EEG signals. However, the GFS method is too simple to affect the accuracy of analysis for real EEG signals.

Dauwels et al. (2010a,b) proposed a method named stochastic event synchrony (SES) lately, and found that SES was better to analyze EEG signals of MCI patients relative to other methods. SES is characterized by calculating the interaction between certain events of EEG signals, extracted the point process from time-frequency representation of EEG signals, and quantified the similarity between point processes (Dauwels et al., 2009a,b; 2012). SES method showed the excellent performance when compared to the EEG signals of MCI patients and NC, and the SES values of EEG signals of MCI patients decreased significantly relative to NC (Dauwels et al., 2010a,b). However, the method was subject to limit of the number of channels, namely, the computation complexity increased greatly when the number of channels was added. The limitation affects the practicability analyzing actual multi-channel EEG signals.

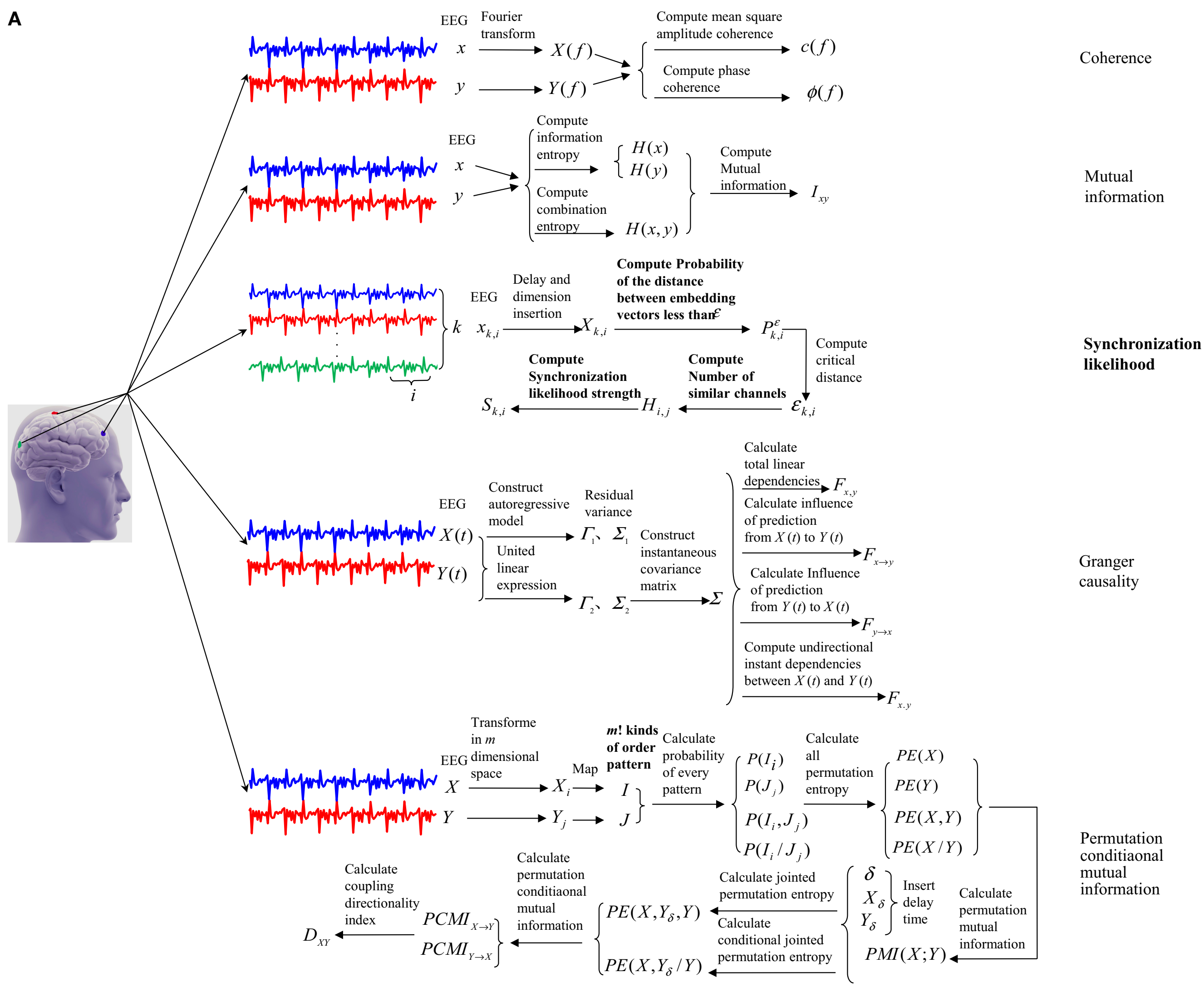

FIGURE 1 | The working pattern of five coupling and six synchronization methods with application to EEG signals of MCI patients. (A) showed working pattern of five coupling methods, and *(continued)*

Cui et al. (2010) proposed a new method named GSI, which improved the S estimator, in order to analyze the multi-dimensional neural series. Before calculate the GSI, the correlation coefficients between neural series were calculated with adopting mainly equal-time correlation method, which is a simple method measuring the linear correlation of two time series, does not estimate the non-linear correlation of two time series, and is also subject to the interference of noise to some extent. For all that, Lee et al. (2010) applied GSI to analyze EEG signals of AD, and found that GSI might act as biological identifier evaluating the cognitive decline of AD patients. However, the performance of GSI has not been reflected in analyzing the EEG signals of MCI systematically.

Recently, Wen et al. (2014b) improved the GSI method, and proposed a new method named GCI. The results showed that the synchronization strength based on GCI was less affected by the change of frequency bands relative to the other two methods, there existed more excellent performance on GCI method according to the change of coupling coefficient versus GSI and S estimator, and GCI was more sensitive than GSI and S estimator on distinguishing the synchronization strength of EEG signals from MCI and NC, especially in the Alpha frequency band. However, this method needed more time to calculate the global synchronization strength relative to GSI and S estimator.

Problems to be Solved in the Future

At present, there are the problems of two aspects, which are to be studied deeply in analyzing the synchronization of multi-channel EEG signals in the future.

(1) The profound relationship among two-channel EEG signals from multi-channel signals needs to be studied in-depth.

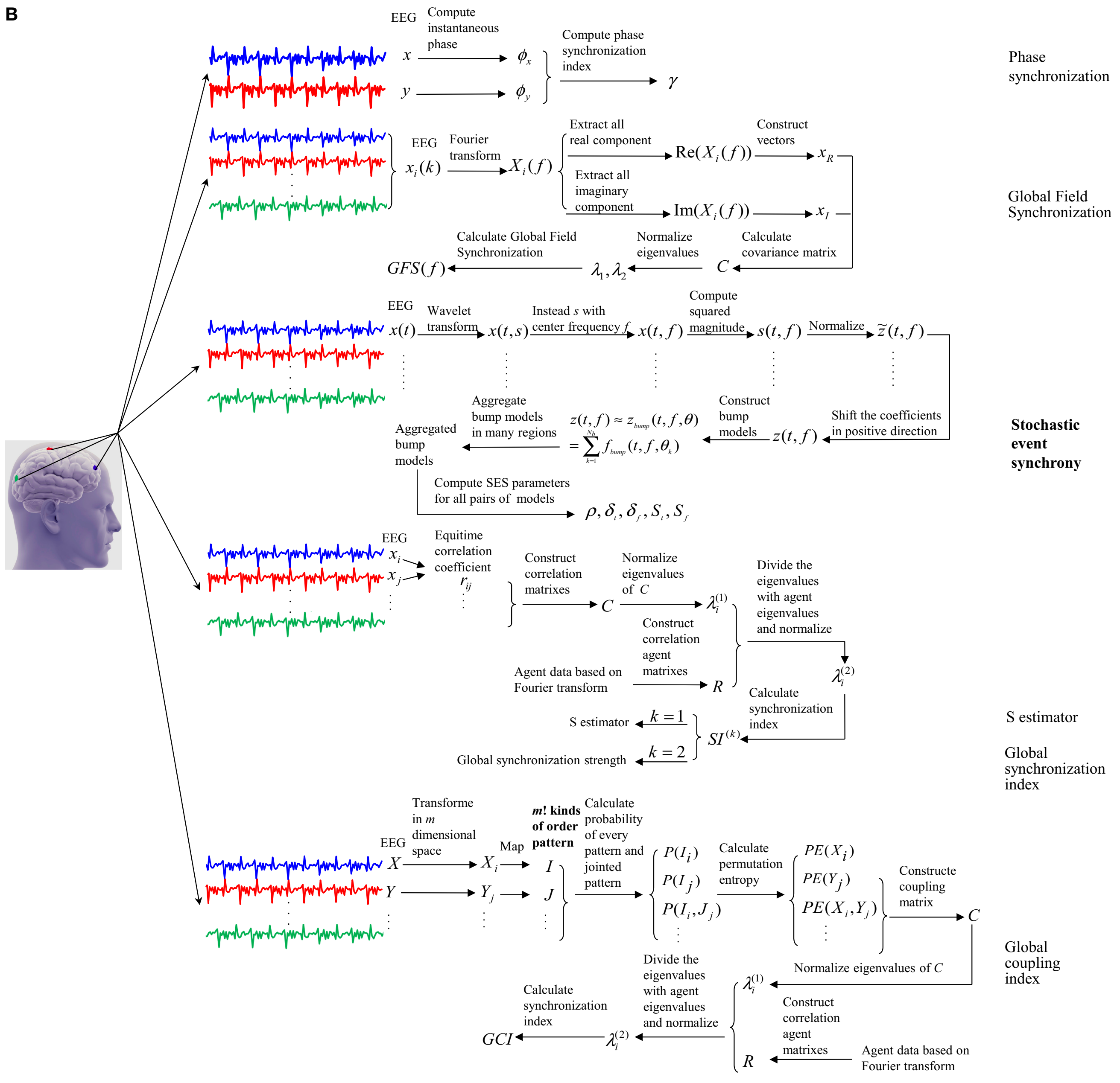

FIGURE 1 | Continued
(B) showed working pattern of six synchronization methods.

Especially requires optimizing existing GCI method, decreases the time complexity of this method in the context of assuring accuracy, transforms the method into a reliable tool for estimating accurately the synchronization strength of multi-channel EEG signals.

(2) It is required to understand how compare the basic performance of several synchronization methods for analyzing multi-channel time series and real EEG signals. Generally, the criteria contains frequency band, coupling coefficient and signal to noise ratio for model data, and significant difference, correlationship, degree of accuracy, and time-consuming for clinical data.

The Principles and Performances of Coupling and Synchronization Methods

This paper summarized the principles and performances of the above coupling and synchronization methods. **Figure 1** showed how the coupling and synchronization methods work in application to EEG signals of MCI patients. And **Table 1** displayed

TABLE 1 | Performance of best indicators from coupling and synchronization methods in analyzing EEG signals of MCI patients.

Methods	Accuracy	Sensitivity	Specificity	*P* value	Best indicators description
Coherence (Brassen et al., 2004)	–	88%	81%	0.004	Alpha band, from frontal to temporal
Mutual information (Liu et al., 2012)	–	–	–	$P < 0.001$	Theta band, all brain regions except in the occipital lobe
Synchronization likelihood (Babiloni et al., 2006)	–	–	–	$P < 7 \times 10^{-6}$ ~0.006	Delta band, F4–P4 of right fronto-parietal
Granger causality (Babiloni et al., 2009)	–	–	–	Alpha1: $P < 0.00001$ Alpha2: $P < 0.00001$	Alpha1 or Alpha2 bands, anterior–posterior
Permutation conditional mutual information (Wen et al., 2014a)	100%	100%	100%	$P < 0.001$	Alpha2 band, right temporal–parietal
Phase synchronization (Tóth et al., 2014)	–	–	–	0.002	Theta band, fronto-parietal in right or left hemisphere
S estimator (Wen et al., 2014b)	–	–	–	0.001	Alpha band, 10 channels including Fp1, Fp2, F7, C5, Fz, Cz, F8, C6, P3, P4
Global field synchronization (Koenig et al., 2005)	–	–	–	$P < 0.0001$	Alpha or Beta band, 19 channels of whole brain
Stochastic event synchrony (Dauwels et al., 2012)	87%	–	–	2×10^{-5}	4–30 Hz, 21 channels of whole brain
Global synchronization index (Wen et al., 2014b)	–	–	–	0.008	Alpha band, 10 channels including Fp1, Fp2, F7, C5, Fz, Cz, F8, C6, P3, P4
Global coupling index (Wen et al., 2014b)	–	–	–	$P < 0.00001$	Alpha band, 10 channels including Fp1, Fp2, F7, C5, Fz, Cz, F8, C6, P3, P4

the performance of the best indicators from these methods in analyzing EEG signals of MCI patients.

Conclusion

In conclusion, the analysis of EEG signals of MCI patients from coupling and synchronization angles was proved to be the two important ways in evaluating and diagnosing MCI. Above studies considered the coupling and synchronization features of EEG signals from the activity of neurons and neural group, and analyzed the EEG signals of MCI patients from different sides. In view of the difference of these studies angles, which led the performance of the methods to show advantages and disadvantages, the results presented various difference, and this paper explained and analyzed the difference in detail. Meanwhile, the future researches need to be focused on the following aspects: exacts the deep features of EEG signals of MCI patients and analyze in-depth the interaction relationship between different EEG signals of MCI.

Explore many methods that calculate and count the coupling strength and direction between different EEG signals of MCI patients; studies in-depth the profound relationship between two-channel EEG signals, enhances the computational accuracy of global synchronization strength, and decrease time complexity; selects some more effective indicators to compare different coupling methods of two-channel EEG signals and synchronization methods of multi-channel EEG signals in all directions.

Acknowledgments

This research was funded in part by National Science Foundation of China (61311130139, 61403331), Doctorial Foundation of Yanshan University in China (B900), Science and Technology Support Programme of Hebei province in China (13212003).

References

Aarabi, A., Wallois, F., and Grebe, R. (2008). Does spatiotemporal synchronization of EEG change prior to absence seizures? *Brain Res.* 1188, 207–221. doi:10.1016/j.brainres.2007.10.048

Ahmadlou, M., and Adeli, H. (2011). Fuzzy synchronization likelihood with application to attention-deficit/hyperactivity disorder. *Clin. EEG Neurosci.* 42, 6–13. doi:10.1177/155005941104200105

Amor, F., Baillet, S., Navarro, V., Adam, C., Martinerie, J., and Le Van Quyen, M. (2009). Cortical local and long-range synchronization interplay in human absence seizure initiation. *Neuroimage* 45, 950–962. doi:10.1016/j.neuroimage.2008.12.011

Babiloni, C., Ferri, R., Binetti, G., Cassarino, A., Forno, G. D., Ercolani, M., et al. (2006). Fronto-parietal coupling of brain rhythms in mild cognitive impairment: a multicentric EEG study. *Brain Res. Bull.* 69, 63–73. doi:10.1016/j.brainresbull.2005.10.013

Babiloni, C., Ferri, R., Binetti, G., Vecchio, F., Frisoni, G. B., Lanuzza, B., et al. (2009). Directionality of EEG synchronization in Alzheimer's disease subjects. *Neurobiol. Aging* 30, 93–102. doi:10.1016/j.neurobiolaging.2007.05.007

Babiloni, C., Frisoni, G. B., Vecchio, F., Pievani, M., Geroldi, C., De Carli, C., et al. (2010). Global functional coupling of resting EEG rhythms is related to white-matter lesions along the cholinergic tracts in subjects with amnesic mild cognitive impairment. *J. Alzheimer Dis.* 19, 859–871. doi:10.3233/JAD-2010-1290

Baccalá, L. A., and Sameshima, K. (2001). Overcoming the limitations of correlation analysis for many simultaneously processed neural structures. *Prog. Brain Res.* 130, 33–48. doi:10.1016/S0079-6123(01)30004-3

Brassen, S., Braus, D. F., Weber-Fahr, W., Tost, H., Moritz, S., and Adler, G. (2004). Late-onset depression with mild cognitive deficits: electrophysiological evidences for a preclinical dementia syndrome. *Dement. Geriatr. Cogn. Disord.* 18, 271–277. doi:10.1159/000080028

Buzsáki, G., and Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science* 304, 1926–1929. doi:10.1126/science.1099745

Cantero, J. L., Atienza, M., Cruz-Vadell, A., Suarez-Gonzalez, A., and Gil-Neciga, E. (2009). Increased synchronization and decreased neural complexity underlie thalamocortical oscillatory dynamics in mild cognitive impairment. *Neuroimage* 46, 938–948. doi:10.1016/j.neuroimage.2009.03.018

Carmeli, C., Knyazeva, M. G., Innocenti, G. M., and De Feo, O. (2005). Assessment of EEG synchronization based on state-space analysis. *Neuroimage* 25, 339–354. doi:10.1016/j.neuroimage.2004.11.049

Cui, D., Liu, X., Wan, Y., and Li, X. (2010). Estimation of genuine and random synchronization in multivariate neural series. *Neural Netw.* 23, 698–704. doi:10.1016/j.neunet.2010.04.003

Darvas, F., Ojemann, J. G., and Sorensen, L. B. (2009). Bi-phase locking – a tool for probing non-linear interaction in the human brain. *Neuroimage* 46, 123–132. doi:10.1016/j.neuroimage.2009.01.034

Dauwels, J., Vialatte, F., and Cichocki, A. (2010a). Diagnosis of Alzheimers disease from EEG signals: where are we standing? *Curr. Alzheimer Res.* 7, 487–505. doi:10.2174/156720510792231720

Dauwels, J., Vialatte, F., Musha, T., and Cichocki, A. (2010b). A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG. *Neuroimage* 49, 668–693. doi:10.1016/j.neuroimage.2009.06.056

Dauwels, J., Vialatte, F., Weber, T., Musha, T., and Cichocki, A. (2009a). Quantifying statistical interdependence by message passing on graphs-part I: multidimensional point processes. *Neural Comput.* 21, 2152–2202. doi:10.1162/neco.2009.11-08-899

Dauwels, J., Vialatte, F., Weber, T., Musha, T., and Cichocki, A. (2009b). Quantifying statistical interdependence by message passing on graphs-part II: multidimensional point processes. *Neural Comput.* 21, 2203–2268. doi:10.1162/neco.2009.11-08-899

Dauwels, J., Weber, T., Vialatte, F., Musha, T., and Cichocki, A. (2012). Quantifying statistical interdependence, part iii: N> 2 point processes. *Neural Comput.* 24, 408–454. doi:10.1162/NECO_a_00235

Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Schaller, C., Elger, C. E., et al. (2001). Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. *Nat. Neurosci.* 4, 1259–1264. doi:10.1038/nn759

Knyazeva, M. G., Jalili, M., Brioschi, A., Bourquin, I., Fornari, E., Hasler, M., et al. (2010). Topography of EEG multivariate phase synchronization in early Alzheimer's disease. *Neurobiol. Aging* 31, 1132–1144. doi:10.1016/j.neurobiolaging.2008.07.019

Knyazeva, M. G., Carmeli, C., Khadivi, A., Ghika, J., Meuli, R., and Frackowiak, R. S. (2013). Evolution of source EEG synchronization in early Alzheimer's disease. *Neurobiol. Aging* 34, 694–705. doi:10.1016/j.neurobiolaging.2012.07.012

Koenig, T., Lehmann, D., Saito, N., Kuginuki, T., Kinoshita, T., and Koukkou, M. (2001). Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naïve patients with schizophrenia: preliminary results. *Schizophr. Res.* 50, 55–60. doi:10.1016/S0920-9964(00)00154-7

Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L., John, E., et al. (2005). Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. *Neurobiol. Aging* 26, 165–171. doi:10.1016/j.neurobiolaging.2004.03.008

Lee, S.-H., Park, Y.-M., Kim, D.-W., and Im, C.-H. (2010). Global synchronization index as a biological correlate of cognitive decline in Alzheimer's disease. *Neurosci. Res.* 66, 333–339. doi:10.1016/j.neures.2009.12.004

Li, X., and Ouyang, G. (2010). Estimating coupling direction between neuronal populations with permutation conditional mutual information. *Neuroimage* 52, 497–507. doi:10.1016/j.neuroimage.2010.05.003

Li, Z., Ouyang, G., Li, D., and Li, X. (2011). Characterization of the causality between spike trains with permutation conditional mutual information. *Phy. Rev. E* 84, 021929. doi:10.1103/PhysRevE.84.021929

Liu, C. J., Huang, C. F., Chou, C. Y., Kuo, W. J., Lin, Y. T., Hung, C. M., et al. (2012). Age- and disease-related features of task-related brain oscillations by using mutual information. *Brain Behav.* 2, 754–762. doi:10.1002/brb3.93

Lungarella, M., and Sporns, O. (2006). Mapping information flow in sensorimotor networks. *PLoS Comput. Biol.* 2:e144. doi:10.1371/journal.pcbi.0020144

Mizuhara, H., and Yamaguchi, Y. (2007). Human cortical circuits for central executive function emerge by theta phase synchronization. *Neuroimage* 36, 232–244. doi:10.1016/j.neuroimage.2007.02.026

Moretti, D. V., Frisoni, G. B., Pievani, M., Rosini, S., Geroldi, C., Binetti, G., et al. (2008). Cerebrovascular disease and hippocampal atrophy are differently linked to functional coupling of brain areas: an EEG coherence study in MCI subjects. *J. Alzheimer Dis.* 14, 285–299.

Pijnenburg, Y., Van Cappellen Van Walsum, A., Knol, D., Scheltens, P., and Stam, C. (2004). EEG synchronization likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task. *Neurophysiol. Clin.* 115, 1332–1339. doi:10.1016/j.clinph.2003.12.029

Pikovsky, A., Rosenblum, M., and Kurths, J. (2003). *Synchronization: A Universal Concept in Nonlinear Sciences*. Cambridge: Cambridge University Press.

Quiroga, R. Q., Kraskov, A., Kreuz, T., and Grassberger, P. (2002). Performance of different synchronization measures in real data: a case study on electroencephalographic signals. *Phys. Rev. E* 65, 041903. doi:10.1103/PhysRevE.65.041903

Rosenblum, M. G., and Pikovsky, A. S. (2001). Detecting direction of coupling in interacting oscillators. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 64, 045202. doi:10.1103/PhysRevE.64.045202

Schreiber, T. (2000). Measuring information transfer. *Phys. Rev. Lett.* 85, 461. doi:10.1103/PhysRevLett.85.461

Smirnov, D. A., and Andrzejak, R. G. (2005). Detection of weak directional coupling: phase-dynamics approach versus state-space approach. *Phys. Rev. E* 71, 036207. doi:10.1103/PhysRevE.71.036207

Sweeney-Reed, C. M., Riddell, P. M., Ellis, J. A., Freeman, J. E., and Nasuto, S. J. (2012). Neural correlates of true and false memory in mild cognitive impairment. *PLoS ONE* 7:e48357. doi:10.1371/journal.pone.0048357

Tóth, B., File, B., Boha, R., Kardos, Z., Hidasi, Z., Gaál, Z. A., et al. (2014). EEG network connectivity changes in mild cognitive impairment – preliminary results. *Int. J. Psychophysiol.* 92, 1–7. doi:10.1016/j.ijpsycho.2014.02.001

Uhlhaas, P. J., and Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* 52, 155–168. doi:10.1016/j.neuron.2006.09.020

Varela, F., Lachaux, J.-P., Rodriguez, E., and Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* 2, 229–239. doi:10.1038/35067550

Vecchio, F., and Babiloni, C. (2011). Direction of information flow in Alzheimer's disease and MCI patients. *Int. J. Alzheimers Dis.* 2011, 214580. doi:10.4061/2011/214580

Vejmelka, M., and Paluš, M. (2008). Inferring the directionality of coupling with conditional mutual information. *Phys. Rev. E* 77, 026214. doi:10.1103/PhysRevE.77.026214

Wen, D., Bian, Z., Lu, C., and Li, X. (2014a). The resting-state EEG coupling analysis of amnestic mild cognitive impairment in T2DM based on permutation conditional mutual information. *Neurophysiol. Clin.*

Wen, D., Xue, Q., Lu, C., Guan, X., Wang, Y., and Li, X. (2014b). A global coupling index of multivariate neural series with application to the evaluation of mild cognitive impairment. *Neural Netw.* 56, 1–9. doi:10.1016/j.neunet.2014.03.001

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., et al. (2007). Modulation of neuronal interactions through neuronal synchronization. *Science* 316, 1609–1612. doi:10.1126/science.1139597

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 03 June 2015
doi: 10.3389/fnagi.2015.00109

Patients with moderate Alzheimer's disease engage in verbal reminiscence with the support of a computer-aided program: a pilot study

Giulio E. Lancioni[1], Nirbhay N. Singh[2], Mark F. O'Reilly[3], Jeff Sigafoos[4], Fiora D'Amico[5], Gabriele Ferlisi[6], Floriana Denitto[7], Floriana De Vanna[8] and Marta Olivetti Belardinelli[9]*

[1] Department of Neuroscience and Sense Organs, University of Bari, Bari, Italy, [2] Medical College of Georgia, Georgia Regents University, Augusta, GA, USA, [3] Department of Special Education, University of Texas at Austin, Austin, TX, USA, [4] Department of Educational Psychology, Victoria University of Wellington, Wellington, New Zealand, [5] S. Raffaele Medical Care Center, Alberobello, Italy, [6] Lega F. D'Oro Research Center, Osimo, Italy, [7] ISPE Medical Care Center, Mola di Bari, Italy, [8] Memory Drops Day Center, Giovinazzo, Italy, [9] Department of Psychology, "Sapienza" University of Rome, Rome, Italy

OPEN ACCESS

Edited by:
Valeria Manera, University of Nice Sophia Antipolis, France

Reviewed by:
Amanda Lazar, University of Washington, USA
Hsiu-Fang Hsieh, Fooyin University, Taiwan

***Correspondence:**
Giulio E. Lancioni, Department of Neuroscience and Sense Organs, University of Bari, Corso Italia 23, 70121 Bari, Italy
giulio.lancioni@uniba.it

Received: 18 February 2015
Accepted: 22 May 2015
Published: 03 June 2015

Citation:
Lancioni GE, Singh NN, O'Reilly MF, Sigafoos J, D'Amico F, Ferlisi G, Denitto F, De Vanna F and Olivetti Belardinelli M (2015) Patients with moderate Alzheimer's disease engage in verbal reminiscence with the support of a computer-aided program: a pilot study. Front. Aging Neurosci. 7:109. doi: 10.3389/fnagi.2015.00109

This study focused on the assessment of a program recently developed for helping patients with moderate Alzheimer's disease engage in computer-mediated verbal reminiscence (Lancioni et al., 2014a). Sixteen participants were involved in the study. Six of them used the original program version with the computer showing a virtual partner posing questions and providing attention and guidance. The other 10 used a slightly modified program version with the computer presenting photos and videos and providing encouragements to talk as well as attention and guidance. Participants were exposed to brief program sessions individually. The results showed that 15 participants (five of those using the first version and all of those using the second version) had a clear and lasting increase in verbal engagement/reminiscence during the intervention sessions with the program. Those 15 participants had mean percentages of intervals with verbal engagement/reminiscence below 10 during baseline and between about 45 and 75 during the intervention. The results' implications and the need for new research were discussed.

Keywords: Alzheimer's disease, reminiscence, computer-aided program, verbal cues, visual cues

Introduction

Alzheimer's disease is a neurodegenerative disorder that causes a progressive decline of the person's general condition, which is reflected in a gradual loss of independence, with a reduction of activity, social interaction, and verbal engagement (De Leo et al., 2011; Melrose et al., 2011; Ambrose, 2012; Bernick et al., 2012; Soto et al., 2012; Spalletta et al., 2012; Wilson et al., 2012; Sikkes et al., 2013; Perri et al., 2014). While it is impossible to prevent the occurrence of the disease or to cure it successfully (i.e., eliminate its effects), a number of pharmacological and behavioral intervention strategies have been recommended to slow down the deterioration process, support adaptive performance, and improve social appearance (Giordano et al., 2010; Ferrero-Arias et al., 2011; Bharwani et al., 2012; Boller et al., 2012; Kim et al., 2012; de Vries, 2013; Schecker et al., 2013; Berk et al., 2014; Kurz and Grimmer, 2014; Tifratene et al., 2014).

Recommended behavioral intervention strategies for persons in the earlier stages of the disease have focused, among others, on assisting those persons with the: (a) performance of daily activities; (b) orientation and travel in indoor and limited outdoor areas; and (c) verbal reminiscence (Lancioni et al., 2010, 2012, 2013a,b, 2014b; Caffò et al., 2012, 2014; Crete-Nishihata et al., 2012; Serrani Azcurra, 2012; Subramaniam and Woods, 2012; Cavallo et al., 2013; Lanza et al., 2014; Singh et al., 2014; Wingbermuehle et al., 2014). In each of these areas, technology-aided programs have been developed with the aim of enabling the persons to achieve satisfactory performance independent of staff intervention (Singh et al., 2014). For example, Lancioni et al. (2009a, 2013b) and Perilli et al. (2013) have successfully assessed computer-aided programs for presenting verbal or visual instructions to help persons with mild and moderate Alzheimer's disease perform multistep daily activities on their own. Caffò et al. (2014) and Lancioni et al. (2013a,b) have shown that persons with moderate Alzheimer's disease can orient and travel independently to specific destinations within their living environments through the use of technology-aided programs providing auditory orientation cues. Lanza et al. (2014) have extended the assessment of orientation technology to limited outdoor spaces (i.e., a hospital campus). They showed that a portable orientation device was effective in helping participants with mild to moderate Alzheimer's disease reach their destinations after a 15-min training on the functioning of the device. Finally, Lancioni et al. (2014a) were able to increase positive verbal engagement/reminiscence in persons with moderate Alzheimer's disease through a computer-aided program that worked independently of staff involvement (cf., Lazar et al., 2014). That is, the participants saw a virtual partner on the computer screen who posed questions about their past experiences and provided them with positive attention and verbal guidance (prompts/encouragements).

Work within each of the aforementioned areas may be considered highly relevant for helping persons with mild and moderate Alzheimer's disease maintain an active role with possible benefits for: (a) their overall functioning and level of satisfaction (i.e., for increasing their positive performance, improving their mood and social appearance, and possibly delaying their decline); and (b) the practical and emotional condition of staff and caregivers working with them (i.e., for providing these personnel some relief and hopefulness; Lancioni et al., 2009a,b, 2010; Woods et al., 2009, 2012; Yasuda et al., 2009; Buettner et al., 2010; Godwin et al., 2013; Lundberg, 2014; Singh et al., 2014). While a number of studies have been carried out to assess the technology-aided programs available for supporting independent activities and orientation/travel, only limited evidence is available with regard to the program for supporting independent (i.e., computer-mediated) verbal engagement/reminiscence.

This study focused on the assessment of such a verbal engagement/reminiscence program to gather new evidence as to its practical consistency, that is, its ability to support verbal reminiscence independent of staff or therapist's guidance (Barlow et al., 2009; Lazar et al., 2014). For the assessment, we used a program version identical to that previously employed by Lancioni et al. (2014a) (i.e., with the computer showing a virtual partner; see above) and a modified version. The latter did not include the virtual partner. It relied on the computer presenting photos and video clips of the participants or of relevant people/events and places (cf., Astell et al., 2010a), and providing a verbal description of and an encouragement to talk about them. The use of the two versions was thought to be important to ascertain whether the program would still work regardless of arrangement variations that one might adopt for practical reasons related to the intervention context or participants. The hypothesis was that both versions could be effective in promoting participants' independent (i.e., computer-mediated) verbal engagement/reminiscence. Sixteen participants with moderate Alzheimer's disease were involved in the study. Six of them (i.e., the first six enrolled in the study) used the program version reported by Lancioni et al. (2014a) while the other 10 used the modified version.

Method

Participants

The first six participants enrolled in the study (Participants 1–6; see **Table 1**), who used the original program version, included three females and three males aged 77–93 (M = 84) years. The other 10 participants (Participants 7–16; see **Table 1**), who used the second program version, included eight females and two males aged 70–92 (M = 82) years. All participants were fairly quiet and generally silent within their context but were capable of responding to verbal questions and encouragements, and of watching photos and videos and talking about them. They had a diagnosis of moderate Alzheimer's disease with scores on the Mini Mental State Examination (Folstein et al., 1975) ranging from 11 to 17 (M = 15) for the first six participants and from 12 to 18 (M = 14) for the last 10 participants (see **Table 1**).

The participants attended centers for persons with Alzheimer's disease and other dementias in which they were involved in self-care (e.g., grooming) and leisure (e.g., music

TABLE 1 | Participants' characteristics.

Participant	Sex	Age	MMSE
1	M	83	14
2	F	93	11
3	M	80	17
4	F	77	16
5	F	85	16
6	M	84	15
7	F	81	12
8	F	88	14
9	M	70	18
10	F	92	13
11	F	91	12
12	F	82	12
13	F	85	14
14	F	84	18
15	F	72	13
16	M	75	17

MMSE stands for Mini Mental State Examination.

listening) activities or other simple occupational activities. In spite of the emphasis on positive activity engagement, they could spend various periods of the day sitting with persons in similar conditions (i.e., attending the same context) in a fairly passive manner and with marginal staff intervention/attention. Those periods of inactivity and virtual silence were considered detrimental for them and an intervention strategy to foster their alertness and involvement was viewed as desirable. Using a simple computer-aided program to help the participants reminisce events of their life and increase their positive verbal engagement seemed a reasonable and affordable intervention strategy. Staff and families, who had seen preliminary versions of such program, supported it. Participants were thought to be comfortable about it and, possibly to enjoy it, based on the information available about them (i.e., their ability to respond to questions and encouragements and to watch and talk about photos and videos). Families had also provided formal consent for the participants' involvement in the study, which had been approved by the Ethics Committee of the Walden Technology S.r.l., Rome, Italy.

Technology and Questions/Topics for the First Program Version

The technology for the first program version matched that used by Lancioni et al. (2014a) and involved a computer system with screen and sound amplifier, a microswitch, and specific software. During intervention sessions, the participant: (a) sat in front of the computer screen with the microswitch (i.e., a push button); and (b) was shown video-recorded sequences of a virtual partner (i.e., a woman matching typical caregiving figures) who greeted him or her, presented questions (relevant topics) for engagement/reminiscence, and provided positive attention, and guidance (i.e., prompts/encouragements). As in Lancioni et al. (2014a), the questions posed by the virtual partner on the screen covered several topics per participant (e.g., cooking and husband's eating, work, church and prayers, children, house, neighbors, music and dance). For each topic, different sets of questions were available. Topics and questions varied across sessions.

A session started with the virtual partner greeting the patient and posing the first question. For example, she could ask about the participant's active role in the local church. Assuming that the participant would respond to the question, the virtual partner displayed positive nodding (possibly accompanied by approving vocal sounds) and, after about 15 s, verbalized a positive comment (e.g., you did so much for your church!). Then, the partner encouraged the participant with a phrase such as "Let's continue, press the push-button" (i.e., the microswitch). If the participant pressed the push-button, the partner showed animation/smiles and presented the second question (e.g., about the participant's singing in church). Following the question, the partner performed as described above and after about 15 s made a positive statement (e.g., I am sure it was lovely!). If the participant did not press the push-button independently, the partner encouraged such a response and then posed the third question (e.g., about the ceremonies or songs the participant liked the most). The procedure continued the same way with approval and new questions until 5 min had elapsed and the session was ended. If a participant did not respond to the partner's encouragement to press the push-button, the encouragement would be repeated at intervals of approximately 15 s. The encouragement could also be programmed at longer intervals and/or uttered at a relatively low intensity if the participant tended to talk for rather long periods of time in relation to the questions presented.

Technology and Visual and Verbal Cues for the Second Program Version

The second program version replaced the appearance of the virtual partner and the questions with photos or 2- to 4-s video clips of the participant him- or herself in special circumstances (e.g., children's weddings or other celebrations) or of relevant people/events and places. The computer accompanied the photos and the videos (the last frame of which remained on view like the photos) with a brief verbal description of and an encouragement to the participant to talk about them. Assuming that the participant would talk about what was on view, the computer produced approving vocal sounds, which were then followed by a positive comment (i.e., as in the first version). An encouragement to press the microswitch to talk about something else occurred after 20 s or more (i.e., if the participant had not activated the microswitch independently). Microswitch activation caused the previous photo or the last frame of the previous video to be replaced by a new photo or video accompanied by a verbal description and an encouragement to the participant to talk about it. In case of no microswitch activation, the computer would provide a new encouragement at intervals of about 20 s. Between 40 and 50 photos and videos were available for each participant. The use of those visual cues (and accompanying verbal cues) was rotated across sessions.

Setting, Sessions, and Data Recording

Computer-aided sessions as well as baseline and control sessions were carried out in a room of the centers that the patients attended. All sessions lasted 5 min. Typically, two or three computer-aided sessions occurred per day per participant (i.e., sessions were carried out on an individual basis). Control sessions were scattered through the intervention phase (see below). Sessions were video-recorded and then scored by a research assistant. A second research assistant joined in the scoring of more than 25% of the sessions to assess interrater agreement. The measures recorded were: microswitch activations and verbal engagement/reminiscence. The first measure was recorded in terms of frequency per session. The latter measure was recorded according to a time sampling procedure, using intervals of 10 s (Kazdin, 2001). Percentages of interrater agreement on the two measures (computed by dividing the smaller activation frequency by the larger one or the intervals with agreement by the total number of intervals and multiplying by 100) were within the 80–100 range, with individual means exceeding 90.

Experimental Conditions

Each program version was introduced according to a non-concurrent multiple baseline design across participants (Barlow et al., 2009). The baseline phase included two or four sessions per participant. The following intervention phase included 80–117 (M = 97) sessions for the participants using the first program version and 73–122 (M = 99) sessions for the participants using the second program version. Differences in number of sessions were largely due to participants' availability. Parallel to the intervention phase, the participants received 9–24 (M = 16) control sessions.

Baseline

During the baseline sessions, the participant sat in front of the computer screen, which was dark, and had the microswitch whose activation did not produce any effects.

Intervention

During the intervention sessions, the participant sat in front of the computer screen with the microswitch, experiencing the conditions described in the technology section regarding the first program version (Participants 1–6) or the second program version (Participants 7–16). Prior to the start of the intervention phase, each participant received five to seven practice sessions during which the research assistant guided him or her in using the microswitch and talking in response to the virtual partner's questions or to the photos/videos and accompanying encouragements (see Technology sections).

Control

During the control sessions, the participant sat with other persons with dementia attending the same context, without any programmed occupation/interaction except for staff providing routine supervision.

Results

The baseline and intervention data for the six participants using the first version of the program are summarized in **Figures 1**, **2**. The three panels of **Figure 1** report the data for Participants 1–3, respectively. The three panels of **Figure 2** report the data for Participants 4–6, respectively. Bars and circles represent mean percentages of intervals with verbal engagement/reminiscence and mean frequencies of microswitch activations per session, respectively, over blocks of sessions. The number of sessions included in each block (i.e., bar-circle combination) is indicated by the numeral above it.

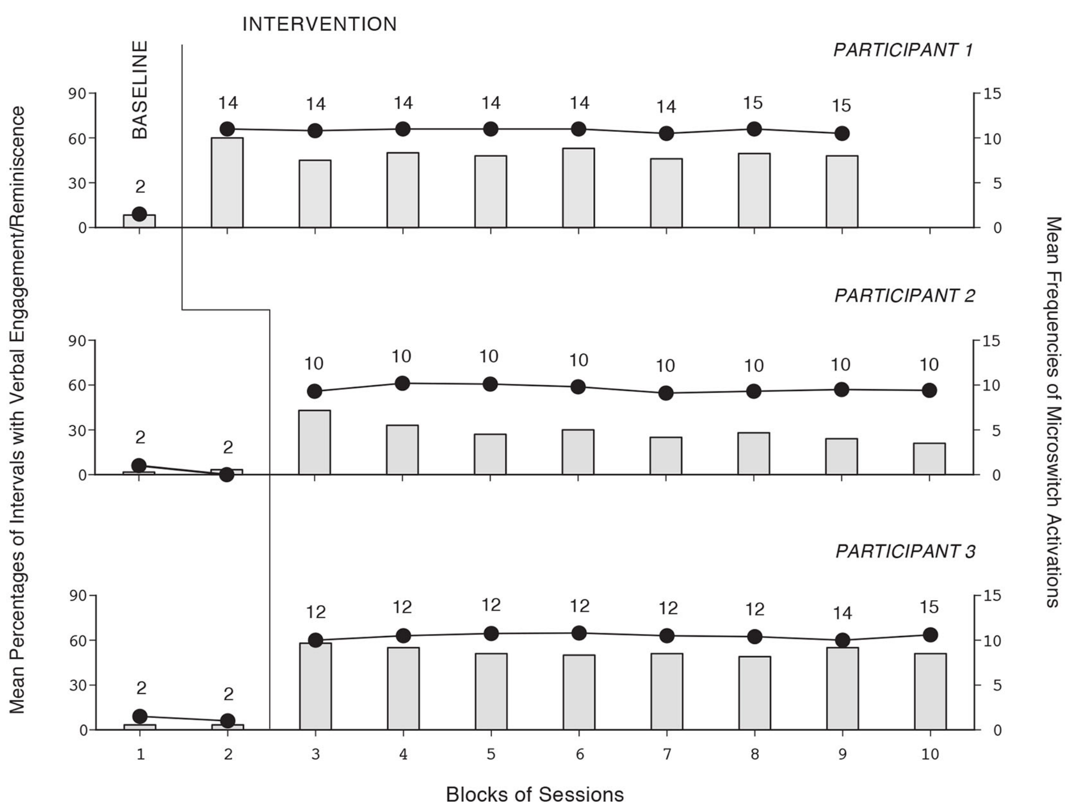

FIGURE 1 | The three panels report the data for Participants 1–3, respectively. Bars and circles represent mean percentages of intervals with verbal engagement/reminiscence and mean frequencies of microswitch activations per session, respectively, over blocks of sessions. The number of sessions included in each block (i.e., bar-circle combination) is indicated by the numeral above it.

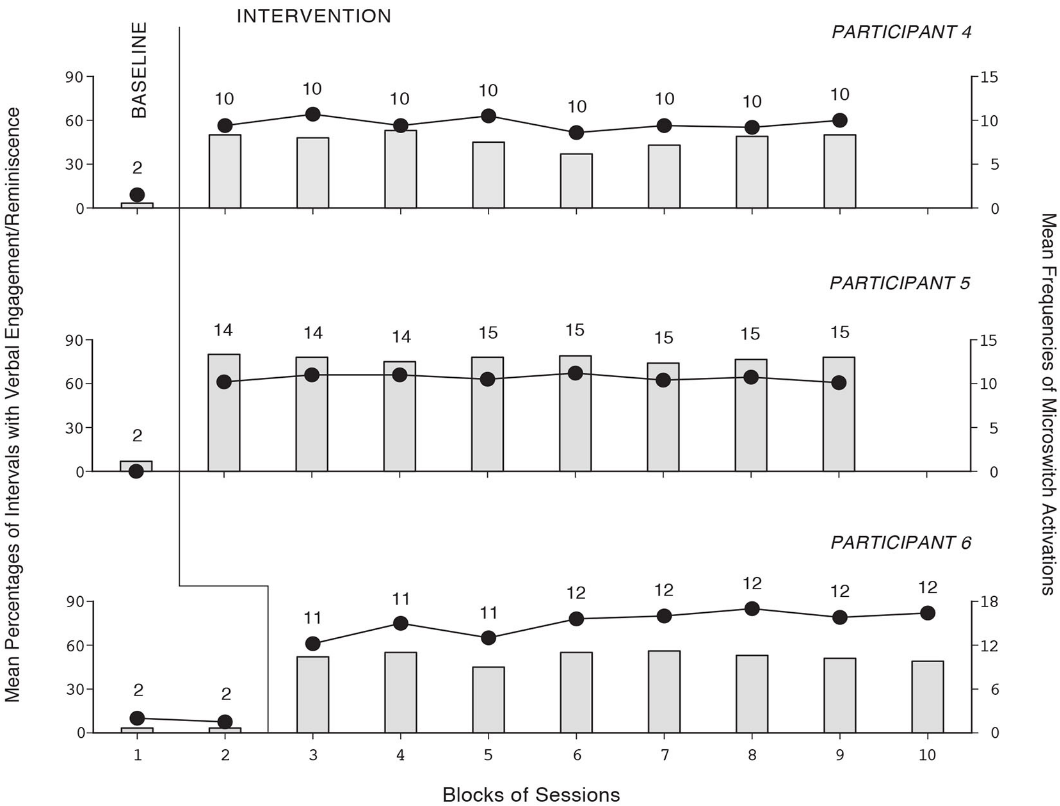

FIGURE 2 | The three panels report the data for Participants 4–6, respectively. Data are plotted as in **Figure 1**.

During the baseline sessions, the participants' mean percentages of intervals with verbal engagement/reminiscence were below 10. Their mean frequencies of microswitch activation were below two per session. During the intervention sessions, all participants showed performance improvement. Their mean percentages of intervals with verbal engagement/reminiscence ranged from near 30 (Participant 2, whose performance level was apparently declining) to about 75 (Participant 5). The participants' mean frequencies of microswitch activation were between about 10 and 15 per session. During the control sessions (not reported in the figures), their mean percentages of intervals with verbal engagement/reminiscence were below 10.

The baseline and intervention data for the 10 participants using the second version of the program are summarized in **Figures 3**, **4**. The five panels of **Figure 3** report the data for Participants 7–11, respectively. The five panels of **Figure 4** report the data for Participants 12–16, respectively. The data are plotted as in **Figures 1**, **2**. During the baseline sessions, the participants' performance matched that of the six participants exposed to the first version of the program. During the intervention sessions, their mean percentages of intervals with verbal engagement/reminiscence ranged from about 45 (Participant 12) to above 70 (Participant 10). Their mean frequencies of microswitch activation ranged from above six to about nine per session. During the control sessions (not reported in the figures), their mean percentages of intervals with verbal engagement/reminiscence were as in baseline.

Discussion

The data show that 15 of the 16 participants had a clear and lasting increase in verbal engagement/reminiscence. The program was applied on an individual basis (i.e., as this seems the most appropriate approach for these participants; Chiang et al., 2010; Dahlin and Rydén, 2011; Subramaniam and Woods, 2012; Blake, 2013; Van Bogaert et al., 2013; Wingbermuehle et al., 2014). Although no comparisons were made between the two program versions, the results of this study and of the one by Lancioni et al. (2014a) suggest that both might be viable solutions for promoting independent (i.e., computer-mediated) verbal engagement/reminiscence in persons with moderate Alzheimer's disease. In light of these still preliminary results, a few considerations might be put forward.

The verbal engagement/reminiscence exhibited by the participants during the intervention might be essentially ascribed to the use of topics (past experiences) that the participants could connect with and to the availability of verbal questions or combinations of visual and verbal cues that worked fairly adequately for them. Apparently, the two versions of the computer-aided program provided sufficient support to the

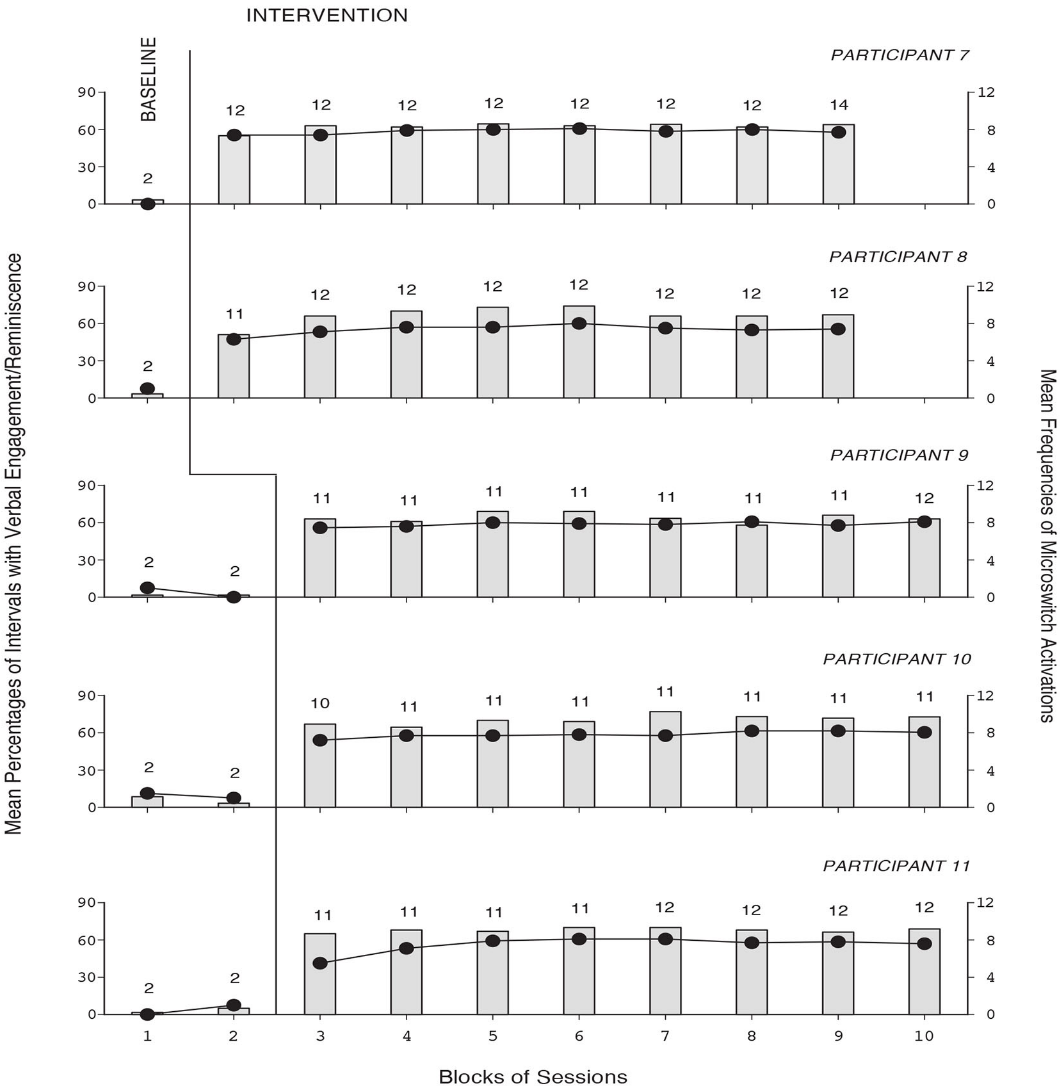

FIGURE 3 | The five panels report the data for Participants 7–11, respectively. Data are plotted as in **Figure 1**.

participants so that they could engage in verbal reminiscence without the presence of a therapist or prompter (Kuwahara et al., 2006, 2010; Astell et al., 2010b; Lazar et al., 2014). Both program versions relied on three main intervention conditions, that is: (a) helping the participants focus their attention on the topics presented; (b) guiding them to shift their attention across various topics, thus providing them the opportunity to vary and expand their verbal engagement/reminiscence; and (c) ensuring the occurrence of positive attention/comments that could encourage the participants during their engagement and reinforce them for it (Kazdin, 2001; Bemelmans et al., 2012; Catania, 2012; Yamagami et al., 2012; Lancioni et al., 2014a).

The second program version adds a critical visual component to the conditions used in the first version. In practice, photos/videos are used to present the topic while the accompanying verbal cues and encouragements help the participant focus on the topic and start talking about it. One would expect this latter version to be as effective as the former in general. In some cases (i.e., when the participants are less attentive to verbal questions), the latter version might even have a slight advantage (cf., Zannino et al., 2010; Lancioni et al., 2012). Obviously, these early data on the two program versions can only be taken as a preliminary demonstration of their applicability and potential (Kennedy, 2005; Lundberg, 2014). Definite statements about them must be postponed until new studies have established their dependability and ascertained possible differences in their levels of impact or relations with participants' characteristics (Kennedy, 2005; Barlow et al., 2009; Davis et al., 2012).

The differences observed among the individual levels of verbal engagement/reminiscence might have reflected the participants' general functioning abilities, their verbal

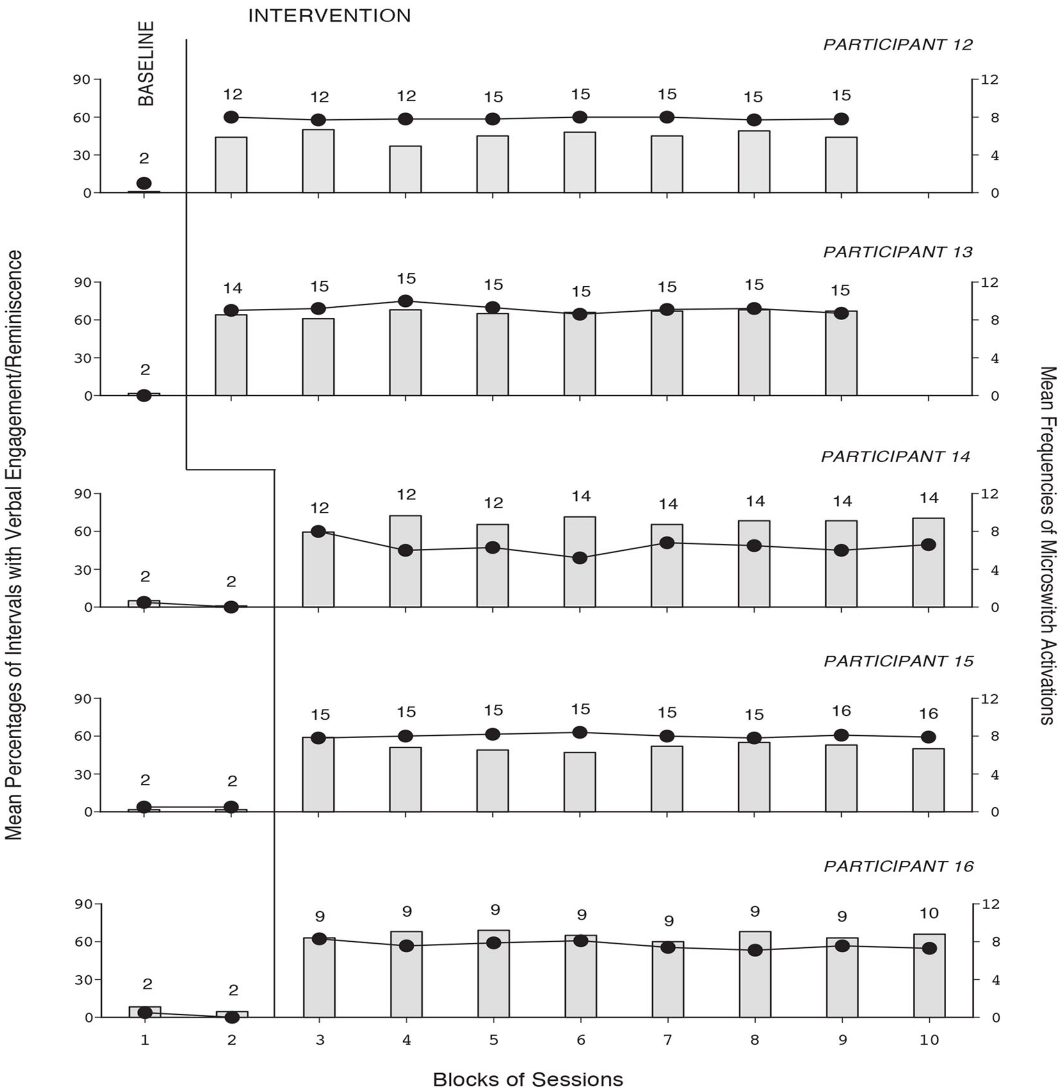

FIGURE 4 | The five panels report the data for Participants 12–16, respectively. Data are plotted as in **Figure 1**.

inclinations, and their tendency toward the reminiscence task. For example, the relatively low and declining performance of Participant 2 might have been due to her rather compromised and deteriorating condition that increasingly curtailed her interest in the topics presented as well as her verbal behavior and active participation (Soto et al., 2012; Spalletta et al., 2012; Wilson et al., 2012; Lancioni et al., 2014a). Careful selection of relevant topics/questions for verbal engagement/reminiscence and strongly motivating comments may help enhance the program effectiveness over time (i.e., at least until the participant's condition seriously deteriorates) (Pierce and Cheney, 2008; Catania, 2012; Noguchi et al., 2013).

In conclusion, the results indicate that a simple program might be used profitably for supporting independent (i.e., computer-mediated) verbal engagement/reminiscence. This encouraging statement needs to be taken with caution given the still preliminary level of the data. A primary goal of new research should be to extend the assessment of the program versions to additional participants to gather extra (necessary) data to determine the solidity of the results and thus the dependability (relative effectiveness) of those versions (Kennedy, 2005; Barlow et al., 2009). New research should also pursue an upgrading of the technology used to support those versions so as to make them more effective and more easily applicable (de Joode et al., 2012; De Joode et al., 2013; Robert et al., 2013). Another research point with important practical implications could be the investigation of staff, families, and participants' views about those program versions (e.g., about their likeableness, desirability and potential within daily contexts, and about possible ways of improving them; Callahan et al., 2008; Meiland et al., 2014; König et al., 2015).

References

Ambrose, C. T. (2012). Neuroangiogenesis: a vascular basis for Alzheimer's disease and cognitive decline during aging. *J. Alzheimers Dis.* 32, 773–788. doi: 10.3233/JAD-2012-120067

Astell, A. J., Ellis, M. P., Alm, N., Dye, R., and Gowans, G. (2010a). Stimulating people with dementia to reminisce using personal and generic photographs. *Int. J. Comput. Healthc.* 1, 177–198. doi: 10.1504/IJCIH.2010.037461

Astell, A. J., Ellis, M. P., Bernardi, L., Alm, N., Dye, R., Gowans, G., et al. (2010b). Using a touch screen computer to support relationships between people with dementia and caregivers. *Interact. Comput.* 22, 267–275. doi: 10.1016/j.intcom.2010.03.003

Barlow, D. H., Nock, M., and Hersen, M. (2009). *Single-Case Experimental Designs.* 3rd Edn. New York: Allyn and Bacon.

Bemelmans, R., Gelderblom, G. J., Jonker, P., and de Witte, L. (2012). Socially assistive robots in elderly care: a systematic review into effects and effectiveness. *J. Am. Med. Dir. Assoc.* 13, 114–120.e1. doi: 10.1016/j.jamda.2010.10.002

Berk, C., Paul, G., and Sabbagh, M. (2014). Investigational drugs in Alzheimer's disease: current progress. *Expert Opin. Investig. Drugs* 23, 837–846. doi: 10.1517/13543784.2014.905542

Bernick, C., Cummings, J., Raman, R., Sun, X., and Aisen, P. (2012). Age and rate of cognitive decline in Alzheimer disease: implications for clinical trials. *Arch. Neurol.* 69, 901–905. doi: 10.1001/archneurol.2011.3758

Bharwani, G., Parikh, P. J., Lawhorne, L. W., VanVlymen, E., and Bharwani, M. (2012). Individualized behavior management program for Alzheimer's/dementia residents using behavior-based ergonomic therapies. *Am. J. Alzheimers Dis. Other Demen.* 27, 188–195. doi: 10.1177/1533317512443869

Blake, M. (2013). Group reminiscence therapy for adults with dementia: a review. *Br. J. Community Nurs.* 18, 228–233. doi: 10.12968/bjcn.2013.18.5.228

Boller, B., Jennings, J. M., Dieudonné, B., Verny, M., and Ergis, A.-M. (2012). Recollection training and transfer effects in Alzheimer's disease: effectiveness of the repetition-lag procedure. *Brain Cogn.* 78, 169–177. doi: 10.1016/j.bandc.2011.10.011

Buettner, L. L., Yu, F., and Burgener, S. C. (2010). Evidence supporting technology-based interventions for people with early-stage Alzheimer's disease. *J. Gerontol. Nurs.* 36, 15–19. doi: 10.3928/00989134-20100831-01

Caffò, A. O., De Caro, M. F., Picucci, L., Notarnicola, A., Settanni, A., Livrea, P., et al. (2012). Reorientation deficits are associated with amnestic mild cognitive impairment. *Am. J. Alzheimers Dis. Other Demen.* 27, 321–330. doi: 10.1177/1533317512452035

Caffò, A. O., Hoogeveen, F., Groenendaal, M., Perilli, V., Damen, M., Stasolla, F., et al. (2014). Comparing two different orientation strategies for promoting indoor traveling in people with Alzheimer's disease. *Res. Dev. Disabil.* 35, 572–580. doi: 10.1016/j.ridd.2013.12.003

Callahan, K., Henson, R., and Cowan, A. K. (2008). Social validation of evidence-based practices in autism by parents, teachers and administrators. *J. Autism Dev. Disord.* 38, 678–692. doi: 10.1007/s10803-007-0434-9

Catania, A. C. (2012). *Learning.* 5th Edn. New York: Sloan.

Cavallo, M., Cavanna, A. E., Harciarek, M., Johnston, H., Ostacoli, L., and Angiletta, C. (2013). "Keep up the good work!": a case study of the effects of a specific cognitive training in Alzheimer's disease. *Neurocase* 19, 542–552. doi: 10.1080/13554794.2012.701643

Chiang, K.-J., Chu, H., Chang, H.-J., Chung, M.-H., Chen, C.-H., Chiou, H.-Y., et al. (2010). The effects of reminiscence therapy on psychological well-being, depression and loneliness among the institutionalized aged. *Int. J. Geriatr. Psychiatry* 25, 380–388. doi: 10.1002/gps.2350

Crete-Nishihata, M., Baecker, R. M., Massimi, M., Ptak, D., Campigotto, R., Kaufman, L. D., et al. (2012). Reconstructing the past: personal memory technologies are not just personal and not just for memory. *Hum. Comput. Interact.* 27, 93–123. doi: 10.1080/07370024.2012.656062

Dahlin, E., and Rydén, M. (2011). Assistive technology for persons with psychiatric disabilities: accessibility and cost-benefit. *Assist. Technol. Res. Ser.* 29, 294–299. doi: 10.3233/978-1-60750-814-4-294

Davis, M., Guyker, W., and Persky, I. (2012). Uniting veterans across distance through a telephone-based reminiscence group therapy intervention. *Psychol. Serv.* 9, 206–208. doi: 10.1037/a0026117

de Joode, E. A., van Boxtel, M. P. J., Verhey, F. R., and van Heugten, C. M. (2012). Use of assistive technology in cognitive rehabilitation: exploratory studies of the opinions and expectations of healthcare professionals and potential users. *Brain Inj.* 26, 1257–1266. doi: 10.3109/02699052.2012.667590

De Joode, E. A., Van Heugten, C. M., Verhey, F. R., and Van Boxtel, M. P. J. (2013). Effectiveness of an electronic cognitive aid in patients with acquired brain injury: a multicentre randomised parallel-group study. *Neuropsychol. Rehabil.* 23, 133–156. doi: 10.1080/09602011.2012.726632

De Leo, G., Brivio, E., and Sautter, S. (2011). Supporting autobiographical memory in patients with Alzheimer's disease using smart phones. *Appl. Neuropsychol.* 18, 69–76. doi: 10.1080/09084282.2011.545730

de Vries, K. (2013). Communicating with older people with dementia. *Nurs. Older People* 25, 30–37. doi: 10.7748/nop2013.05.25.4.30.e429

Ferrero-Arias, J., Goñi-Imízcoz, M., González-Bernal, J., Lara-Ortega, F., Da Silva-González, A., and Díez-Lopez, M. (2011). The efficacy of nonpharmacological treatment for dementia-related apathy. *Alzheimer Dis. Assoc. Disord.* 25, 213–219. doi: 10.1097/WAD.0b013e3182087dbc

Folstein, M., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Giordano, M., Dominguez, L. J., Vitrano, T., Curatolo, M., Ferlisi, A., Di Prima, A., et al. (2010). Combination of intensive cognitive rehabilitation and donepezil therapy in Alzheimer's disease (AD). *Arch. Gerontol. Geriatr.* 51, 245–249. doi: 10.1016/j.archger.2009.11.008

Godwin, K. M., Mills, W. L., Anderson, J. A., and Kunik, M. E. (2013). Technology-driven interventions for caregivers of persons with dementia: a systematic review. *Am. J. Alzheimers Dis. Other Demen.* 28, 216–222. doi: 10.1177/1533317513481091

Kazdin, A. E. (2001). *Behavior Modification in Applied Settings.* 6th Edn. New York: Wadsworth.

Kennedy, C. (2005). *Single Case Designs for Educational Research.* New York: Allyn and Bacon.

Kim, S.-Y., Yoo, E.-Y., Jung, M.-Y., Park, S.-H., and Park, J.-H. (2012). A systematic review of the effects of occupational therapy for persons with dementia: a meta-analysis of randomized controlled trials. *NeuroRehabilitation* 31, 107–115. doi: 10.3233/NRE-2012-0779

König, A., Crispim Junior, C. F., Derreumaux, A., Bensadoun, G., Petit, P. D., Bremond, F., et al. (2015). Validation of an automatic video monitoring system for the detection of instrumental activities of daily living in dementia patients. *J. Alzheimers Dis.* 44, 675–685. doi: 10.3233/JAD-141767

Kurz, A., and Grimmer, T. (2014). Efficay of memantine hydrochloride once-daily in Alzheimer's disease. *Expert Opin. Pharmacother.* 15, 1955–1960. doi: 10.1517/14656566.2014.945907

Kuwahara, N., Abe, S., Yasuda, K., and Kuwabara, K. (2006). "Networked reminiscence therapy for individuals with dementia by using photo and video sharing," in *Proceedings of the 8th International ACM SIGACCESS Conference on Computers and Accessibility (Assets '06)* (New York: ACM Press), 125–132.

Kuwahara, N., Yasuda, K., Tetsutani, N., and Morimoto, K. (2010). Remote assistance for people with dementia at home using reminiscence systems and a schedule prompter. *Int. J. Comput. Healthc.* 1, 126–143. doi: 10.1504/ijcih.2010.037458

Lancioni, G. E., Perilli, V., O'Reilly, M. F., Singh, N. N., Sigafoos, J., Bosco, A., et al. (2013a). Technology-based orientation programs to support indoor travel by persons with moderate Alzheimer's disease: impact assessment and social validation. *Res. Dev. Disabil.* 34, 286–293. doi: 10.1016/j.ridd.2012.08.016

Lancioni, G. E., Perilli, V., Singh, N. N., O'Reilly, M. F., Sigafoos, J., Cassano, G., et al. (2012). Technology-aided pictorial cues to support the performance of daily activities by persons with mild or moderate Alzheimer's disease. *Res. Dev. Disabil.* 33, 265–273. doi: 10.1016/j.ridd.2011.09.017

Lancioni, G. E., Singh, N. N., O'Reilly, M. F., Sigafoos, J., Ferlisi, G., Zullo, V., et al. (2014a). A computer-aided program for helping patients with moderate Alzheimer's disease engage in verbal reminiscence. *Res. Dev. Disabil.* 35, 3026–3033. doi: 10.1016/j.ridd.2014.07.047

Lancioni, G. E., Singh, N. N., O'Reilly, M. F., Sigafoos, J., Pangrazio, M. T., Megna, M., et al. (2009a). Persons with moderate Alzheimer's disease improve activities and mood via instruction technology. *Am. J. Alzheimers Dis. Other Demen.* 24, 246–257. doi: 10.1177/1533317509332627

Lancioni, G. E., Singh, N. N., O'Reilly, M. F., Sigafoos, J., Renna, C., Pinto, K., et al. (2014b). Persons with moderate Alzheimer's disease use simple technology aids to manage daily activities and leisure occupation. *Res. Dev. Disabil.* 35, 2117–2128. doi: 10.1016/j.ridd.2014.05.002

Lancioni, G. E., Singh, N. N., O'Reilly, M. F., Sigafoos, J., Renna, C., Ventrella, M., et al. (2013b). Supporting daily activities and indoor travel of persons with moderate Alzheimer's disease through standard technology resources. *Res. Dev. Disabil.* 34, 2351–2359. doi: 10.1016/j.ridd.2013.04.020

Lancioni, G. E., Singh, N. N., O'Reilly, M. F., Sigafoos, J., Tatulli, E., Rigante, V., et al. (2010). Technology-aided verbal instructions to help persons with mild or moderate Alzheimer's disease perform daily activities. *Res. Dev. Disabil.* 31, 1240–1250. doi: 10.1016/j.ridd.2010.07.021

Lancioni, G., Singh, N., O'Reilly, M., Zonno, N., Flora, A., Cassano, G., et al. (2009b). Persons with mild and moderate Alzheimer's disease use verbal-instruction technology to manage daily activities: effects on performance and mood. *Dev. Neurorehabil.* 12, 181–190. doi: 10.1080/17518420903029493

Lanza, C., Knörzer, O., Weber, M., and Riepe, M. W. (2014). Autonomous spatial orientation in patients with mild to moderate Alzheimer's disease by using mobile assistive devices: a pilot study. *J. Alzheimers Dis.* 42, 879–884. doi: 10.3233/JAD-140063

Lazar, A., Thompson, H., and Demiris, G. (2014). A systematic review of the use of technology for reminiscence therapy. *Health Educ. Behav.* 41, 51S–61S. doi: 10.1177/1090198114537067

Lundberg, S. (2014). The results from a two-year case study of an information and communication technology support system for family caregivers. *Disabil. Rehabil. Assist. Technol.* 9, 353–358. doi: 10.3109/17483107.2013.814170

Meiland, F. J. M., Hattink, B. J. J., Overmars-Marx, T., de Boer, M. E., Jedlitschka, A., Ebben, P. W. G., et al. (2014). Participation of end users in the design of assistive technology for people with mild to severe cognitive problems: the European Rosetta project. *Int. Psychogeriatr.* 26, 769–779. doi: 10.1017/s1041610214000088

Melrose, R. J., Ettenhofer, M. L., Harwood, D., Achamallah, N., Campa, O., Mandelkern, M., et al. (2011). Cerebral metabolism, cognition and functional abilities in Alzheimer disease. *J. Geriatr. Psychiatry Neurol.* 24, 127–134. doi: 10.1177/0891988711405333

Noguchi, D., Kawano, Y., and Yamanaka, K. (2013). Care staff training in residential homes for managing behavioural and psychological symptoms of dementia based on differential reinforcement procedures of applied behaviour analysis: a process research. *Psychogeriatrics* 13, 108–117. doi: 10.1111/psyg.12006

Perilli, V., Lancioni, G. E., Hoogeveen, F., Caffò, A. O., Singh, N. N., O'Reilly, M. F., et al. (2013). Video prompting versus other instruction strategies for persons with Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen.* 28, 393–402. doi: 10.1177/1533317513488913

Perri, R., Monaco, M., Fadda, L., Caltagirone, C., and Carlesimo, G. A. (2014). Neuropsychological correlates of behavioral symptoms in Alzheimer's disease, frontal variant of frontotemporal, subcortical vascular and Lewy body dementias: a comparative study. *J. Alzheimers Dis.* 39, 669–677. doi: 10.3233/JAD-131337

Pierce, W. D., and Cheney, C. D. (2008). *Behavior Analysis and Learning.* 4th Edn. New York: Psychology Press.

Robert, P. H., Konig, A., Andrieu, S., Bremond, F., Chemin, I., Chung, P. C., et al. (2013). Recommendations for ICT use in Alzheimer's disease assessment: Monaco CTAD expert meeting. *J. Nutr. Health Aging* 17, 653–660. doi: 10.1007/s12603-013-0046-3

Schecker, M., Pirnay-Dummer, P., Schmidtke, K., Hentrich-Hesse, T., and Borchardt, D. (2013). Cognitive interventions in mild Alzheimer's disease: a therapy-evaluation study on the interaction of medication and cognitive treatment. *Dement. Geriatr. Cogn. Dis. Extra* 3, 301–311. doi: 10.1159/000354190

Serrani Azcurra, D. J. (2012). A reminiscence program intervention to improve the quality of life of long-term care residents with Alzheimer's disease: a randomized controlled trial. *Rev. Bras. Psiquiatr.* 34, 422–433. doi: 10.1016/j.rbp.2012.05.008

Sikkes, S. A., Pijnenburg, Y. A., Knol, D. L., de Lange-de Klerk, E. S., Scheltens, P., and Uitdehaag, B. M. (2013). Assessment of instrumental activities of daily living in dementia: diagnostic value of the Amsterdam instrumental activities of daily living questionnaire. *J. Geriatr. Psychiatry Neurol.* 26, 244–250. doi: 10.1177/0891988713509139

Singh, N. N., Lancioni, G. E., Sigafoos, J., O'Reilly, M. F., and Winton, A. S. W. (2014). "Assistive technology for people with Alzheimer's disease," in *Assistive Technologies for People with Diverse Abilities*, eds G. E. Lancioni and N. N. Singh (New York: Springer), 219–250.

Soto, M. E., Secher, M., Gillette-Guyonnet, S., Abellan van Kan, G., Andrieu, S., Nourhashemi, F., et al. (2012). Weight loss and rapid cognitive decline in community-dwelling patients with Alzheimer's disease. *J. Alzheimers Dis.* 28, 647–654. doi: 10.3233/JAD-2011-110713

Spalletta, G., Calatagirone, C., Girardi, P., Gianni, W., Casini, A. R., and Palmer, K. (2012). The role of persistent and incident major depression on rate of cognitive deterioration in newly diagnosed Alzheimer's disease patients. *Psychiatry Res.* 198, 263–268. doi: 10.1016/j.psychres.2011.11.018

Subramaniam, P., and Woods, B. (2012). The impact of individual reminiscence therapy for people with dementia: systematic review. *Expert Rev. Neurother.* 12, 545–555. doi: 10.1586/ern.12.35

Tifratene, K., Sakarovitch, C., Rouis, A., Pradier, C., and Robert, P. (2014). Mild cognitive impairment and anti-Alzheimer disease medication: a cross sectional study of the French National Alzheimer Databank (BNA). *J. Alzheimers Dis.* 38, 541–549. doi: 10.3233/JAD-131103

Van Bogaert, P., Van Grinsven, R., Tolson, D., Wouters, K., Engelborghs, S., and Van der Mussele, S. (2013). Effects of SolCos model-based individual reminiscence in older adults with mild to moderate dementia due to Alzheimer disease: a pilot study. *J. Am. Med. Dir. Assoc.* 14, 528.e9–528.e13. doi: 10.1016/j.jamda.2013.01.020

Wilson, R. S., Segawa, E., Boyle, P. A., Anagnos, S. E., Hizel, L. P., and Bennett, D. A. (2012). The natural history of cognitive decline in Alzheimer's disease. *Psychol. Aging* 27, 1008–1017. doi: 10.1037/a0029857

Wingbermuehle, C., Bryer, D., Berg-Weger, M., Tumosa, N., McGillick, J., Rodriguez, C., et al. (2014). Baseball reminiscence league: a model for supporting persons with dementia. *J. Am. Med. Dir. Assoc.* 15, 85–89. doi: 10.1016/j.jamda.2013.11.006

Woods, R. T., Bruce, E., Edwards, R. T., Elvish, R., Hoare, Z., Hounsome, B., et al. (2012). REMCARE: reminiscence groups for people with dementia and their family caregivers–effectiveness and cost-effectiveness pragmatic multicentre randomised trial. *Health Technol. Assess.* 16, v–xv, 1–116. doi: 10.3310/hta16480

Woods, R. T., Bruce, E., Edwards, R. T., Hounsome, B., Keady, J., Moniz-Cook, E. D., et al. (2009). Reminiscence groups for people with dementia and their family carers: pragmatic eight-center randomised trial of joint reminiscence and maintenance versus usual treatment: a protocol. *Trials* 10:64. doi: 10.1186/1745-6215-10-64

Yamagami, T., Takayama, Y., Maki, Y., and Yamaguchi, H. (2012). A randomized controlled trial of brain-activating rehabilitation for elderly participants with dementia in residential care homes. *Dement. Geriatr. Cogn. Dis. Extra* 2, 372–380. doi: 10.1159/000342614

Yasuda, K., Kuwahara, N., and Morimoto, K. (2009). Remote reminiscence talking and scheduling prompter for individuals with dementia using video phone. *Univer. Access Hum. Comput. Interact. Addressing Divers. Lect. Notes Comput. Sci.* 5614, 429–438. doi: 10.1007/978-3-642-02707-9_49

Zannino, G. D., Perri, R., Salamone, G., Di Lorenzo, C., Caltagirone, C., and Carlesimo, G. A. (2010). Manipulating color and other visual information influences picture naming at different levels of processing: evidence from Alzheimer subjects and normal controls. *Neuropsychologia* 48, 2571–2578. doi: 10.1016/j.neuropsychologia.2010.05.003

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 03 September 2015
doi: 10.3389/fnagi.2015.00133

Social robots in advanced dementia

Meritxell Valentí Soler [1], Luis Agüera-Ortiz [1,2], Javier Olazarán Rodríguez [1,3], Carolina Mendoza Rebolledo [4], Almudena Pérez Muñoz [4], Irene Rodríguez Pérez [4], Emma Osa Ruiz [4], Ana Barrios Sánchez [4], Vanesa Herrero Cano [4], Laura Carrasco Chillón [4], Silvia Felipe Ruiz [4], Jorge López Alvarez [1], Beatriz León Salas [1], José M. Cañas Plaza [5], Francisco Martín Rico [5], Gonzalo Abella Dago [5] and Pablo Martínez Martín [6,7]*

[1] Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofía Foundation, Madrid, Spain, [2] CIBERSAM-Carlos III Institute of Health Madrid, Madrid, Spain, [3] Maria Wolff Foundation, Madrid, Spain, [4] Health Care Area, Alzheimer Center Reina Sofía Foundation, Madrid, Spain, [5] RoboticsLab, Rey Juan Carlos University, Madrid, Spain, [6] CIBERNED-Carlos III Institute of Health, Madrid, Spain, [7] Applied Research Area, National Center of Epidemiology, Carlos III Institute of Health, Madrid, Spain

Edited by:
Philippe Robert, University of Nice Sophia Antipolis, France

Reviewed by:
Valeria Manera, University of Nice Sophia Antipolis, France
Philippe Robert, University of Nice Sophia Antipolis, France
Jérémy Bourgeois, Université Nice Sophia Antipolis, France

****Correspondence:***
Meritxell Valentí Soler, CIEN Foundation, Calle Valderrebollo, 5 Valderrebollo Street, 28031 Madrid, Spain
merivalenti@gmail.com

Received: *23 February 2015*
Accepted: *29 June 2015*
Published: *03 September 2015*

Citation:
Valentí Soler M, Agüera-Ortiz L, Olazarán Rodríguez J, Mendoza Rebolledo C, Pérez Muñoz A, Rodríguez Pérez I, Osa Ruiz E, Barrios Sánchez A, Herrero Cano V, Carrasco Chillón L, Felipe Ruiz S, López Alvarez J, León Salas B, Cañas Plaza JM, Martín Rico F, Abella Dago G and Martínez Martín P (2015) Social robots in advanced dementia. Front. Aging Neurosci. 7:133. doi: 10.3389/fnagi.2015.00133

Aims: Pilot studies applying a humanoid robot (NAO), a pet robot (PARO) and a real animal (DOG) in therapy sessions of patients with dementia in a nursing home and a day care center.

Methods: In the nursing home, patients were assigned by living units, based on dementia severity, to one of the three parallel therapeutic arms to compare: CONTROL, PARO and NAO (Phase 1) and CONTROL, PARO, and DOG (Phase 2). In the day care center, all patients received therapy with NAO (Phase 1) and PARO (Phase 2). Therapy sessions were held 2 days per week during 3 months. Evaluation, at baseline and follow-up, was carried out by blind raters using: the Global Deterioration Scale (GDS), the Severe Mini Mental State Examination (sMMSE), the Mini Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI), the Apathy Scale for Institutionalized Patients with Dementia Nursing Home version (APADEM-NH), the Apathy Inventory (AI) and the Quality of Life Scale (QUALID). Statistical analysis included descriptive statistics and non-parametric tests performed by a blinded investigator.

Results: In the nursing home, 101 patients (Phase 1) and 110 patients (Phase 2) were included. There were no significant differences at baseline. The relevant changes at follow-up were: (Phase 1) patients in the robot groups showed an improvement in apathy; patients in NAO group showed a decline in cognition as measured by the MMSE scores, but not the sMMSE; the robot groups showed no significant changes between them; (Phase 2) QUALID scores increased in the PARO group. In the day care center, 20 patients (Phase 1) and 17 patients (Phase 2) were included. The main findings were: (Phase 1) improvement in the NPI irritability and the NPI total score; (Phase 2) no differences were observed at follow-up.

Keywords: dementia, Alzheimer disease, therapy, robotics, human-robot interaction, technology, animal assisted therapy, apathy

Introduction

Dementia, including Alzheimer's disease, is expected to affect to 75.62 million people by 2030 and 135.46 million by 2050. The prevention and treatment of secondary causes of dementia (hypothyroidism, vitamin B12 deficiency, Lyme disease, neurosyphillis...) and the control of risk factors (smoking, underactivity, obesity, hypertension, diabetes, lack of education...) may decrease the incidence (Prince et al., 2013). Research focused on finding a cure for dementia is key, but in the meantime, we must bear in mind that patients with dementia need the most appropriate treatment. New drugs and non-pharmacological treatments are currently being researched.

Animal-assisted therapy (AAT), the use of animals in therapy sessions, is one such non-pharmacological tool currently under investigation. The Cochrane Database of Systematic Reviews published a protocol to study "AAT for people with serious mental illness" (Downes et al., 2013). In 2006, the British National Institute for Health and Clinical Excellence (NICE) published guidelines for people with dementia (Fairbairn, 2006) and included AAT as an approach that may be considered a non-pharmacological intervention for non-cognitive symptoms and behavior. AAT seems to calm agitated behavior and has positive effects on the quality of social interaction and mood disturbances, although no effect was observed on cognitive performance (Bernabei et al., 2013).The presence of an animal involves an increase in the frequency and duration of visual contact and smiles. Interaction with a real animal, rather than a stuffed one, increases the frequency of verbalization. Studies have shown a decrease in verbal aggression and agitation with reduced behavior problems, although the need for drug treatment was not changed. However, it has been observed that agitation increases when therapy with animals was withdrawn. The effect of animal therapy was independent of the severity of the dementia (Filan and Llewellyn-Jones, 2006).

However, AAT is not always possible. Animals are often not allowed in nursing homes or day care centers, due to the risk of injury to patients, staff or visitors, the possibility of allergic reactions, and the potential nuisance of cleaning up after the animals. Patients or staff may have undesired reactions to animals, both negative (i.e., Fear) and overly positive (i.e., becoming too attached). Aggressive patients could frighten or harm the animals. And the cost of animal care (space, time and money) might exceed the benefits of a few hours of therapy per day.

Thus, the alternative of replacing real animals with animal-shaped objects became an object of investigation (Nakajima et al., 2001). In recent years, social robots have been also used as reasonable substitutes for animals in therapy for people suffering from dementia (Wada et al., 2008; Shibata, 2012).

Robots have less needs for space, time, or care. Their sensors can respond to environmental changes (movements, sounds...) simulating interaction with the patient. They can monitor patients or be used in the therapy. Other potential benefits of therapy with robots are that there are no known adverse effects, specially trained personnel are not required and they can repeat the script in the same way as many times as it is required.

In 2009, a systematic review examining the literature on the effects of assistive social robots in health care for the elderly, especially in the role of providing companions for patients, was published (Broekens et al., 2009). The main conclusions were that most of the elderly people liked the robots and the robots can improve: health (by lowering levels of stress and increasing immune system response), mood (decreasing feelings of loneliness) and communication (increasing it). Moreover, the robots lessened the severity of dementia as measured by specific scales in some studies.

Bemelmans et al reviewed the literature in 2012 and found that the most of the studies reported positive effects of companion-type robots on (socio) psychological (e.g., mood, loneliness, and social connections and communication) and physiological (e.g., stress reduction) parameters (Bemelmans et al., 2012).

In the present study, animals and robots were added into the therapy sessions at a center for dementia patients. They were employed just as any other tool the therapists might use, in order to discover the potential effect of the tool without changes in the therapists' actions, the session content or the environment of the patients.

Objective

Pilot studies were carried out in order to test the effect of introducing a humanoid robot (NAO), a pet robot (PARO) and a real trained animal (DOG) in the therapeutic sessions for patients with dementia in relation to behavior changes, apathy and quality of life.

In a nursing home, where institutionalized patients with dementia are living in controlled conditions, the objective was to compare the effects of therapy sessions involving:

- (Phase 1) a humanoid robot (NAO), who is able to use oral language (phrases previously recorded) and move like a human; an animal-shaped robot (PARO), who does not use oral language but sounds and moves like an animal; and with conventional therapy (CONTROL).
- (Phase 2) a trained dog (DOG); an animal-shaped robot (PARO), who has been used as reasonable substitute for animals in therapy for people suffering from dementia; and with conventional therapy (CONTROL).

In a day care center, where dementia patients attend for 8 h a day approximately, the objective was to compare the baseline with the follow-up effects of therapy sessions involving the robots:

- (Phase 1) NAO and
- (Phase 2) PARO.

Materials and Methods

Patients

All dementia patients being cared for at the Alzheimer Center Reina Sofía Foundation (ACRSF) (Olazarán et al., 2012), a public nursing home and day care center, were invited to participate. All the participants, and their legal guardians or families, received information and signed an informed consent form approved by the CIEN Foundation Ethical Committee. Inclusion criteria were a diagnosis of neurodegenerative dementia, being cared for at ACRSF and possessing a signed consent form. Exclusion criteria were: fear of the robot or dog and severe acute illness (requiring hospitalization or intensive medical care).

Therapeutic Tools

The robots used in this study were:

PARO

A social robot with the appearance, movement and sounds of a baby seal. It has programmable behavior and sensors for posture, touch, sound, and light. Its eyes, which are big, black and with long eyelashes, can open and close; it can also move its neck (laterally and up-and-down), anterior flippers and tail. Although its movements are silent, it emits short and sharp squeals like a real seal. It is very soft and white in color, with hard Velcro covering the access to the mechanism (so it is not easy to access it during therapy sessions). It cannot move forward or change its sounds and weighs 2.7 kg.

NAO

A white humanoid robot, measuring 58 cm tall and weighing 4.3 kg. It has sensors for movement, touch, sonar, sound, and vision. It can talk and sing. It has a robotic voice, but it is possible to replace it with mp3 recordings of a child-like human voice that is easier for patients to understand. It can move its neck and arms, walk, or dance. Software was developed to allow the robot to act out a script for therapy sessions. These scripts included effects like speech, music and movements. During the therapy session, the therapist could control the activation of and progression through the script using remote control software installed in an Android device. The therapists were able to pause the script, repeat sections of it, or jump to another section. It was also possible to use this software to remotely operate the robot in order to make it walk or move its head (Martin et al., 2013).

The animals used were dogs: two adult black Labrador Retrievers. Both had received prior training for therapy. Each dog participated in half of the sessions with each group. The therapists received training prior to the sessions on the use of animals, and the animals were allowed to adapt to the Center before beginning the research activities. Therapists specially trained to work with animals attended all the sessions with the dogs, in order to monitor the course of therapy.

Otherwise, the tools used in the control group were the same as in the other two groups. It was necessary to adapt certain tools used in the sessions for its use with the robots and the dogs: specially designed vests with pockets and Velcro were produced, and flash cards were laminated.

Design

Nursing Home

A controlled clinical trial of parallel groups, randomized by blocks (living units) and stratified by dementia severity, comparing therapy with robots and dogs against standard care was carried out.

One hundred fifty six patients with dementia reside in the ACRSF nursing home. All patients receive similar care, in terms of: medical and custodial care, non-pharmacological therapy and personalized nutrition, therapy programming, and physical exercise. They live in similarly designed floors, with natural lighting and large spaces tailored to their needs. Residents live on different floors or living units depending on the severity of their dementia. The floors with patients of similar severity were grouped by threes: three floors of patients with mild-moderate dementia, three floors of patients with moderate-severe dementia, and three floors of patients with severe dementia. For each dementia severity group, each floor was randomly assigned to one of the three therapies (randomization by blocks). All the environmental conditions were controlled for, so that the specific tool used by the therapist in the sessions was the only difference in the sessions experienced by the different therapy groups.

The study had 2 year-long phases, carried out during two consecutive years (2012 and 2013), comparing two different modalities of experimental therapies to each other and to standard care. The therapies compared were:

- Phase 1: CONTROL, NAO (humanoid social robot), PARO (animal-esque social robot).
- Phase 2: CONTROL, PARO (animal-esque robot), DOG (real animal).

All the patients included were assigned to only one of the three therapeutic groups, worked with only one tool (Control, PARO, NAO, or DOG) and were evaluated before and after the study sessions. Randomization was performed before the baseline evaluations using a six-sided die.

Day Care Center

Forty people are cared for at the ACRSF day care center. A pretest-posttest design was used, due to the small number of participants and the inability to control the differences between their medical and nursing care, routines and nutrition. All patients participated in sessions with only one of the therapeutic tools: NAO in the first phase and PARO in the second. Patients were divided by the therapists in two therapeutic groups according to dementia severity: mild-moderate dementia and moderate-severe dementia.

Therapy

The therapy sessions were performed 2 days a week during 3 months.

All therapeutic sessions were conducted by the same therapist, with the same structure as the other therapeutic programs, at the same time of day and for the same duration of time (30–40 min).

The therapists were certified occupational and physical therapists, and neuropsychologists employed by the ACRSF. They received instructions on the implementation and possible uses of robots and animals as they had no previous expertise in this area. The animal therapists and robot engineers did not participate in the therapy; they only monitored the session from one side of the room, out of the patients' view. Session guides were written and followed in every session.

The therapists used the same model of standard therapy, introducing the experimental tools as one more element of the therapy. It is important to note that the object of investigation was the effect of the specific tools, not the effect of the therapy itself, so the tools had to be used for the same purpose and in the same way in the three therapeutic groups if possible. Only one robot or dog was used in every session.

The patient interacted with the robots, the animals and the therapists to perform several therapeutic activities, including: identifying numbers, words, and colors using flash cards; practicing the use of everyday objects such as combs; sensory stimulation exercises using different textured fabrics. . .

The robots and the animals were wearing specially designed vests with pockets and Velcro, in order to carry the objects used in the sessions, and move from patient to patient.

All sessions had the same overall structure: greeting the group, introduction, therapeutic exercises (cognitive or physical therapy) and ending.

The introduction included the presentation of the target tool, orientation activities (spatial, temporal, and personal orientation), and motivation to participate in the therapy session.

Therapeutic exercises were small units of activities, focused on the stimulation of memory, language, calculation, movement, praxis, and the use of the different senses. Activities involved physical exercises, questions and answers, music, videos, and manipulation or touching several objects. Between the exercises, there were brief pauses to encourage the collaboration and participation of all users.

At the end of the session, the therapists reviewed what the group did with everyone, asked whether or not they liked participating in the sessions, and lead the group in a farewell song.

Group sessions were employed for patients with mild or mild-moderate dementia, and individual sessions were used with patients with moderate-severe and severe dementia. The group sessions were conducted with 9–15 participants seated in a circle with the therapist and the tools in the inside, moving from patient to patient. In the individual sessions, the therapist was sitting in front of the patient, at the same level, providing stimuli one by one.

Sessions with four levels of difficulty were designed:

1. Mild difficulty level (performed with patients from the day care center). An extensive cognitive session was designed, and the therapist selected a different part of the session each day to avoid repetitiveness and the participants' boredom. The physical therapy session consisted of a complete set of exercises involving head, neck and upper and lower limbs. The robot was programmed to move faster, given the better physical condition of the majority of the patients from the day care center.
2. Mild-moderate level of difficulty. Three sessions were designed: therapy with music, cognitive therapy and physical therapy.
3. Moderate-severe difficulty level. Two sessions were designed: cognitive therapy and physical therapy.
4. Severe difficulty level. One session was designed using language stimulation, music, passive movement and sensory stimuli.

All therapy sessions were recorded on video for *post-hoc* observational analysis. Two cameras with tripods were used and were placed outside the circle formed by the patients. There were several recording sessions previous to the start of the study to get the patients and therapists used to its presence, thereby reducing the Hawthorne effect.

Assessments

Evaluation was carried out by blinded raters at baseline and follow-up using the following validated scales:

- The Global Deterioration Scale (GDS) (Reisberg et al., 1982), which was given by a neurologist,
- The Severe Mini Mental State Examination (sMMSE) (Harrell et al., 2000; Buiza et al., 2011) and the Mini Mental State Examination (MMSE) (Folstein et al., 1975; Lobo et al., 1999), which were given by a neuropsychologist,
- The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994; Vilalta-Franch et al., 1999; Boada et al., 2005), the Apathy Scale for Institutionalized Patients with Dementia Nursing Home version (APADEM-NH) (Agüera-Ortiz et al., 2015), which was used with patients in the nursing home only, and the Apathy Inventory (AI) (Robert et al., 2002), which was used with patients from the day care center only, and was given by a psychiatrist,
- And the Quality of Life in Late-stage Dementia (QUALID) (Weiner et al., 2000; Garre-Olmo et al., 2010), which was given by a sociologist.

When the evaluations required interviewing the nursing staff about patient functioning, the raters interviewed the same staff members for each patient at baseline and follow up whenever possible.

Medical information was also collected for subsequent analysis. The wash-out period between phases was 9 months long.

Data Analysis

Statistical analysis, apart from descriptive statistics, included the Wilcoxon, Mann-Whitney and Kruskal-Wallis tests for comparisons, performed by a blinded researcher. Non-parametric tests were used as the data did not meet the assumptions for use of parametric statistics. The statistical analysis was done using Stata software (Stata©. Stata Corp., College Station, Texas, USA version: 15).

Results

All patients, families and legal guardians received written information and informational meetings were organized.

One hundred and forty eight people signed the informed consent forms. Before the first evaluation, 22 participants died, two people moved to another center and one person withdrew consent.

In the first experimental phase, two people suffered acute illnesses and did not complete the treatment. During the wash out period, 31 additional people signed the consent forms, 12 patients died, nine people moved to other centers and one person withdrew consent.

In the second experimental phase, three people did not complete the treatment due to illnesses or absences from ACRSF (**Figure 1**).

Nursing Home

Phase 1

In the first phase, 101 patients with moderate/severe dementia (GDS 4: 2%, GDS 5: 17%, GDS 6: 44% and GDS 7:37%), mean age 84.68 years old (range: 58–100 years), 88% of which were women, were included.

Dementia diagnosis was: 84.2% Alzheimer disease, 10.9% mixed dementia, 3% Parkinson's disease dementia, 1% dementia with Lewy bodies, 1% Frontotemporal dementia.

There were 38 people in the CONTROL group, 33 in the PARO group and 30 in the NAO group. Evaluation showed no significant differences between groups at baseline.

All groups showed a statistically significant increase in GDS scores, indicating a decreased functional level (Fisher's exact < 0.000) at follow-up.

Scores on QUALID, sMMSE, and NPI (total score) showed no statistically significant changes between groups at follow-up (**Figure 2**).

In contrast, statistically significant differences were found after treatment in MMSE scores (a significant decrease in the NAO group), APADEM-NH scores (both the PARO and the NAO groups had significant decreases in total score, and the NAO group in cognitive inertia score), and several NPI items: delusions (a significant increase in the NAO group), apathy (a significant decrease in the NAO group) and irritability/lability (a significant increase in the PARO group) (**Figures 3**, **4** and **Table 1**).

There were no statistically significant differences between the NAO and PARO groups.

Phase 2

In the second phase, 110 patients with moderate/ severe dementia (GDS 5: 22%, GDS 6: 30%, and GDS 7: 48%), mean age 84.7

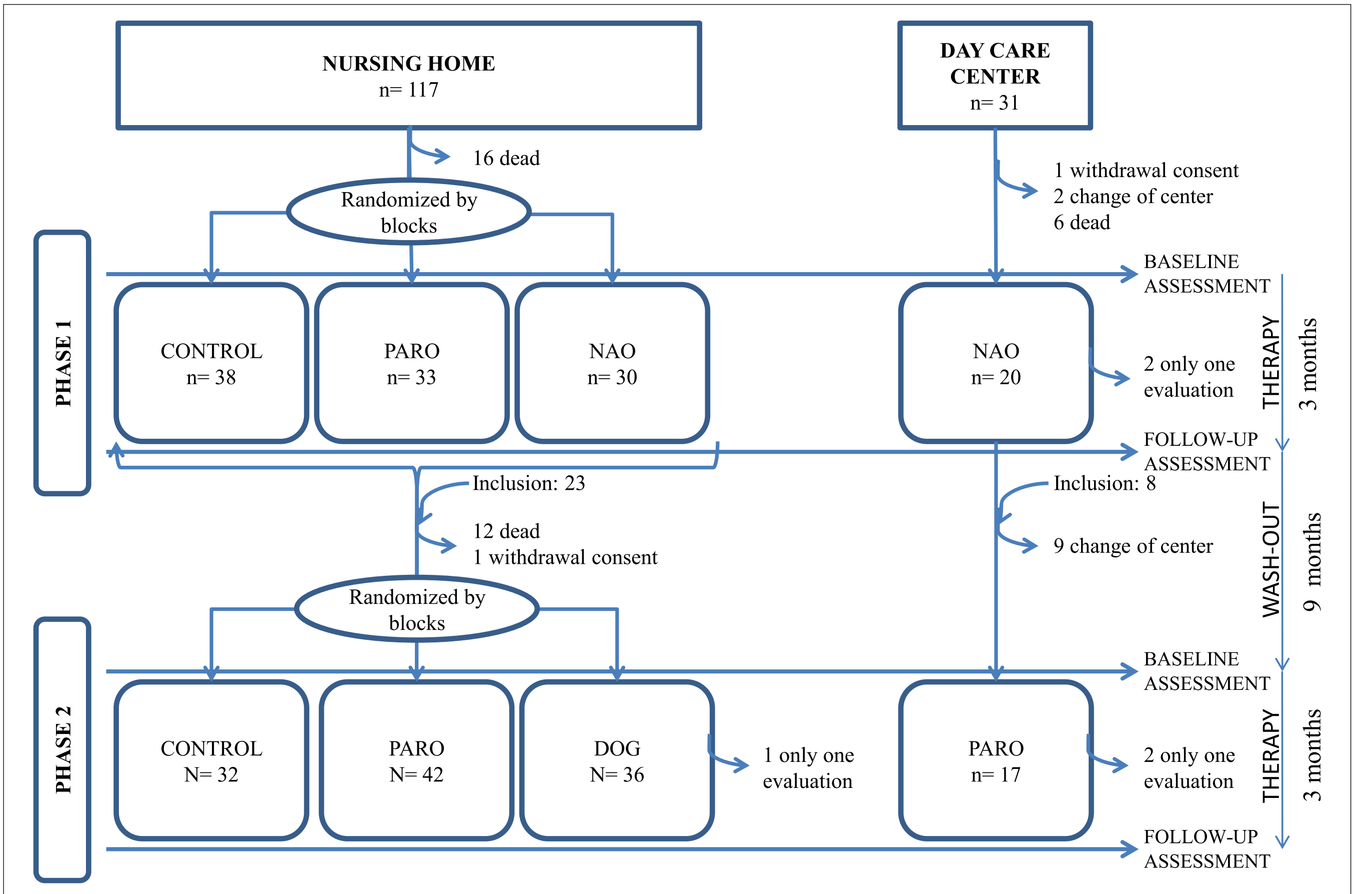

FIGURE 1 | All patients whose families/guardians gave consent and who fit inclusion/exclusion criteria were included. Therapy sessions: each group worked only with a tool (conventional, PARO, NAO, or DOG) in the nursing home; in the day care center all participants worked with NAO in the first phase, and PARO in the second. Assessments were realized before and after the study sessions. The wash-out period allowed the entry of new participants. Randomization was carried out before the study sessions only in the nursing home.

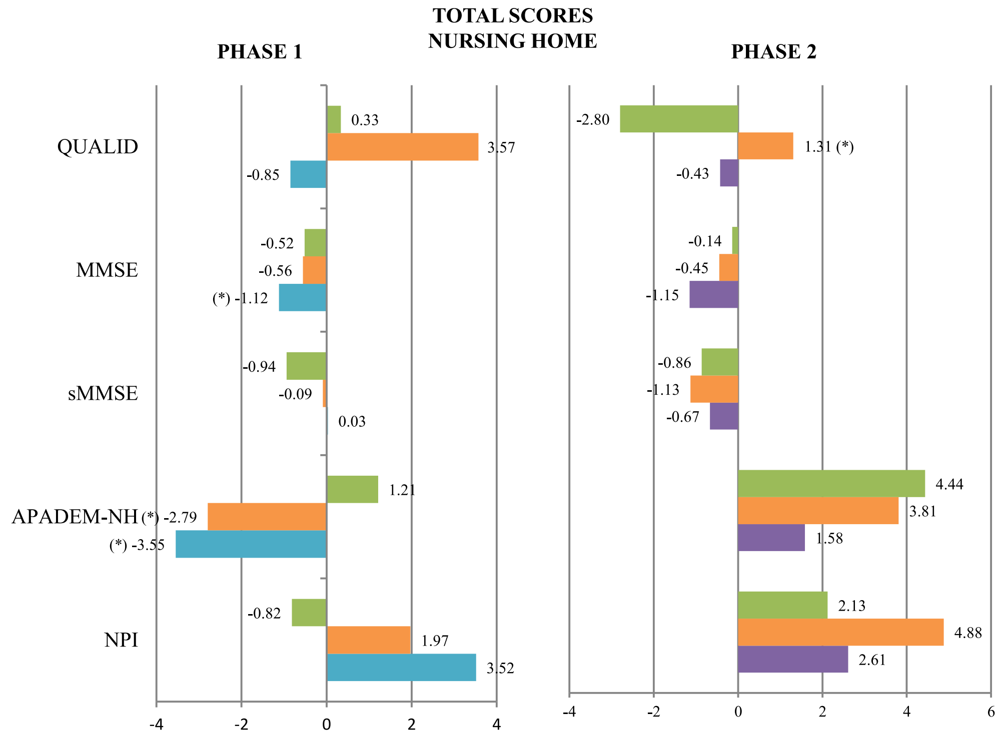

FIGURE 2 | Mean change at follow-up evaluation in the QUALID, MMSE, sMMSE, APADEM-NH, and NPI scores in the three patients groups of Phase 1 and Phase 2. CONTROL (green), PARO (orange), NAO (blue), and DOG (purple) (*): Statistically significant differences between the groups at follow-up were observed. *P* not corrected <0.05. The scales are represented on the vertical axis and the mean change in the units of measure of each scale is represented on the horizontal axis.

years old (range: 59–101 years), 90% of which were women, were included.

Dementia diagnosis was: 88.2% Alzheimer disease, 7.3% mixed dementia, 3.6% Parkinson's disease dementia, 1.8% dementia with Lewy bodies, 0.9% Frontotemporal dementia.

There were 32 people in the CONTROL group, 42 in the PARO group and 36 in the DOG group. Evaluation showed no significant differences between groups at baseline, except on the NPI irritability item (CONTROL group: 3.78 ± 3.3; PARO group: 2.14 ± 3.05; DOG group: 2.13 ± 3.28; $p = 0.0215$).

All groups showed a statistically significant increase in GDS scores, indicating a decreased functional level (Fisher's exact < 0.000) at follow-up.

There were no statistically significant differences in MMSE, sMMSE, APADEM-NH, and Total NPI scores between groups at follow-up (**Figure 2**).

On the contrary, statistically significant differences were found after treatment in QUALID scores (a significant increase in the PARO group), and several NPI items: hallucinations and irritability/lability (a significant increase in the PARO and the DOG groups vs. the CONTROL group than decreases), disinhibition (a significant increase in the PARO group vs. the DOG group) and night-time behavior disturbances (a significant decrease in the PARO group vs. the DOG group) (**Figure 4** and **Table 1**).

Day Care Center

Phase 1

In phase 1, 20 patients with moderate/severe dementia, mean age 77.9 years (range: 68–87), 50% women, were included.

Dementia diagnosis was: 75% Alzheimer disease, 15% mixed dementia, 5% Parkinson's disease dementia, 5% dementia with Lewy bodies.

After the sessions with NAO, follow-up evaluation showed: an increase in GDS scores (changes from baseline to follow-up: GDS 3:15–10%; GDS 4: 5% (no change); GDS 5: 40–30%; GDS 6: 25–30%; GDS 7: 15–25%). There were no statistically significant changes in sMMSE and MMSE scores.

Significant decrease was seen in: NPI-irritability/lability scores and total NPI scores (**Figure 5** and **Table 1**).

Phase 2

In the second phase, 17 patients with moderate/ severe dementia, mean age 79 years (range: 69–87), 58.8% women, were included.

Dementia diagnosis was: 82.4% Alzheimer disease and 17.6% mixed dementia.

At follow-up, after sessions with PARO: GDS scores increased (GDS 4:5.88–0%; GDS 5: 41.18% (no change); GDS 6: 35.29–29.4%; GDS 7: 17.65–29.4%). There were no statistically significant changes in sMMSE and MMSE scores, or in any other variable (**Figure 5**).

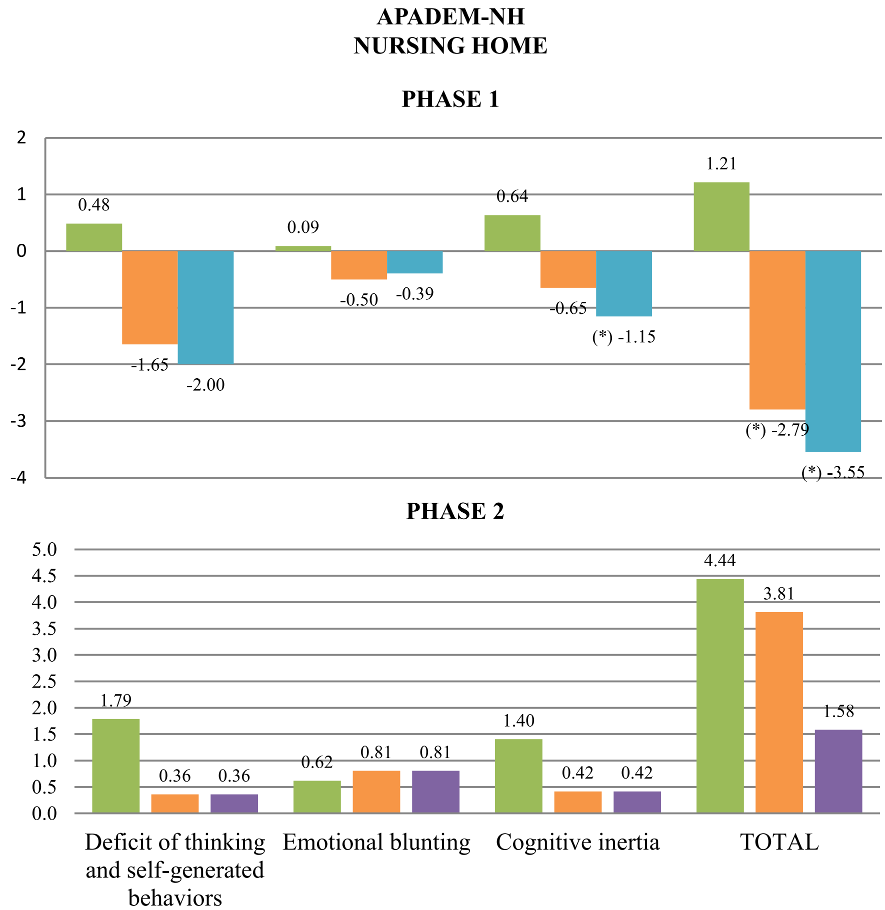

FIGURE 3 | Mean change at follow-up in APADEM-NH scores, by item and total, for the three patients groups of Phase 1 and Phase 2. CONTROL (green), PARO (orange), NAO (blue), and DOG (purple) (*): Statistically significant differences between the groups at follow-up were observed. *P* not corrected <0.05. The scales are represented on the horizontal axis and the mean change in the units of measure of each scale is represented on the vertical axis.

Discussion

To our knowledge, this is the first study, in one single center, where an animal-esque robot, a humanoid robot and trained therapy dogs were compared as potential tools for therapy for people with dementia. These new tools were the only change introduced to the patients by the intervention, because changes in personnel and environment were carefully controlled for limiting the effect of possible confounding effects.

In order to control for environmental factors, the regular therapists performed the sessions, rather than new therapists trained in the use of robots or dogs who would be unfamiliar to the patients. However, while there are therapists who specialize in animal therapy, there are currently no therapists who specialize in therapy using robots. Additionally, while the application of animal-esque robots in therapy targeted toward people with dementia has been documented, to our knowledge this is the first time that the NAO robot has been used for this purpose. Therefore, although some more training in AAT might have improved the results, it might have also introduced a bias in favor of the dog, because there is greater body of knowledge and more training materials concerning AAT than robot assisted therapy.

The measures used were internationally validated scales which have proven to be sensitive and specific measures of the target symptoms. All evaluations were performed by professionals trained in the use of the measures. The changes observed after the introduction of these new tools affected all of the investigated variables:

Quality of life (QoL), measured with the QUALID scale, was only studied in the nursing home groups. In the first phase no changes were observed, but in the second one, the group of patients who worked with the conventional therapy showed improvement, while the group who worked with the animal robot slightly worsened. In 2009 Tapus et al. proposed a customized protocol for the use of social auxiliary robots as tools to improve the QoL of people with dementia, through motivation, encouragement, and companionship for users suffering from cognitive changes related to aging and/or Alzheimer's disease (Tapus, 2009). A social robot, AIBO, was used for 7 weeks with community-residing and institutionalized

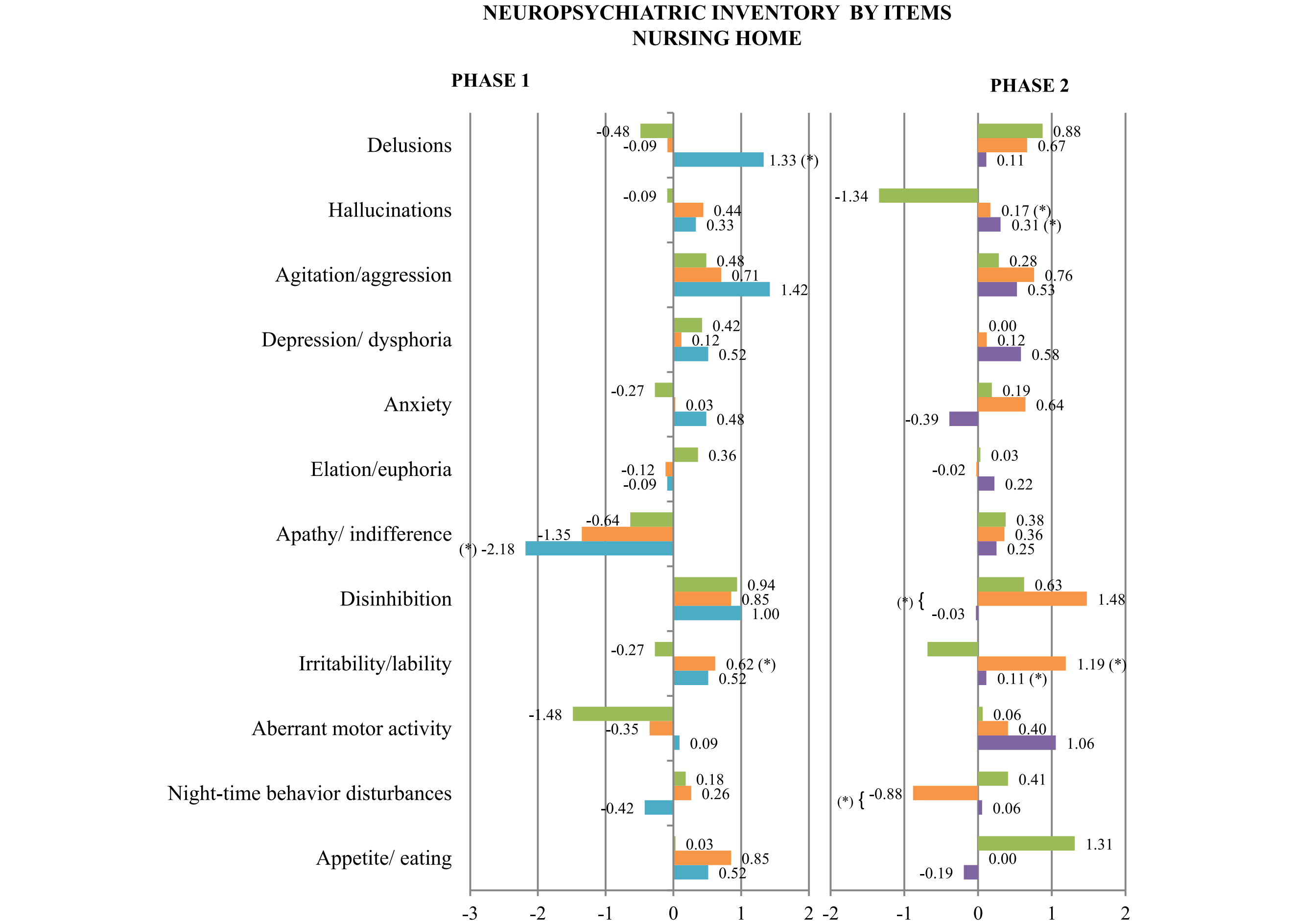

FIGURE 4 | Mean change at follow-up in NPI scores, by item, for the three patients groups of Phase 1 and Phase 2. CONTROL (green), PARO (orange), NAO (blue), and DOG (purple) (*): Statistically significant differences between the groups at follow-up were observed. *P* not corrected <0.05. The scales are represented on the vertical axis and the mean change in the units of measure of each scale is represented on the horizontal axis.

elderly and incapacitated patients. These patients showed significant improvements in QoL as measured by some health-related QoL questionnaires (Kanamori et al., 2003). In contrast, our study has barely shown significant changes in QoL, with the only change being a slight decrease in the QoL of patients in the animal robot group.

Global deterioration scale and **cognitive state** (measured with MMSE and sMMSE) worsened in all the follow-up evaluations as was expected in a progressive and degenerative disease. Only one exception was observed: after the use of NAO, in the nursing home, the sMMSE remained the same. In the same group and experiment, a significant decrease in the MMSE score was observed. Although the MMSE and the sMMSE are both screening scales for cognitive decline, the sMMSE is more appropriate for people with moderate and severe dementia, such as the people who participated in this program. A literature review found that animal-assisted interventions with elderly patients with dementia has a positive effect on communication and coping ability, but not on cognitive performance (Bernabei et al., 2013). In 2008, an improvement in dementia patients' cortical neuronal activity was observed using a 21-channel EEG after the use of PARO (Wada et al., 2008). Several studies (Tapus et al., 2009; Chan and Nejat, 2010; Fasola and Mataric, 2010) describe the use of social robots as a tool for monitoring and encouraging cognitive activities of the elderly and/or individuals suffering from dementia as improving task performance and reducing user frustration. Increased cortical neuronal activity or greater motivation to perform and complete cognitive tasks could lead to a better cognitive test outcome in social robots groups, but in this study, changes between groups were not observed.

Twelve **neuropsychiatric symptoms** were analyzed via the NPI, the APADEM-NH and the AI. **Apathy** is a prominent symptom in dementia. The APADEM-NH scale, a tool developed at the ACRSF, was used to measure apathy. The scale has the advantage of accurately measuring apathy independently of the patient's degree of dementia or depression. As the APADEM-NH is not suitable for people who are not living in a nursing home, the AI was used in the day care center. The apathy item of the NPI scale was additionally used to examine apathy. In the nursing home, in the first phase, statistically significant improvement was seen in the total scores on the APADEM-NH of patients in both robot groups, and in the scores on

TABLE 1 | Baseline and follow-up means, standard deviation (SD) and *p*-value (P) in every variable of the study with statistically significant change in the patient groups [CONTROL (C), PARO (P), NAO (N), and DOG (D)] in the nursing home and the day care center.

		Variable		CONTROL				PARO				P C-P	NAO				P C-N	P P-N
				Baseline mean	*SD*	Follow-up mean	*SD*	Baseline mean	*SD*	Follow-up mean	*SD*		Baseline mean	*SD*	Follow-up mean	*SD*		
Nursing home	Phase 1	MMSE		3.64	5.42	3.12	4.72	3.20	4.95	2.74	4.72	0.282	3.55	5.18	2.42	4.49	**0.022**	0.145
		SMMSE		8.67	10.14	7.73	9.56	7.97	8.84	8.12	9.68	0.239	7.76	8.65	7.79	9.00	0.702	0.586
		APADEM-NH	Total	43.21	21.80	44.42	23.59	48.40	19.12	44.74	22.29	**0.049**	45.06	20.69	41.52	22.59	**0.030**	0.564
			Cognitive inertia	10.73	5.89	11.36	6.32	11.97	5.27	11.15	5.79	0.251	12.03	5.48	10.88	6.30	**0.034**	0.313
		NPI	TOTAL	27.36	14.01	26.55	16.05	22.17	12.96	24.44	17.10	0.246	27.94	15.03	31.45	21.55	0.238	0.782
			Delusions	0.91	1.99	0.42	1.54	0.66	1.98	0.59	2.23	0.455	0.79	1.82	2.12	3.90	**0.011**	0.063
			Apathy/indifference	8.73	2.54	8.09	3.43	9.26	2.28	7.82	3.35	0.292	8.85	2.55	6.67	3.96	**0.047**	0.275
			Irritability/lability	2.58	2.97	2.30	3.02	1.89	2.99	2.56	3.78	**0.033**	3.21	3.66	3.73	3.67	0.085	0.728
		Variable		**CONTROL**				**PARO**				**P C-P**	**DOG**				**P C-D**	**P P-D**
				Baseline mean	***SD***	**Follow-up mean**	***SD***	**Baseline mean**	***SD***	**Follow-up mean**	***SD***		**Baseline mean**	***SD***	**Follow-up mean**	***SD***		
	Phase 2	QUALID		27.70	7.82	24.72	6.68	25.44	7.56	26.75	8.16	**0.044**	24.91	7.39	24.33	6.68	0.101	0.547
		NPI	Total	26.53	20.33	28.66	19.08	24.40	16.15	29.29	19.60	0.294	19.72	15.15	22.33	14.67	0.649	0.364
			Hallucinations	1.81	3.18	0.47	1.54	0.93	2.32	1.10	1.92	**0.020**	0.17	0.74	0.47	1.21	**0.004**	0.625
			Disinhibition	0.91	2.68	1.53	3.36	0.62	1.41	2.10	3.88	0.172	0.92	2.52	0.89	2.61	0.599	**0.026**
			Irritability/lability*	3.78	3.31	3.09	4.17	2.14	3.06	3.33	4.23	**0.003**	2.14	3.29	2.25	2.93	**0.024**	0.873
			Night-time behavior disturbances	1.16	2.26	1.56	3.19	2.43	3.51	1.55	2.78	0.078	1.11	2.69	1.17	2.36	0.771	**0.028**

		Variable		NAO				P
				Baseline mean	*SD*	Follow-up mean	*SD*	
Day care C.	Phase 1	NPI	TOTAL	33.65	21.91	22.47	12.89	**0.007**
			Irritability/lability	3.25	3.41	1.57	2.67	**0.046**

**Significant differences between groups at baseline evaluation. P not corrected <0.05. Bold values are $p < 0.05$.*

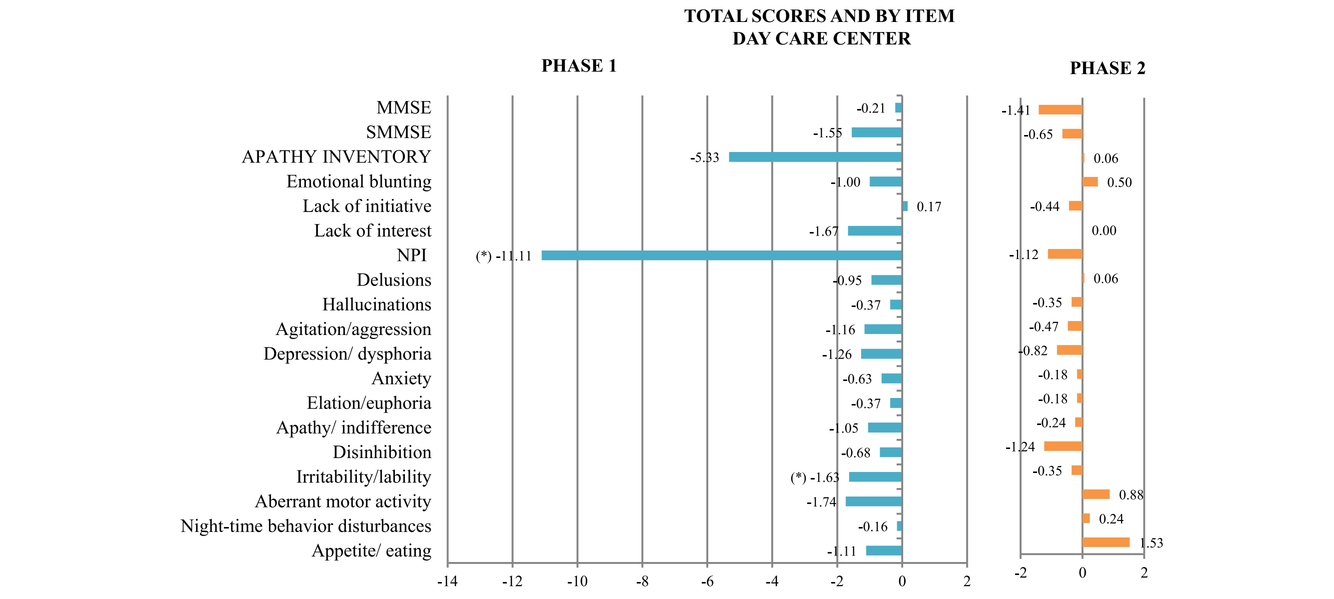

FIGURE 5 | Mean change at follow-up in scores on all the scales used, both totals and by item, in the day care center group of Phase 1, with NAO (blue), and Phase 2, with PARO (orange). (*) Statistically significant differences between the groups at follow-up were observed. *P* not corrected <0.05. The scales are represented on the vertical axis and the mean change in the units of measure of each scale is represented on the horizontal axis.

the apathy item of the NPI scale and the cognitive inertia item of the APADEM-NH of patients in the NAO group. This results replicate previous studies were, despite a lack of methodological rigor, it is apparent that non-pharmacological interventions have the potential to reduce apathy in dementia (Brodaty and Burns, 2012). In the second phase, no statistically significant difference in measures of apathy was found. An explanation could be that apathy in institutionalized patients with advanced dementia seems to increase in time (Wetzels et al., 2010) and therapeutic interventions may have a window in mild and moderate dementia, but not in advanced dementia (López and Agüera-Ortiz, 2014). In the day care center, there was no statistically significant difference in apathy.

Analysis of the NPI scores of all patients in this study reveals a random assortment of changes that were minimal at best. Statistically significant changes were observed in:

- The NAO group:
  - Impairment in delusions and
  - Improving in apathy (Phase 1 nursing home), total score and irritability/lability (day care center)
- The PARO group:
  - Impairment in irritability/lability (nursing home), hallucinations (Phase 2 nursing home) and disinhibition (vs. the DOG group)
  - Improving in night-time behavior disturbances (vs. the DOG group).
- The DOG group:
  - Impairment in hallucinations, irritability/lability

Measures of irritability on the NPI item in the nursing home groups at baseline for Phase 2 showed statistically significant differences between groups, which casts some doubt on the significance of the follow up results.

The changes observed in hallucinations and in the DOG group were produced more by the improvement in the other therapeutic groups, than by its impairment.

A decrease in agitation after the use of animal assisted interventions has been described in the literature (Churchill et al., 1999; Richeson, 2003; O'Neil et al., 2011; Bernabei et al., 2013), as a decrease in behavioral symptoms after the use of a therapy dog during the day time hours ($p < 0.05$) with no significant differences during the evening hours (McCabe et al., 2002). Behavioral improvement, as defined by a reduction in anxiety and aggressiveness, has also been previously reported after the use of PARO (Shibata and Coughlin, 2014). These previous findings were not replicated in this study.

Limitations

The study was designed in order to minimize any potential biases: 3 months of therapy were used in order to decrease the novelty effect, the raters and statistician were blinded, several recording sessions were held before the study began to get the patients and therapists used to the presence of the camera and decrease the Hawthorne effect, interaction between ACRSF regular caregivers and the robots and dogs was avoided to reduce potential informant bias, and while active participation in the therapy sessions was encouraged in order to decrease selection bias patients were not forced to interact with the therapist or the tools.

Throughout the study, several participants left the center or unit or died, and several patients joined the study late. Most of these changes did not occur during the interventions. Some participants were only evaluated once, due to hospitalization, illness or absence from the center: only 1.6% of participants were lost to follow up in the first year and 2.3% in the second.

This study was a pilot study in a sample, not representative of the general population, with a low number of participants. The changes after the use of the three new tools were minimal, and some of the statistical significant changes may be false positives, due to the high number of comparisons made and to the relatively small sample sizes. It is not possible to conclusively state that these tools were the cause of the changes seen, because of several possible confounding factors (i.e., differences in participants' pharmacologic regimens or type of dementia). However, these factors were controlled for, and will be investigated in future research.

In the nursing home, randomization was done by unit, not by individual participant. Although individual randomization would have been optimal, it would have required moving residents to different units for the sessions and would have introduced major changes in the daily routines and environments of the participants. Additionally, the environments and the characteristics of the individuals in units of the same dementia level are very similar. Baseline evaluation showed no difference between any of the nursing home groups on any of the measures (except in irritability in the nursing home in Phase 2), indicating that there is no significant difference between people who live in different units in the variables analyzed in this study.

Concluding Remarks

In a controlled pilot study of parallel groups in institutionalized patients with moderate/severe dementia comparing 3 months of assisted therapy with:

- A humanoid robot, an animal-shaped robot and conventional therapy, the main findings were: a decrease in apathy in the humanoid and animal shaped robot groups; increased delusions in the group treated with the humanoid robot and increased irritability in both robot groups; and a decrease in scores on the MMSE, but not the sMMSE, in the humanoid robot group. There were no statistically significant differences between the humanoid and animal shaped robot groups.
- An animal-shaped robot, a real therapy dog and conventional therapy, the main findings were: a decrease in quality of life in the animal shaped robot group compared to the conventional therapy group; increased hallucinations and irritability in both the robot and animal groups compared to the control group; increased disinhibition in the animal-shaped robot group and decreased disinhibition in the humanoid robot group, decreased night-time behavior disturbances in the animal-shaped robot group and increased night-time behavior disturbances in the dog group.

In a study of robot therapy sessions for patients with moderate/severe dementia cared for at a day care center, participants showed improvements in irritability and global neuropsychiatric symptoms after participating in sessions with the humanoid robot, but not after sessions with the animal-shaped robot.

Future Studies

Randomized controlled trials are needed with a larger amount of patients, in order to better understand the effects of robots and dogs on the therapy of people with dementia.

Additionally, new scales that are internationally validated and more sensitive and specific are needed, in order to detect the slight changes in behavior, emotion and cognition that were observed during the session but were not significant enough to appear in the analysis.

As a result of this study, our team is going to focus on the use of humanoid robots in cognitive therapy for people with mild dementia and in the use of pet robots for people with moderate to severe dementia.

Grants

This study received grants from the Spanish Ministry of Science and Innovation (PI10/02567) and the Spanish Ministry of Health, Social Policy and Equality (IMSERSO 231/2011).

Acknowledgments

Thank you to the patients and their families and friends, for their cooperation to make feasible research programs like this one. The authors want to acknowledge for their collaboration to the rest of the members of the Robotherapy Working Group: Miguel Ángel Fernández Blázquez, Marina Ávila Villanueva, Belén Frades Payo, Isabel Ramos García, Isabel Cruz Orduña, Luis Ignacio Casanova Peño, Sara Saiz Bailador, Belén González Lahera, Susana Morales Martínez, Lidia Espada Raboso, Gema Melcon Borrego, Cristina Martín Carmona and Raquel Díaz Rodríguez. Special thanks to Hydra-Sata Association and Bocalan Foundation for making the third year of the study possible by training the therapists, providing the therapy dogs, and attending every session. Thank you to the "Association of users and friends of the guide dogs of Madrid" who were unable to participate in this study despite great enthusiasm and desire to. The authors also recognize the staff of the ACRSF and CIEN Foundation who helped to carry out this program. And thank you to Sloane Heller for the language assessment.

References

Agüera-Ortiz, L., Gil-Ruiz, N., Cruz-Orduña, I., Ramos-García, I., Osorio, R. S., Valentí-Soler, M., et al. (2015). A novel rating scale for the measurement of apathy in institutionalized persons with dementia: the APADEM-NH. *Am. J. Geriatr. Psychiatry* 23, 149–159. doi: 10.1016/j.jagp.2013.01.079

Bemelmans, R., Gelderblom, G. J., Jonker, P., and de Witte, L. (2012). Socially assistive robots in elderly care: a systematic review into effects and effectiveness. *J. Am. Med. Dir. Assoc.* 13, 14–120.e1. doi: 10.1016/j.jamda.2010.10.002

Bernabei, V., De Ronchi, D., La Ferla, T., Moretti, F., Tonelli, L., Ferrari, B., et al. (2013). Animal-assisted interventions for elderly patients affected by dementia or psychiatric disorders: a review. *J. Psychiatr. Res.* 47, 762–773. doi: 10.1016/j.jpsychires.2012.12.014

Boada, M., Tárraga, L., Modinos, G., López, O. L., and Cummings, J. L. (2005). Neuropsychiatric inventory-nursing home version (NPI-NH): Spanish validation. *Neurol. Barc. Spain* 20, 665–673.

Brodaty, H., and Burns, K. (2012). Nonpharmacological management of apathy in dementia: a systematic review. *Am. J. Geriatr. Psychiatry* 20, 549–564. doi: 10.1097/JGP.0b013e31822be242

Broekens, J., Heerink, M., and Rosendal, H. (2009). Assistive social robots in elderly care: a review. *Gerontechnology* 8, 94–103. doi: 10.4017/gt.2009.08.02.002.00

Buiza, C., Navarro, A., Díaz-Orueta, U., González, M. F., Alaba, J., Arriola, E., et al. (2011). Short evaluation of cognitive state in advanced stages of dementia: preliminary results of the Spanish validation of the severe mini-mental state examination. *Rev. Esp. Geriatr. Gerontol.* 46, 131–138. doi: 10.1016/j.regg.2010.09.006

Chan, J., and Nejat, G. (2010). Promoting engagement in cognitively stimulating activities using an intelligent socially assistive robot. *IEEE* 533–538. doi: 10.1109/AIM.2010.5695806. Available online at: http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=5695806&isnumber=5695712

Churchill, M., Safaoui, J., McCabe, B. W., and Baun, M. M. (1999). Using a therapy dog to alleviate the agitation and desocialization of people with Alzheimer's disease. *J. Psychosoc. Nurs. Ment. Health Serv.* 37, 16–22.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., and Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44, 2308–2314.

Downes, M. J., Dean, R., and Bath-Hextall, F. J. (2013). *Animal-assisted Therapy for People with Serious Mental Illness (Protocol), Cochrane Database of Systematic Reviews*. Loughborough: John Wiley & Sons.

Fairbairn, A. (2006). *Dementia: Supporting People with Dementia and their Carers in Health and Social Care.* Available online at: https://www.nice.org.uk/guidance/cg42

Fasola, J., and Mataric, M. J. (2010). Robot motivator: increasing user enjoyment and performance on a physical/cognitive task. *IEEE* 274–279. doi: 10.1109/DEVLRN.2010.5578830. Available online at: http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=5578830&isnumber=5578820

Filan, S. L., and Llewellyn-Jones, R. H. (2006). Animal-assisted therapy for dementia: a review of the literature. *Int. Psychogeriatr.* 18, 597–611. doi: 10.1017/S1041610206003322

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198.

Garre-Olmo, J., Planas-Pujol, X., López-Pousa, S., Weiner, M. F., Turon-Estrada, A., Juvinyà, D., et al. (2010). Cross-cultural adaptation and psychometric validation of a Spanish version of the Quality of Life in Late-Stage Dementia Scale. *Qual. Life Res.* 19, 445–453. doi: 10.1007/s11136-010-9594-8

Harrell, L. E., Marson, D., Chatterjee, A., and Parrish, J. A. (2000). The Severe Mini-Mental State Examination: a new neuropsychologic instrument for the bedside assessment of severely impaired patients with Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 14, 168–175.

Kanamori, M., Suzuki, M., Oshiro, H., Tanaka, M., Inoguchi, T., Takasugi, H., et al. (2003). "Pilot study on improvement of quality of life among elderly using a pet-type robot," in *2003 IEEE International Symposium on Computational Intelligence in Robotics and Automation, 2003*, Vol. 1 (Shizuoka), 107–112. doi: 10.1109/CIRA.2003.1222072

Lobo, A., Saz, P., Marcos, G., Día, J. L., de la Cámara, C., Ventura, T., et al. (1999). Revalidation and standardization of the cognition mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population. *Med. Clin.* 112, 767–774.

López, J., and Agüera-Ortiz, L. (2014). *Apatía en la Demencia. De la Neurobiología a la Clínica., Informaciones Psiquiátricas*, 15–34. Available online at: http://www.informacionespsiquiatricas.com

Martin, F., E., C., M., J., Valenti, M., and Martinez-Marti, P. (2013). Robotherapy with dementia patients. *Int. J. Adv. Robot. Syst.* 10, 1–71. doi: 10.5772/54765

McCabe, B. W., Baun, M. M., Speich, D., and Agrawal, S. (2002). Resident dog in the Alzheimer's special care unit. *West. J. Nurs. Res.* 24, 684–696.

Nakajima, K., Nakamura, K., Yonemitsu, S., Oikawa, D., Ito, A., Higashi, Y., et al. (2001). "Animal-shaped toys as therapeutic tools for patients with severe dementia," in *Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2001.* Vol 4 (Aichi), 3796–3798. doi: 10.1109/IEMBS.2001.1019665

O'Neil, M. E., Freeman, M., Christensen, V., Telerant, R., Addleman, A., and Kansagara, D. (2011). *A Systematic Evidence Review of Non-pharmacological Interventions for Behavioral Symptoms of Dementia, VA Evidence-based Synthesis Program Reports*. Washington, DC: Department of Veterans Affairs.

Olazarán, J., Agüera-Ortiz, L., Osorio, R. S., León-Salas, B., Dobato, J. L., Cruz-Orduña, I., et al. (2012). Promoting research in advanced dementia: early clinical results of the Alzheimer Center Reina Sofía Foundation. *J. Alzheimers Dis.* 28, 211–222. doi: 10.3233/JAD-2011-110875

Prince, M., Guerchet, M., and Prina, M. (2013). *Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050*. London: Alzheimer's disease International (ADI).

Reisberg, B., Ferris, S. H., de Leon, M. J., and Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *Am. J. Psychiatry* 139, 1136–1139.

Richeson, N. E. (2003). Effects of animal-assisted therapy on agitated behaviors and social interactions of older adults with dementia. *Am. J. Alzheimers Dis. Other Demen.* 18, 353–358.

Robert, P. H., Clairet, S., Benoit, M., Koutaich, J., Bertogliati, C., Tible, O., et al. (2002). The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int. J. Geriatr. Psychiatry* 17, 1099–1105. doi: 10.1002/gps.755

Shibata, T. (2012). Therapeutic seal robot as biofeedback medical device: qualitative and quantitative evaluations of robot therapy in dementia care. *Proc. IEEE* 100, 2527–2538. doi: 10.1109/JPROC.2012.2200559

Shibata, T., and Coughlin, J. F. (2014). Trends of robot therapy with neurological therapeutic seal robot, PARO. *J. Robot. Mechatron.* 26, 418–425.

Tapus, A. (2009). "Improving the quality of life of people with dementia through the use of socially assistive robots," *in Advanced Technologies for Enhanced Quality of Life, 2009. AT-EQUAL '09* (Iasi), 81–86.

Tapus, A., Tapus, C., and Mataric, M. (2009). "The role of physical embodiment of a therapist robot for individuals with cognitive impairments," in *Robot and Human Interactive Communication, 2009. RO-MAN 2009. The 18th IEEE International Symposium* (Toyama), 103–107.

Vilalta-Franch, J., Lozano-Gallego, M., Hernández-Ferrándiz, M., Llinàs-Reglà, J., López-Pousa, S., and López, O. L. (1999). The neuropsychiatric inventory. Psychometric properties of its adaptation into Spanish. *Rev. Neurol.* 29, 15–19.

Wada, K., Shibata, T., Musha, T., and Kimura, S. (2008). Robot therapy for elders affected by dementia. *IEEE Eng. Med. Biol. Mag.* 27, 53–60. doi: 10.1109/MEMB.2008.919496

Weiner, M. F., Martin-Cook, K., Svetlik, D. A., Saine, K., Foster, B., and Fontaine, C. S. (2000). The quality of life in late-stage dementia (QUALID) scale. *J. Am. Med. Dir. Assoc.* 1, 114–116.

Wetzels, R. B., Zuidema, S. U., de Jonghe, J. F. M., Verhey, F. R. J., and Koopmans, R. T. C. M. (2010). Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. *Am. J. Geriatr. Psychiatry* 18, 1054–1065.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 17 March 2015
doi: 10.3389/fnagi.2015.00024

'Kitchen and cooking,' a serious game for mild cognitive impairment and Alzheimer's disease: a pilot study

*Valeria Manera[1], Pierre-David Petit[1], Alexandre Derreumaux[1], Ivan Orvieto[2], Matteo Romagnoli[2], Graham Lyttle[3], Renaud David[1,4] and Philippe H. Robert[1,4]**

[1] EA CoBTeK/IA (Cognition Behavior Technology), Institut Claude Pompidou, University of Nice Sophia Antipolis, Nice, France, [2] Testaluna S.r.l., Milano, Italy, [3] Kainos Evolve Ltd., Belfast, UK, [4] Centre Edmond et Lily Safra pour la Recherche sur la Maladie d'Alzheimer – Centre Mémoire de Ressources et de Recherche – Institut Claude Pompidou – CHU de Nice, Nice, France

OPEN ACCESS

Edited by:
P. Hemachandra Reddy, Texas Tech University, USA

Reviewed by:
Cristina Muscio, Fondazione Europea Ricerca Biomedica – Centro Eccellenza Alzheimer – Ospedale Briolini, Italy
Ioannis Tarnanas, University of Bern, Switzerland

***Correspondence:**
Philippe H. Robert, Centre Edmond et Lily Safra pour la Recherche sur la Maladie d'Alzheimer – Centre Mémoire de Ressources et de Recherche – Institut Claude Pompidou – CHU de Nice, 10 Rue Molière, 06000 Nice, France
robert.p@chu-nice.fr

Received: 14 January 2015
Accepted: 22 February 2015
Published: 17 March 2015

Citation:
Manera V, Petit P-D, Derreumaux A, Orvieto I, Romagnoli M, Lyttle G, David R and Robert PH (2015) 'Kitchen and cooking,' a serious game for mild cognitive impairment and Alzheimer's disease: a pilot study. Front. Aging Neurosci. 7:24. doi: 10.3389/fnagi.2015.00024

Recently there has been a growing interest in employing serious games (SGs) for the assessment and rehabilitation of elderly people with mild cognitive impairment (MCI), Alzheimer's disease (AD), and related disorders. In the present study we examined the acceptability of 'Kitchen and cooking' – a SG developed in the context of the EU project VERVE (http://www.verveconsortium.eu/) – in these populations. In this game a cooking plot is employed to assess and stimulate executive functions (such as planning abilities) and praxis. The game is installed on a tablet, to be flexibly employed at home and in nursing homes. Twenty one elderly participants (9 MCI and 12 AD, including 14 outpatients and 7 patients living in nursing homes, as well as 11 apathetic and 10 non-apathetic) took part in a 1-month trail, including a clinical and neuropsychological assessment, and 4-week training where the participants were free to play as long as they wanted on a personal tablet. During the training, participants met once a week with a clinician in order to fill in self-report questionnaires assessing their overall game experience (including acceptability, motivation, and perceived emotions). The results of the self reports and of the data concerning game performance (e.g., time spent playing, number of errors, etc) confirm the overall acceptability of Kitchen and cooking for both patients with MCI and patients with AD and related disorders, and the utility to employ it for training purposes. Interestingly, the results confirm that the game is adapted also to apathetic patients.

Keywords: serious game, Alzheimer disease, mild cognitive impairment, apathy, executive functions

Introduction

The term dementia indicates a decline in mental ability severe enough to interfere with activities of daily life (Dubois et al., 2010). Due to the increasing average lifespan, the occurrence of dementia has risen dramatically, thus engendering high socio-economic costs. For this reason, the early detection and the treatment of dementia are considered as a research priorities (Ballard et al., 2011). Dementia is characterized by the presence of cognitive symptoms, such impaired memory, attention, orientation and executive functions, which are often associated to behavioral and psychological symptoms, such as apathy or agitation (Aalten et al., 2003). Dementia can result from different causes, the most common being Alzheimer's disease (AD), and it is often preceded by a predementia stage, known as mild cognitive impairment (MCI), characterized by a cognitive decline greater than expected for an individual's age, but which does not interfere notably with activities of daily life (Petersen et al., 1999; Gauthier et al., 2006).

Serious games (SG) – which are digital applications specialized for purposes other than entertaining (such as educating, informing, or enhancing cognitive and/or physical functions) – are now widely recognized as promising non-pharmacological tools to help assess and evaluate patients' functional impairments, as well as to help the patients' treatment, stimulation, and rehabilitation (Robert et al., 2014). Boosted by the publication of a Nature letter showing that video game training can enhance cognitive control in older adults (Anguera et al., 2013), there is now a growing interest in developing SG specifically adapted to people with AD and related disorders. Preliminary evidence shows that SG can successfully be employed to train physical and cognitive abilities in people with AD, MCI, and related disorders. McCallum and Boletsis (2013) performed a literature review of the experimental studies conducted to date on the use of SG in neurodegenerative disorders. In summary, the results of the 15 reported studies suggest that: (1) physical games (or exergames, i.e., games that promote physical fitness) can positively affect several health areas of the players with mild AD and MCI, such as balance and gait (Padala et al., 2012), and voluntary motor control (Legouverneur et al., 2011); (2) cognitive games (i.e., games which target cognitive improvement) can improve a number of cognitive functions, such as attention and memory (Stavros et al., 2010; Weybright et al., 2010; Rosen et al., 2011) and visuo-spatial abilities (Yamaguchi et al., 2011); (3) both physical and cognitive games can have a positive impact on social and emotional functions, for instance they can improve the mood and increase positive affect and sociability (Weybright et al., 2010; Boulay et al., 2011; Yamaguchi et al., 2011) and reduce depression (Férnandez-Calvo et al., 2011).

Despite these promising results, a number of studies showed that elderly people and people with AD have problems in using many of the SG currently available on the market. Their difficulties include problems in getting familiar with the game technology and embarrassment about using the tools designed for the game (e.g., Wollersheim et al., 2010; Legouverneur et al., 2011). Furthermore, certain games were considered too demanding or even risky for elderly people (e.g., Sohnsmeyer et al., 2010). These difficulties derive from the fact that most of the SG currently employed have been developed for entertainment purposes (e.g., the Nintendo Wii Fit, Wii Sports, and Big Brain Academy) and with a "typical healthy user" in mind. To overcome this problem, SG targeting specifically AD and related disorders are starting to emerge (e.g., Benveniste et al., 2010; Nor Wan Shamsuddin et al., 2011; Tarnanas et al., 2013).

The purpose of the present paper is to report the results of a feasibility study conducted with patients with MCI and AD and related disorders with the game "Kitchen and cooking," a SG game developed in the context of the European FP7 project VERVE (Vanquishing Fear through e-inclusion, http://verveconsortium.eu/). Kitchen and cooking is born from the tight collaboration between clinicians and game designers. Based on a recent survey showing that food is the most interesting topic for elderly people living in nursing homes (Leone et al., 2012), we developed the game based on a cooking plot, where participants can play different scenarios/recipes. Kitchen and cooking targets executive functions, specifically planning abilities, but includes also activities training attention and object recognition, as well as praxis. Following the recommendations of Robert et al. (2014) and Fua et al. (2013), the game can keep track of participants' performance overtime, and thus can be employed also for assessment purposes. Furthermore, it takes into account the users' impairments: for instance, after a number of errors, the user is helped with some prompts. Finally, it is installed on a tablet, which is an inexpensive and easy to use interface that can be employed anywhere.

In order to test how the SG is used in different environments, we included both outpatients and patients living in nursing homes. Furthermore, we included both apathetic and non-apathetic patients, as one challenges of the project VERVE was to develop new technologies to support the treatment of people with apathy associated to aging, or to neurological disorders.

Materials and Methods

Participants

Nine MCI patients (seven female and two male; mean age = 75.8 years; SD = 9.1; age range = 60–84) and 12 patients with AD or related disorders (eight female, four male; mean age = 80.3 years; SD = 6.3; age range = 70–90) voluntarily participated in this study. Patients were recruited either at the Nice Research Memory Center and CoBTeK research unit (CMRR), located at the Institut Claude Pompidou (MCI: $N = 6$, AD: $N = 8$) or in a nursing home working with the CMRR (MCI: $N = 3$, AD: $N = 4$). MCI diagnosis was conducted according to the National Institute on Aging and Alzheimer Association group clinical criteria (Albert et al., 2011), and the AD diagnosis was made according to the NINCDS ADRDA criteria (McKhann et al., 1984). Participants were not included if they had an active episode of major depression, if they had major perceptual (visual or auditory) impairments, rigidity or trembling (according to the UPDRS III; Fahn and Elton, 1987) or epilepsy. The mini mental state exam (MMSE) was used to evaluate the level of cognitive impairment for each group (Folstein et al., 1975). AD patients scored between 15 and 24 (M = 18.4, SD = 3.2) and MCI patients scored from 24 to 30 (M = 27.2, SD = 1.9). The presence of apathy was evaluated by means of the diagnostic criteria for apathy (Mulin et al., 2011), and the criteria have been used to divide the population in apathetic versus non-apathetic subjects. In addition, the severity of apathy was assessed using the Apathy Inventory – clinician version (Robert et al., 2009), a 12-point scale evaluating the presence of reduced initiation, interest, and emotional blunting.

Characteristics of MCI and AD subjects are presented in **Table 1**. The age, level of education, and gender distribution were not significantly different between the two groups. All participants gave their informed written consent before beginning the study. The study was performed in compliance with the Declaration of Helsinki, and was approved by the local ethics committees.

Materials and Procedure

A flowchart summarizing the study procedure with the different experimental sessions is reported in **Figure 1**. Participants performed a 4-week training with 'Kitchen and cooking' game installed on a tablet. During the training, participants were asked to play at home as much as they wanted, and they meet five times with a trained clinician. During the inclusion visit, after signing the informed consent, participants underwent the cognitive and functional assessment (see below). During the first session with the clinician (S1), they underwent a preliminary game training for Kitchen and cooking, in which the clinician showed all the ingredients/objects used in the different scenarios (in order to ensure that the objects were recognizable), and showed which gestures needed to be performed to complete the different game actions. Second, participants played one of the available scenarios in front of the clinician, who provided additional explanations (if necessary) in order to allow the participant to successfully complete the scenario. Finally, participants completed some self-report questionnaires to assess the game acceptability and interest. The homework for week 1 was to play as much as they wanted to the scenario seen in S1 (participants were allowed to try and play other scenarios, if they wanted). After 1-week participants meet again with the clinician (S2) and played with him the scenario played in S1, together with a new scenario, which represented the homework for week 2. The structure of S3 and S4 sessions was identical to that of S2, and every week participants exercised on a new scenario. During the last session with the clinician (S5), taking place at the end of week 4, participants played again the scenario performed during week 4, and they completed the same self-report questionnaires assessing the game acceptability and interest administered after S1.

Cognitive and Functional Assessment

Global functioning was evaluated during the inclusion visit by means of the MMSE, the Instrumental Activities of Daily Living scale (IADL; Mathuranath et al., 2005) and the Independence in Activity of Daily Living index (ADL; Katz et al., 1970). Attention and mental flexibility were measured with the Trail-Making Test, versions A (Lezak et al., 2004). Executive functions (specifically, selective attention, and inhibition control) were evaluated using the interference scores from the Victoria Stroop Test (Word/Dot and Interference/Dot, Bayard et al., 2011). Memory performance was evaluated by means of the Visual Association Test (VAT; Lindeboom et al., 2002).

'Kitchen and Cooking' Game

"Kitchen and cooking" game is a SG developed in the context of the European FP7 project VERVE (Vanquishing Fear through e-inclusion, http://verveconsortium.eu/), a project which aimed to develop new technologies to support the treatment of people at risk of social exclusion, either because of fear and apathy associated with aging, or because of a neurological disorder. The CMRR and the CoBTeK team designed the cognitive task embedded in the game. The game was developed by Testaluna s.r.l. (Milan, Italy), and Kainos Evolve Ltd (Belfast, UK) developed the game interface used by the clinicians.

TABLE 1 | Characteristics and group comparisons for mild cognitive impairment (MCI) and Alzheimer's disease (AD) participants.

	MCI group (N = 9)	AD group (N = 12)	*p*
Female, *n* (%)	7 (77.8%)	8 (66.7%)	0.577
Age (years), mean ± SD	75.8 ± 9.1	80.3 ± 6.3	0.422
Level of education, *n* (%)			0.738
Primary education	2 (22.2%)	4 (33.3%)	
Secondary education	3 (33.3%)	3 (25.0%)	
Secondary education	2 (22.2%)	1 (8.3%)	
Higher education	2 (22.2%)	4 (33.3%)	
Residency, *n* (%)			1.000
Outpatients	6 (66.7%)	8 (66.6%)	
Nursing home	3 (33.3%)	4 (33.3%)	
MMSE, mean ± SD	27.2 ± 1.9	18.4 ± 3.2	**0.000***
IADL-E, mean ± SD	5.8 ± 2.0	9.5 ± 4.0	**0.028***
ADL, mean ± SD	2.1 ± 2.9	2.3 ± 2.0	0.917
TMT A (sec), mean ± SD	65.3 ± 41.0	176.4 ± 153.2	**0.015***
Victoria Stroop Test (word/dot), mean ± SD	1.31 ± .35	1.78 ± .52	**0.023***
Victoria Stroop Test (interference/dot) time, mean ± SD	1.93 ± .98	2.68 ± 1.29	0.129
VAT, mean ± SD	11.3 ± 1.3	7.9 ± 2.8	**0.000***
Presence of diagnostic criteria for Apathy, *n* (%)	3 (33.3%)	8 (66.7%)	0.130
Apathy inventory, mean ± SD	1.8 ± 2.9	4.6 ± 2.5	**0.041***

*Group comparisons were made using Mann–Whitney U test (*p < 0.05) and chi-square (*p < 0.05) for categorical testing.*

	Inclusion	S1	S2 End Week 1	S3 End Week 2	S4 End Week 3	S5 End Week 4
Informed consent	X					
MMSE	X					
IADL-E and ADL	X					
TMT A, Victoria Stroop Test, VAT	X					
Diagnostic criteria for Apathy, Apathy Inventory	X					
Preliminary game training		X				
Meeting with clinician / game training		X	X	X	X	X
Self report questionnaires Interest, satisfaction, motivation, PANAS, fatigue		X				X

FIGURE 1 | Flowchart summarizing the activities performed in the different experimental sessions.

Kitchen and cooking is based on a cooking plot, where participants can play four different scenarios/recipes: pizza, yogurt cake, chicken breast in cream sauce, and finally salmon wrap. In each scenario, participants need: (a) to select the correct ingredients from the fridge and cupboards, a searching task with engages object recognition and sustained attention (*gnosis* activity); (b) to plan which actions need to be performed, and in which order, a task requiring planning abilities (*executive functions* activity); and finally, to perform specific gestures to accomplish each action (e.g., to rotate the finger to mix the ingredients), a task which requires praxis abilities (*praxis* activity). Depending on the scenario, the number of objects to be recognized ranges from 5 to 7, the number of executive functions activities ranges from 5 to 8, and the number of praxis ranges from 7 to 13.

The game can keep track of the time spent playing a scenario and of the time spent on each of the game activities (gnosis, executive functions, and praxis), of the total number of scenarios played (successfully completed or not), and of the number of errors performed in each game activity.

A demo showing Kitchen and cooking can be seen on the website of the Association Innovation Alzheimer, at the following link: http://www.innovation-alzheimer.fr/projets-en/verve-en/

Self Report Questionnaires

At the end of S1 and S5 participants were administered self-report questionnaires concerning the game experience. Specifically, the perceived satisfaction was assessed through a 10 cm analogical scale, in which participants were asked to bisect a line ranging from 'not satisfied at all' to 'really satisfied' in order to indicate their degree of satisfaction for the game. Perceive interest was assessed through a 4-item 1–7 Likert scale adapted from Gourlan et al. (2013). Similarly, motivation was evaluated through an adaptation of the scale proposed by Gourlan et al. (2013), a 24-item 0–7 Likert scale which measures separately intrinsic motivation (e.g., "I play because it is fun") and external motivation ("I play because my friends/family members say I should"). Experienced emotions were assessed through the PANAS scale (Watson et al., 1988), a 20-item 0–5 Likert scale evaluating separately self-reported positive and negative emotions. Finally, fatigue was evaluated through the French adaptation of the Piper Fatigue Scale (11 rating questions, scale 0–10; Gledhill et al., 2002).

Statistics Analyses

All statistical analyses were computed using SPSS 20.0. In order to verify the acceptability of the intervention, we computed: (a) the number of participants that successfully completed the training; (b) the mean scores of the acceptability questionnaires administered after S1 and S5; (c) the mean time spent playing, and the number of scenarios played (in total and at home). Group comparisons were performed using diagnosis (MCI vs. AD), residence (outpatients vs. patients in nursing home) and presence of diagnostic criteria for apathy (yes vs. no) as independent between-subject factors. As the distribution of the data was not normal, group comparisons were performed using non-parametric Mann–Whitney *U* test. Comparisons between the acceptability questionnaires after S1 and S5 were performed using paired-sample *t*-tests.

In order to verify whether the assessment of the different game activities (gnosis, executive functions, and praxis) was in line with the classical functional and neuropsychological assessment, we computed for each participant the mean time spent to complete a scenario, and the errors and mean time spent on each game activity in S1 (first session), and we submitted them to separate Mann–Whitney *U* test, with diagnosis (MCI vs. AD), residence (outpatients vs. patients in nursing home) and presence of diagnostic criteria for apathy (yes vs. no) as independent between-subject factors. We also compute correlations between the time spent on each game activity in S1 and the classical cognitive and functional assessment using Pearsons' correlation coefficient (two-tails).

Finally, in order to verify if game activities improved with training, for each scenario we compared the time spent to perform each activity (gnosis, executive functions, and praxis) during the first session (S1, S2, S3, or S4 depending on the scenario and participant) and the next session (1 week after) using paired-sample *t*-tests. Group comparisons on the improvement scores (difference in time spent on an activity between two consecutive sessions) were performed with Mann–Whitney *U* test using diagnosis (MCI vs. AD), residence (outpatients vs. patients in nursing home) and presence of diagnostic criteria for apathy (yes vs. no) as independent between-subject factors. We also computed Pearsons' correlations between game improvement scores and the total time spent playing during the training.

Results

Cognitive, Functional, and Behavioral Assessment

Demographic, cognitive, and functional characteristics of the patients are presented in **Table 1**. Compared to MCI participants, AD participants had significantly lower MMSE scores ($p < 0.001$) and IADL-E ($p = 0.028$), confirming the presence of a significant impairment in the activities of daily living. Furthermore, participants were slower at the TMT A ($p = 0.015$), more sensitive to interference in the Victoria Stroop Test – Word/Dot index ($p = 0.023$), and scored lower at the VAT memory task ($p < 0.001$) compared to MCI participants. Finally, AD participants had a higher Apathy Inventory compared to MCI participants ($p = 0.041$). However, no significant difference between groups was found concerning the presence of diagnostic criteria for apathy ($\chi 2 = 2.29$, $p = 0.130$). No significant difference between groups was found for the ADL, and the Victoria Stroop Test – Interference/Dot index.

Intervention Acceptability

Training Completion and Self-Report Questionnaires

The 4-weeks training was successfully completed by 20 out of 21 participants (one participant abandoned the study after the first week). The results of the self-report questionnaires (mean scores between S1 and S5) showed that, as a group, participants reported to be highly satisfied concerning the game experience (Mean = 8.2/10, SD = 1.3), interested by the game (Mean = 17.1/28, SD = 5.6), and motivated by the activity. Specifically, intrinsic motivation (Mean = 3.9/7, SD = 1.3), was significantly higher than external motivation [Mean = 2.5/7, SD = 1.2; $t_{(15)} = 4.37$, $p = 0.001$]. Furthermore, participants reported to be not very fatigued (Mean = 3.7/10; SD = 1.2), and to have experienced more positive emotions (PANAS pos, $M = 2.7/5$; SD = 0.8) than negative emotions [PANAS neg, $M = 1.4/5$, SD = 0.6, $t_{(18)} = 5.86$, $p < 0.001$]. The interest, satisfaction, motivation (intrinsic and extrinsic) fatigue, and experienced emotions (positive and negative) did not change from S1 to S5 (*t* ranging from 0.15 to 1.8, *p*s ranging from 0.092 to 0.880), thus confirming the overall positive evaluation of the game also after a repeated training.

Results according to diagnosis, residence, and presence of diagnostic criteria for apathy are shown in **Table 2**. Group comparisons revealed that AD participants reported to be significantly more satisfied compared to the MCI participants ($p = 0.043$). Furthermore, apathetic participants reported to experience fewer positive emotions ($p = 0.008$) compared to non-apathetic participants. No difference in the self-report scales was found between outpatients and patients living in nursing homes (all *p*s > 0.323).

Game Experience

The acceptability of the intervention was corroborated also by the data concerning the time that patients spent playing, and the number of scenarios played. During the 4-week trial participants played a mean of 55.8 scenarios (SD = 64.9; range = 10–284), for a mean playtime of more than 5 h (5h22m; SD = 4h19m; range = 32m–17h40m), corresponding to a mean of 1h21m

TABLE 2 | Intervention acceptability.

	MCI (N = 9)	AD (N = 12)	Outpatients (N = 14)	Nursing home (N = 7)	Apathetic (N = 11)	Non-apathetic (N = 10)
Satisfaction, scale 0–10 (mean ± SD)	**7.6 (1.2)**	**8.6 (1.3)**	8.4 (1.4)	8.0 (1.3)	8.1 (1.4)	8.3 (1.3)
Interest scale 0–28 (mean ± SD)	18.3 (5.6)	16.0 (5.7)	17.1 (5.8)	17.1 (5.8)	17.3 (6.2)	16.9 (5.2)
Intrinsic motivation scale 1–7 (mean ± SD)	3.6 (1.4)	4.3 (1.1)	3.9 (1.2)	4.1 (1.6)	4.4 (1.1)	3.5 (1.3)
External motivation scale 1–7 (mean ± SD)	2.3 (1.4)	2.7 (1.0)	2.5 (1.0)	2.3 (1.9)	2.9 (1.3)	2.1 (1.1)
PANAS positive emotions scale 1–5 (mean ± SD)	2.6 (0.9)	2.8 (0.7)	2.8 (0.8)	2.5 (0.7)	**2.3 (0.6)**	**3.1 (0.8)**
PANAS negative emotions scale 1–5 (mean ± SD)	1.4 (0.7)	1.4 (0.6)	1.4 (0.5)	1.6 (0.9)	1.5 (0.8)	1.4 (0.5)
Fatigue scale 0–10 (mean ± SD)	3.8 (1.1)	3.5 (1.3)	3.6 (1.3)	3.8 (1.1)	3.7 (1.1)	3.7 (1.3)
Number of scenario played (mean ± SD)	54.1 (49.3)	57 (76.8)	**72.2 (74.7)**	**22.9 (9.6)**	74 (85.3)	35.7 (21)
Total time played (mean ± SD)	05h09m (04h12 m)	05h33m (04h34m)	06h18m (04h59m)	03h31m (01h26m)	**07h18m (05h04m)**	**03h16m (01h49m)**

Results of the self report questionnaires (mean between S1 and S5), number of scenarios and total time played by MCI vs. AD patients, outpatients vs. patients living in nursing homes, and by apathetic vs. non-apathetic patients according to the Apathy diagnostic criteria. Results in bold indicate a significant difference at the Mann–Whitney U test (p < 0.05).

hours per week. Almost 85% of the scenarios were played at home (Mean = 47.4, SD = 64.3), for a mean playtime at home of 3h48m (SD = 4h19m range = 0m–16h28m). Over 70% of the scenarios were successfully completed (Mean = 70.2%, SD = 25%; range = 18.2%–100%).

Results according to diagnosis, residence, and presence of diagnostic criteria for apathy are shown in **Table 2**. No significant difference in the number of scenarios ($p = 0.422$) or time played ($p = 0.808$) was found between MCI and AD participants. Outpatients played more scenarios compared to patients in nursing home ($p = 0.031$), but the difference in the time spent playing did not reach statistical significance ($p = 0.224$). Interestingly, apathetic patients played longer than non-apathetic patients ($p = 0.016$), while no difference in the number of scenarios played was found ($p = 0.654$).

Game Assessment

Time for Scenario Completion, Gnosis, Executive Functions, and Praxis

Results according to diagnosis, residence and presence of diagnostic criteria for apathy are shown in **Table 3**. AD participants took significantly longer to complete a scenario compared to MCI participants ($p = 0.004$). Furthermore, the first time a scenario was played with the clinician ($t0$), AD participants were significantly slower in the gnosis ($p = 0.002$), executive functions ($p = 0.046$), and praxis activities ($p = 0.006$) compared to MCI participants, and made more errors in the praxis activity ($p = 0.046$) thus suggesting that the game assessment was sensitive to differences in the level of general cognitive impairment. AD participants were significantly slower than MCI participants also when the scenario was played again with the clinician after 1 week of training at home ($t1$; gnosis time, $p = 0.002$; executive functions time, $p = 0.003$; praxis time, $p = 0.004$). No difference in the errors was found (all ps > 0.056). No difference in the mean time spent to complete a scenario, gnosis, executive functions, and praxis time/errors was found between outpatients and patients living in nursing homes (all ps > 0.157), nor between apathetic and non-apathetic participants (all ps > 0.175).

Correlations Between Classical Cognitive Assessment and Game Assessment

The game gnosis time in S1 showed a significant correlation with the MMSE [$r_{(20)} = -0.68$, $p = 0.001$], the TMT A time [$r_{(20)} = 0.59$, $p = 0.006$], thus confirming that the object search and selection task can be considered a good proxy for attentional processes. As expected, the game executive functions time showed a significant correlation with the Victoria Stroop Test [Word/Dot index, $r_{(20)} = 0.70$, $p = 0.001$; Interference/Dot index, $r_{(20)} = 0.55$, $p = 0.013$], an index of inhibition control. Finally, the praxis time correlated significantly with the MMSE [$r_{(20)} = -0.53$, $p = 0.016$] and with both indexes of the Victoria Stroop Test [Word/Dot index, $r_{(20)} = 0.71$, $p < 0.001$; Interference/Dot index, $r_{(20)} = 0.60$, $p = 0.005$]. No other significant correlation was found (all ps > 0.153).

Improvement in the Game Activities During the Training

Every scenario was played with the clinician twice: the first time to practice the recipe ($t0$, in S1, S2, S3, or S4 depending on the scenario and participant), and the second time 1 week later ($t1$), before practicing another recipe. As the scenarios differ in length and complexity, we could not compare performance in S1 and S5, and we compared instead, for each scenario, performance in $t0$ and $t1$. Comparisons between the game assessment made during $t0$ and $t1$ revealed no differences in the gnosis time ($p = 0.115$), but a significant reduction is praxis and executive function time, with participants becoming faster in the praxis ($p = 0.001$) and executive functions activities from the practice to the follow up round ($p = 0.017$). No difference in the number of errors was

TABLE 3 | Game assessment.

	MCI ($N = 9$)	AD ($N = 12$)	Outpatients ($N = 14$)	Nursing home ($N = 7$)	Apathetic ($N = 11$)	Non-apathetic ($N = 10$)
Scenario duration (mean ± SD)	**7m26s (2m51s)**	**11m44s (2m56s)**	9m21s (3m50s)	10m59s (2m53s)	10m28s (3m25s)	9m15s (3m47s)
Gnosis time $t0$ (mean ± SD)	**1m35s (0m48s)**	**3m06s (1m02s)**	2m20s (1m05s)	2m35s (1m28s)	2m45s (1m12s)	2m01s (1m07s)
Gnosis time $t1$ (mean ± SD)	**1m07s (0m30s)**	**2m52s (1m41s)**	1m41s (1m05s)	2m50s (2m03s)	2m18s (1m47s)	1m49s (1m14s)
Executive functions time $t0$ (mean ± SD)	**3m25s (1m04s)**	**4m37s (1m22s)**	4m14s (1m22s)	3m46s (1m24s)	4m16s (1m11s)	2m51s (1m36s)
Executive functions time $t1$ (mean ± SD)	**2m13s (1m11s)**	**4m31s (1m36s)**	3m26s (2m00s)	3m34s (1m35s)	3m44s (1m38s)	3m10s (2m05s)
Praxis time $t0$ (mean ± SD)	**3m13s (0m49s)**	**4m25s (1m02s)**	3m47s (1m06s)	4m04s (1m10s)	4m04s (1m00s)	3m39s (1m14s)
Praxis time $t1$ (mean ± SD)	**2m22s (0m35m)**	**4m07s (1m21m)**	3m10s (1m19s)	3m37s (1m32s)	3m37s (1m27s)	2m58s (1m16s)

Mean time to complete a scenario, and mean time spent on each game activity in t0 (first time a scenario was played with the clinician) and t1 (1 week later) for MCI vs. AD patients, outpatients vs. patients living in nursing homes, and by apathetic vs. non-apathetic patients. Results in bold indicate a significant difference at the Mann–Whitney U test (p < 0.05).

found for any of the activities (all $ps > 0.519$). The improvement in the executive functions was greater for MCI compared to AD patients. Specifically, MCI participants showed a more consistent reduction in the time spent in the activity ($p = 0.010$; see **Figure 2**) and in the mean number of errors ($p = 0.025$) in $t1$ vs. $t0$ compared to AD participants. Furthermore, outpatients improved in the gnosis (reduction of time from $t0$ to $t1$) more than patients living in nursing home ($p = 0.14$). No significant difference between apathetic and non-apathetic patients was found.

A significant correlation was found between the improvement in the gnosis and the praxis [$r_{(20)} = 0.55, p = 0.013$], and between the praxis and the executive functions [$r_{(20)} = 0.68, p = 0.001$], thus suggesting that participants that became faster in the gnosis and executive functions became also faster in the praxis. The correlation between gnosis and executive functions did not reach statistical significance [$r_{(20)} = 0.43, p = 0.057$].

A significant correlation was found between the time spent playing during the 4-week training and the improvement shown in the gnosis [$r_{(20)} = 0.52$, $p = 0.020$] and executive functions time [$r_{(20)} = 0.46$, $p = 0.040$], thus suggesting that gnosis and executive functions (as assessed by the game) could be improved by exercise. The correlation between time spent playing and improvement in the praxis time was in the same direction, but did not reach statistical significance [$r_{(20)} = 0.36, p = 0.124$].

Discussion

The results of the present feasibility study confirm that Kitchen and cooking was acceptable and interesting for both patients with MCI and AD. This interpretation is confirmed by the fact that 20 out of 21 participants successfully completed the 4-week training, and by the fact that participants rated the game experience as interesting, reported to be highly satisfied and motivated by the game, to experience more positive emotions than negative emotions, and not to be fatigued both at the beginning and at the end of the training. Moreover, participants played a mean of almost one and a half hours per week (corresponding to 14 scenarios), thus suggesting that they played also outside the meetings with the clinician. Interestingly, there was a huge variability in the playing time: while a few participants played almost only with the clinician, some others played up to 70 scenarios per week, thus suggesting that the game most probably met their interest, and was particularly adapted to them. This variability in the playing time confirms that adaptation to the patients' interest and level impairment is a key challenge in designing SGs with training purposes (Robert et al., 2014).

We are convinced that a critical factor in the success of the intervention was the presence of the clinician. We designed Kitchen and scenario as a tool to help the patient to train outside the clinical consultation, but the periodic supervision of the clinician is necessary to explain the functioning to the patient and the family, keep track of the evolution of the performance, to adapt the intervention step by step to the patients' changing needs and to maintain the motivation.

Another interesting finding was that we found a significant difference in the number of scenarios played depending of the place of residence, with outpatients playing significantly more compared to patients in nursing home. The proportion of AD/MCI was not significantly different between outpatients and patients living in nursing home, suggesting that the level of impairment was similar in the two groups, and thus was not the critical variable in explaining the effect. One possible explanation concerns the level of initial engagement/commitment to the training. Outpatients needed to come to the Memory consultation five times during the 4-week training, which implies that they were very committed when they decided to take part in the study. On the contrary, for patients living in nursing homes the trainings with the clinician took place in the nursing home, which makes possible that some participants accepted even if they had a lower commitment. Another possibility is that outpatients played more because they were followed more closely by a family caregiver. The level of external motivation reported at the beginning and at the end of the training (e.g., "I play because my friends/family say I should") did not differ between the two groups. However, it is possible that the simple sharing experience stimulated patients to play more.

The major limitation of these results is the small number of participants included in the study. The study was designed as a pilot experiment most specifically oriented to a feasibility target. In addition, it was important in order to fit the European commission requirement to include both outpatients and patients living in nursing home. This is obviously of interest, but it increases the heterogeneity of the population.

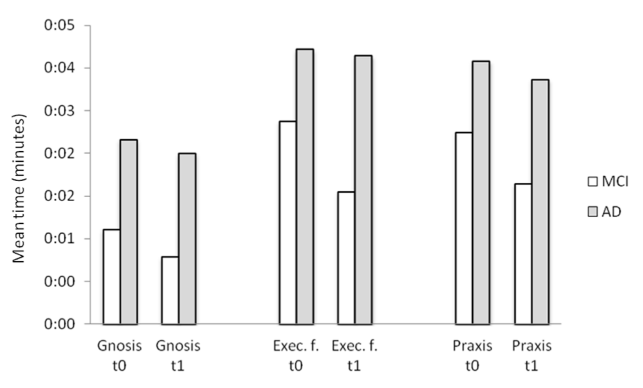

FIGURE 2 | Mean time spent on the different game activities the first time a scenario was played (t0) and one week after (t1) for MCI and AD patients.

A Serious Game for Apathy

Apathy is one of the most common neuropsychiatric symptoms of AD and related disorders, occurring in almost 65% of dementia patients (Ferri et al., 2005; König et al., 2014). Apathy is associated with a higher degree of global functional impairment (Doron et al., 2013) and therefore to a loss of autonomy in activities of daily living (Boyle et al., 2003; Robert et al., 2009). One of the challenges of the project VERVE was to design SG that, due to their playful nature, may be particularly adapted to target apathetic patients. The results of this feasibility study suggest that Kitchen and cooking was adapted to apathetic participants. Indeed, apathetic participants reported to be as interested, motivated, and satisfied by the game experience as non-apathetic participants, a result which in interesting on its own. Critically, apathetic patients played *more* during the 4-week training compared to non-apathetic patients, suggesting that they were not impaired in this specific goal-directed activity. At a first glance, this may seem counterintuitive. A possible explanation concerns the fact that non-apathetic participants have more interests and external activities compared to apathetic participants, and thus had less time that they wish to dedicate to the game. Future studies including qualitative interviews may be useful to corroborate this interpretation.

Kitchen and Cooking as an Assessment Tool

Correlation analysis revealed that performance in the different game activities was consistent with performance in the classical functional and neuropsychological tests. Specifically, the game gnosis time at the beginning of the training correlated with the TMT A time, thus confirming that the object search and selection task can be considered a good proxy for attentional processes, and the game executive functions time showed a significant correlation with the Victoria Stroop Test, an index of inhibition control. Furthermore, AD participants spent more time to complete a scenario compared to MCI participants, and were slower in the gnosis, praxis, and executive functions time, thus suggesting that the assessment made with Kitchen and scenario was in line with that made using classical assessment instruments.

This SG was not designed to substitute the classical functional, behavioral, and neuropsychological assessment. However, the present results suggest that it may be useful to complement classical assessment methods. For instance, it could be easily employed to track the evolution of executive functions and attentional deficits overtime. Furthermore, due to its playful nature, it may be particularly adapted to patients whose performance is strongly influenced by test anxiety. For instance a heavily impaired performance at the classical tests associated to preserved functioning in the SG activity may prompt the clinician to be more cautious in the interpretation of the test results.

Kitchen and Cooking a Training Tool

The results of the training suggest that performance in the different game activities could be improved overtime. After 1 week of practicing on a scenario, participants became faster in both executive functions activity and praxis activity. Our training was designed to test feasibility and not the improvement in performance, so we did not ask participants to play every scenario in the first (S1) and last session (S5) with the clinician, meaning that we were unable to quantify exactly the improvement observed over 4 weeks. However, as patients were able to improve significantly their performance in 1 week, it is likely that the improvement in performance between S1 and S5 would be even more pronounced. This hypothesis is supported by the finding that participants who played more improved more in the game activities, specifically in the gnosis and executive functions.

Interestingly, MCI participants improved significantly more in the executive functions activity compared to AD participants. These results supports the view that early interventions targeting predementia stage are more effective in training cognitive abilities such as executive functions (REF), and suggest that Kitchen and cooking (employed as a training tool) may be specifically adapted to people with MCI.

Conclusion

Kitchen and cooking is a SG game developed with the tight collaboration between clinicians and game designers in the context of the European FP7 project VERVE. This study suggests that Kitchen and cooking was acceptable, interesting and motivating for both patients with MCI and AD, and that it was adapted also to apathetic participants. This suggests that Kitchen and cooking could be an additional tool for clinicians in order to stimulate apathetic patients. Given these promising results, we are going to use the game in clinical practice, and propose the game to the patients coming for consultation to our Memory clinic and to the patients in the day centers, with a special focus on apathetic patients showing a loss or reduction in self-initiated behaviors, but preserved environmental-stimulated behaviors (Robert et al., 2009). This will allow us to collect additional data on the usability and acceptability of the game, and on its efficacy over longer training periods. Also, in order to allow the patients to select among a variety of activities, and to meet the interests of a wider variety of patients, we aim at creating new SGs.

Acknowledgments

This study was supported by a grant from the FP7 European Commission Seventh Framework Programme VERVE project (Vanquishing fear and apathy through e-inclusion: http://www.verveconsortium.com/) and by the Innovation Alzheimer association.

References

Aalten, P., de Vugt, M. E., Lousberg, R., Korten, E., Jaspers, N., Senden, B., et al. (2003). Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dement. Geriatr. Cogn. Disord.* 15, 99–105. doi: 10.1159/000067972

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., et al. (2013). Videogame training enhances cognitive control in older adults. *Nature* 501, 97–102. doi: 10.1038/nature12486

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., and Jones, E. (2011). Alzheimer's disease. *Lancet* 377, 1019–1031. doi: 10.1016/S0140-6736(10)61349-9

Bayard, S., Erkes, J., and Moroni, C. (2011). Victoria Stroop Test: normative data in a sample group of older people and the study of their clinical applications in the assessment of inhibition in Alzheimer's disease. *Arch. Clin. Neuropsychol.* 26, 653–661. doi: 10.1093/arclin/acr053

Benveniste, S., Jouvelot, P., and Péquignot, R. (2010). "The MINWii Project: renarcissization of patients suffering from Alzheimer's disease through videogame-based music therapy," in *Proceedings of the 9th International Conference on Entertainment Computing, ICEC'2010*, Coex Séoul, Corée, 8–11.

Boulay, M., Benveniste, S., Boespug, S., Jouvelot, P., and Rigaud, A. S. (2011). A pilot usability study of MINWii, a music therapy game for demented patients. *Technol. Healthcare* 19, 233–246. doi: 10.3233/THC-2011-0628

Boyle, P. A., Malloy, P. F., Salloway, S., Cahn-Weiner, D. A., Cohen, R., and Cummings, J. L. (2003). Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *Am. J. Geriatr. Psychiatry* 11, 214–221. doi: 10.1097/00019442-200303000-00012

Doron, M., Bastian, T., Maire, A., Dugas, J., Perrin, E., Gris, F., et al. (2013). Estimation of physical activity monitored during the day-to-day life autonomous wearable device (SVELTE project). *Conf. Proc. IEEEEng. Med. Biol. Soc*. 4629–4632. doi: 10.1109/EMBC.2013.6610579

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., et al. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* 9, 1118–1127. doi: 10.1016/S1474-4422(10)70223-4

Fahn S., and Elton R. L. (1987). "Unified Parkinson's disease rating scale," in: *Recent Developments in Parkinson's Disease*, eds S. Fahn, C. D. Marsden, D. Calne, and M. Goldstein (Florham Park, NJ: Macmillan Health Care Information), 153–163.

Férnandez-Calvo, B., Rodriguez-Pérez, R., Contador, I., Rubio-Santorum, A., and Ramos, F. (2011). Efficacy of cognitive training programs based on new software technologies in patients with Alzheimer Type dementia. *Psicothema* 23, 44–50.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., et al. (2005). Global prevalence of dementia: a Delphi consensus study. *Lancet* 366, 2112–2117. doi: 10.1016/S0140-6736(05)67889-0

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental test" a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatry. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Fua, K. C., Gupta, S., Pautler, D., and Farber, I. (2013). "Designing serious games for elders," in *Proceedings Foundations of Digital Games*, Chania, 291–297.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., et al. (2006). Mild cognitive impairment. *Lancet* 367, 1262–1270. doi: 10.1016/S0140-6736(06)68542-5

Gledhill, J. A., Rodary, C., Mahe, C., and Laizet, C. (2002). French validation of the revised piper fatigue scale. *Rech. Soins. Infirm.* 68, 50–65.

Gourlan, M., Sarrazin, P., and Trouilloud, D. (2013). Motivational interviewing as a way to promote physical activity in obese adolescents: a randomised-controlled trial using self-determination theory as an explanatory framework. *Psychol. Health* 28, 1265–1286. doi: 10.1080/08870446.2013.800518

Katz, S., Down, T. D., Cash, H. R., and Grotz, R. C. (1970). Progress in the development of the index of ADL. *Gerontologist* 10, 20–30. doi: 10.1093/geront/10.1_Part_1.20

König, A., Aalten, P., Verhey, F., Bensadoun, G., Petit, P. D., Robert, P., et al. (2014). A review of current information and communication technologies: can they be used to assess apathy? *Int. J. Geriatr. Psychiatry* 29, 345–358. doi: 10.1002/gps.4017

Legouverneur, G., Pino, M., Boulay, M., and Rigaud, A. (2011). Wii sports, a usability study with MCI and Alzheimer's patients. *Alzheimer's Dement.* 7, S500–S501. doi: 10.1016/j.jalz.2011.05.2398

Leone, E., Piano, J., Deudon, A., Alain, B., Wargnier, A. M., Balard, P., et al. (2012). "What are you interested in?" —A survey on 601 nursing homes residents activities interests. *Adv. Aging Res.* 1, 13–21. doi: 10.4236/aar.2012.12002

Lezak, M., Howieson, M., and Loring, D. (2004). *Neuropsychological Assessment*, 4th Edition. New York: Oxford University Press.

Lindeboom, J., Schmand, B., Tulner, L., Walstra, G., and Jonker, C. (2002). Visual association test to detect early dementia of the Alzheimer type. *J. Neurol. Neurosurg. Psychiatry* 73, 126–133. doi: 10.1136/jnnp.73.2.126

Mathuranath, P. S., George, A., Cherian, P. J., Mathew, R., and Sarma, P. S. (2005). Instrumental activities of daily living scale for dementia screening in elderly people. *Int. Psychogeriatr.* 17, 461–474. doi: 10.1017/S1041610205001547

McCallum, S., and Boletsis, C. (2013). "DementiaGames: a literature review of dementia-related Serious Games," in *Serious Games Development and Applications –Lecture Notes in Computer Science*, Vol. 8101, eds M. Ma, M. F. Oliveira, S. Petersen, and J. B. Hauge (Berlin: Springer Publishing), 15–27. doi: 10.1007/978-3-642-40790-1_2

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 34, 939–944. doi: 10.1212/wnl.34.7.939

Mulin, E., Leone, E., Dujardin, K., Delliaux, M., Leentjens, A., Dessi, B., et al. (2011). Diagnostic criteria for apathy in clinical practice. *Int. J. Geriatr. Psychiatry* 26, 158–165. doi: 10.1002/gps.2508

Nor Wan Shamsuddin, S., Lesk, V., and Ugail, H. (2011). Virtual environment design guidelines for elderly people in early detection of dementia. *World Acad. Sci. Eng. Technol.* 59, 751–755.

Padala, K. P., Padala, P. R., Malloy, T. R., Geske, J. A., Dubbert, P. M., Dennis, R. A., et al. (2012). Wii-fit for improving gait and balance in an assisted living facility: a pilot study. *J. Aging Res.* 2012, 1–6. doi: 10.1155/2012/597573

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.* 56, 303–308. doi: 10.1001/archneur.56.3.303

Robert, P. H., König, A., Amieva, H., Andrieu, S., Bremond, F., Bullock, R., et al. (2014). Recommendations for the use of serious games in people with Alzheimer's disease, related disorders and frailty. *Front. Aging Neurosci.* 6:54. doi: 10.3389/fnagi.2014.00054

Robert, P., Onyike, C. U., Leentjens, A. F. G., Dujardin, K., Aalten, P., Starkstein, S., et al. (2009). Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur. Psychiatry* 24, 98–104. doi: 10.1016/j.eurpsy.2008.09.001

Rosen, A. C., Sugiura, L., Kramer, J. H., Whiteld-Gabrieli, S., and Gabrieli, J. D. (2011). Cognitive training changes hippocampal function in mild cognitive impairment: a pilot study. *J. Alzheimers Dis.* 26, 349–357. doi: 10.3233/JAD-2011-0009

Sohnsmeyer, J., Gilbrich, H., and Weisser, B. (2010). Effect of a six-week intervention with an activity-promoting videogame on isometric muscle strength in elderly subjects. *Int. J. Comp. Sci. Sport* 9, 75–79.

Stavros, Z., Fotini, K., and Magda, T. (2010)."Computer based cognitive training for patients with mild cognitive impairment (MCI)," in *Proceedings of the 3rd International Conference on Pervasive Technologies Related to Assistive Environments*, *PETRA'10* (Petras, RI: ACM), 1–3. doi: 10.1145/1839294.1839319

Tarnanas, I., Schlee, W., Tsolaki, M., Müri, R., Mosimann, U., and Nef, T. (2013). Ecological validity of virtual reality daily living activities screening for early dementia: longitudinal study. *JMIR Serious Games* 1, e1. doi: 10.2196/games.2778

Watson, D., Clark, L. A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063–1070. doi: 10.1037/0022-3514.54.6.1063

Weybright, E., Dattilo, J., and Rusch, F. (2010). Effects of an interactive videogame (Nintendo Wii) on older women with Mild Cognitive Impairment. *Ther. Recreation. J.* 44, 271–287.

Wollersheim, D., Merkes, M., Shields, N., Liamputtong, P., Wallis, L., Reynols, F., et al. (2010). Physical and psychosocial effects of Wii videogame use among older women. *Int. J. Emerging Tech. Soc.* 8, 85–98.

Yamaguchi, H., Maki, Y., and Takahashi, K. (2011). Rehabilitation for dementia using enjoyable video-sports games. *Int. Psychogeriatr*. 23, 674–676. doi: 10.1017/S1041610210001912

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

OPINION
published: 11 March 2015
doi: 10.3389/fnagi.2015.00026

Clinical trial design of serious gaming in mild cognitive impairment

Cristina Muscio[1,2]*, *Pietro Tiraboschi*[3], *Ugo P. Guerra*[4], *Carlo A. Defanti*[1] and *Giovanni B. Frisoni*[5,6]

[1] Fondazione Europea Ricerca Biomedica, Centro Eccellenza Alzheimer, Ospedale Briolini, Bergamo, Italy, [2] Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy, [3] Division of Neurology V/Neuropathology, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy, [4] Fondazione Poliambulanza, Nuclear Medicine Department, Brescia, Italy, [5] Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS Centro San Giovanni di Dio-Fatebenefratelli, Brescia, Italy, [6] Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland

Keywords: serious games, Alzheimer's disease, mild cognitive impairment, biomarker enrichment strategy, outcome measures, clinical trials

OPEN ACCESS

Edited by:
Philippe Robert, University of Nice Sophia Antipolis, France

Reviewed by:
Alexandra König, EA CoBTek CHU de Nice - Université de Nice Sophia Antipolis, France
Julian Alvarez, Lille1 University, France
Francois Bremond, Inria, France

Correspondence:
Cristina Muscio, cristina.muscio@gmail.com

Received: *18 January 2015*
Accepted: *23 February 2015*
Published: *11 March 2015*

Citation:
Muscio C, Tiraboschi P, Guerra UP, Defanti CA and Frisoni GB (2015) Clinical trial design of serious gaming in mild cognitive impairment. Front. Aging Neurosci. 7:26. doi: 10.3389/fnagi.2015.00026

Introduction

The "Global Impact of Dementia: 2013–2050" (Alzheimer's Disease International, 2013), released ahead of the December 2013 G8 Dementia Summit in London, estimated that 44.35 million people in the world were living with dementia in 2013. This number was predicted to increase to 75.6 million in 2030, and 135.5 million in 2050. This dramatic increase will have profound implications for social and economic costs (Alzheimer's Disease International, 2010). Since the most common dementia subtype (50–75%) is Alzheimer's disease (AD), its early detection and clinical effectiveness of its prevention and treatment represent a major public health concern and have been identified as a research priority (Alzheimer's Disease International, 2009; Ballard et al., 2011; Foster et al., 2014).

Recently, there has been a growing interest in employing Information and Communication Technologies (ICT) to evaluate patient's cognitive and functional impairment for early detection of AD (Wan Shamsuddin et al., 2011; Tarnanas et al., 2014). Beyond being important for assessment, ICT can also play a key role in the patient's treatment, stimulation, and rehabilitation (Robert et al., 2014). This is the idea underlying the current use of Serious Games (SGs), which are a broader reapplication of videogames resources integrating gaming and serious purposes. Lately, a few studies have started to investigate the efficacy of SGs used as an ICT intervention, which target cognitive decline, in people with AD and mild cognitive impairment (MCI). Until now, however, rigorous studies are still lacking. To overcome the current methodological issues and to evaluate the efficacy of SGs in secondary prevention (that currently is being pursued and is considered one of the potentially attainable goals of treatment, Foster et al., 2014), the purpose of the present opinion paper is to highlight the importance of defining harmonized SGs parameters, and to propose the implementation of biomarkers as enrichment strategy and outcome measures in SGs trial design. We will now review the history and state-of-art types and use of SGs, before describing in more detail our proposal.

History of Serious Games: Origin, Typologies, Target

SGs are games designed for a primary purpose other than entertainment, enjoyment or fun (Michael and Chen, 2005). The historical origin of this oxymoron dates back to Neo-Platonists, who referred the term "*serio ludere*" to light-hearted approach in literature dealing with serious matters (Manning, 2004). The first use of SG oxymoron close to its current use seems to be in book written (Abt's, 1970), even though with a more extensive meaning. In fact, a SG could indeed be a computer game, a game, a role-playing game or even an outdoor game (Alvarez and Djaouti, 2012). The SG term in a digital context was firstly used in 2002, with the start of the Serious Game Initiative led by David Rejeski and Ben Sawyer in the US (De Gloria et al., 2014).

To date, SGs have been applied in many sectors, including education, training, defense, health, communications, marketing, politics, and the list is continually expanding (Alvarez and Djaouti, 2012). Since SGs addresses a set of markets, they are constituted by a wide variety of different types. Considering the dual nature of SGs, a system that classifies SGs according to both the "serious" and the "game" dimensions was proposed by Djaouti et al. (2011)[1]. This model has classified 3080 SGs so far.

Examples of SGs include (see Alvarez and Djaouti, 2012, for a review): (i) military games, commonly dedicated to tactical and strategic training as well as recruitment for the army; (ii) edugames for educational and training purposes, also usable in a school context; (iii) advergames, where the gameplay is centered around a commercial message; (iv) newsgames that are based on current events or certain journalistic issues; (v) SGs dedicated to health sector aimed to improve player's cognitive or physical abilities; etc.

SGs do not target exclusively young gamers. A considerable proportion (20–29%) of regular digital gamers are indeed older than 50 years (ESA, 2011; BIU, 2014). In this respect, it is worth noting the increase by 32% in the number of US females gamers aged 50 and older from 2012 to 2013 (ESA, 2014). Because the number of elderly people who play video games in the past decades has steadily increased and is predicted to grow further (Robert et al., 2014), even small beneficial effects may have significant public health implications (Alzheimer's Disease International, 2014).

The State-of-Art Use of Cognitive Serious Games with Healthy Older Adults and Ad Patients

The cognitive effect of SGs played by older adults has not yet been studied thoroughly (Weybright et al., 2010; Alzheimer's Disease International, 2014). In the context of research focused on successful cognitive aging and on the possibility to modify the cognitive decline normally associated with healthy aging (Zinke et al., 2014), anyway, SGs have been demonstrated to be a motivating tool with some beneficial effects in improving cognitive functions in healthy older adults (Nouchi et al., 2012; Anguera et al., 2013). In the study reported by Anguera et al. (2013), indeed, it's worth mentioning that: (i) SG improved both trained and untrained cognitive abilities, which is commonly referred to as a transfer effect, that is the effect due to a training not only on skills or performance that are trained, but also on skills or performance that are not trained (Nouchi et al., 2012); (ii) untrained abilities that improved were sustained attention and working memory, which are known to be involved in everyday functioning; and (iii) performance gains remained stable 6 months after training without booster sessions. This transfer effect of SG on the improvement of executive functions and processing speeds in the elderly has been also demonstrated with a short-term training (Nouchi et al., 2012), suggesting that a possible transfer effect from laboratory-based tasks to real world ones may be expected. Neurophysiological findings support training-induced neuroplasticity as the mechanistic basis of these SG effects (Anguera et al., 2013).

However, whether AD patients or population at high risk for developing AD (i.e., MCI) may benefit from SGs is unknown (Robert et al., 2014).

Recently, some studies have started to employ SGs with people with AD and MCI as a cutting-edge cognition-focused intervention (**Table 1**). Cognition-focused interventions fall under the broader umbrella of non-pharmacological interventions, and can be defined as interventions that directly or indirectly target cognitive functioning as opposed to interventions that focus primarily on behavioral, emotional or physical functions (Bahar-Fuchs et al., 2013). These interventions are typically designed to promote intellectual stimulation and minimize cognitive impairment (Weybright et al., 2010). Progressive decline of cognitive functions is indeed a clinical feature of AD and has been found to be associated with impairment in activities of daily living (Tomaszewski Farias et al., 2009). Thus, intervention aimed at prevention and rehabilitation of such decline may promote a longer independent life at home and decrease the burden of dementia on patients and families.

Despite the promising results and the increasing interest in applying cognitive SGs to AD/MCI patients, rigorous feasibility and efficacy studies are still lacking, partly reflecting the only recent interest in employing SGs in cognitively impaired patients (Robert et al., 2014). The main methodological issues are: limitation of randomized controlled studies and lack of harmonized procedures (i.e., absence of standardized SG parameters such as when, where and with whom SGs have to be played), as well as small sample size and questionable choice of patient selection and outcome measures. However, these issues are common in studies addressing cognition-focused interventions (Woods et al., 2012; Bahar-Fuchs et al., 2013).

Future Perspectives

Definition of Harmonized SGS Parameters

To overcome the current lack of harmonized procedures, one important aspect to be taken into account in the SG trial design includes the definition of parameters such as when, where and with whom SGs are more adapted to be played by AD/MCI patients.

According to the recommendations reported in (Robert et al., 2014), SGs for MCI patients' stimulation could be considered adapted to be used both everyday and once a week; at home, in day centers and in the nursing homes; with a therapist, a professional caregiver and a family caregiver.

In our opinion, SG trials should take into account these methodological recommendations, and assess SG feasibility and efficacy due to when, where, with whom SG is played by patients.

[1] http://serious.gameclassification.com

TABLE 1 | Main findings of studies applying only cognitive or both physical and cognitive SGs to AD/MCI patients.

Author and year	Group	Sample size	Serious game	Study design	Outcome measure(s)	Main findings
Stavros et al., 2010	MCI	59 (30 experimental, 29 control subjects)	Complete Brain Workout	N/A. Experimental program: tasks of visual attention, visual spatial abilities, visual memory, and executive function: 20 weekly sessions in 6 months. Control program: no participation in any type of intervention.	Neuropsychological change on cognitive tests.	Improvement of attention, verbal memory and ADL in the experimental group.
Weybright et al., 2010	MCI	2	Nintendo Wii™ Sport Bowling	Single-subject multiple baseline ABAB design. A = television-watching phase: 15-min, 4 times a week, 3–2 weeks. B = Wii™ bowling game intervention: 15-min, 4 times a week, 2–3 weeks.	Checklist based on observations of videotapes focusing on patients' attention and positive feelings.	Improvement of attention and positive feelings during Wii™ bowling game session.
Rosen et al., 2011	MCI	12 (6 experimental, 6 control subjects)	Adaptive games from Posit Science	Randomized pilot study. Experimental program: 7 exercises designed to improve processing speed and accuracy in auditory processing: 100 min per session for 24 sessions. Control program: listening to audio books, reading online newspapers, and playing a visuospatially-oriented computer game: 90 min per session for 24 sessions.	Neuropsychological change on cognitive tests and brain function change as measured in an auditory-verbal fMRI task.	Improvement of memory and left hippocampal activation in the experimental group.
Yamaguchi et al., 2011	AD, Parkinson's disease PD, Vascular dementia VD (mild-to-moderate)	7 AD, 1 PD, 1 VD	Xavix Hot Plus	Single group pre-/post-test design. Video sports-games specifically devised for rehabilitation (requiring, for example, to move legs to the sound of music or to grab coins which appearing on the TV screen) played once a week for 10 weeks.	General cognitive, visuospatial and constructive functions, and behavioural changes on neuropsychological and multidimensional scales, respectively.	Post-test improvement of general cognitive, visuospatial and constructive functions, and sociability.
Boulay et al., 2011	AD (mild-to-moderately severe)	7	MinWii (MINDs)	Pilot usability study. 1 training and 4 testing sessions focused on music therapy and cognitive stimulation, once per week for 3 months.	Efficacy (number of errors during each task), efficiency (time to complete each task, number of verbal interventions provided by the moderator) and satisfaction indicators (satisfaction questionnaire).	Clear learning effect and positive impact on satisfaction.

(Continued)

TABLE 1 | Continued

Author and year	Group	Sample size	Serious game	Study design	Outcome measure(s)	Main findings
Férnandez-Calvo et al., 2011	AD (mild)	45 (15 experimental, 30 control subjects)	Big Brain Academy	Randomized controlled trial. Experimental program: exercises designed to stimulate 5 cognitive domains such as thinking, memory, computation, reasoning ability, and identification: 3 times a week for 12 weeks. Two control programs: (i) a traditional stimulation program 3 times a week for 12 weeks, or (ii) no participation in any type of intervention.	Neuropsychological, behavioral, and functional changes on pertinent tests.	Slower rates of cognitive decline and fewer depressive symptoms in the experimental group.
Mosimann et al., 2014	MCI due to AD	158 (50 experimental, 53 active control, 55 passive control subjects)	Novel serious game	N/A. Experimental program: a 5-week SG training protocol (a virtual museum cognitive stimulation environment), 4 times per week for 90 min each day. Control programs not specified.	SG performance, neuropsychological change on cognitive tests and default mode network connectivity change as measured by resting-state electroencephalography.	Greater spatial improvement in functional connectivity (associated with better performances in executive function, verbal encoding and retrieval tasks) and increased activation in prefrontal and temporo-parietal areas in the experimental group.

As far as "with whom" is concerned, we think that it could also be interesting to study SGs played by multiple players physically co-present or by online patients connected from remote locations. One of SG strengths is indeed its possible role in promoting social interactions among patients with cognitive impairment (Robert et al., 2014).

Biomarkers as Enrichment Strategy and Outcome Measures

It is generally estimated that up to one third of patients enrolled in AD trials do not have AD (Delrieu et al., 2014), leading to dilution of observable treatment effects (Aisen, 2011). However, AD pathology can be identified in living subjects through pathophysiological markers indicative of abnormal amyloid deposition that, in addition to a specific cognitive profile, moves a patient from a status of MCI of undetermined etiology to that of prodromal AD (Dubois et al., 2014). CSF Aβ1-42 and/or PET-amyloid imaging, as well as hippocampal atrophy on MRI, have indeed been qualified as enrichment biomarkers to enroll predemented AD subjects in regulatory clinical trials (see EMA/CHMP/SAWP/893622/2011 and EMA/CHMP/SAWP/809208/2011 qualification opinions). Inclusion of biomarkers into clinical trials for treatment of early AD has until now been recommended for pharmacological studies alone. However, both pharmacological and non-pharmacological studies can share the same issues that may have contributed to their failures (Doody et al., 2014; Salloway et al., 2014), including for example misdiagnosis of patients and insensitivity of outcome measures.

To overcome the above-mentioned limitations of cognition-focused interventions pertaining to patient selection and outcome measures, and to evaluate the efficacy of SG in secondary prevention, we propose to implement in the SG trial design: (i) a biomarker enrichment strategy to enroll MCI due to AD, and (ii) the use of biomarkers as outcome measures in combination with clinical ones.

A biomarker enrichment strategy would be expected to support screening out non-AD cases and screening in AD ones, reducing the diagnostic inaccuracy at enrollment and, thus, minimizing the masking of treatment effects that occurs when misdiagnosed patients are recruited (Morris and Selkoe, 2011). Once identified MCI due to AD using enrichment biomarkers, it could also be relevant to randomize these patients after stratifying them into different groups based on positivity on one or more biomarkers, in order to evaluate a possible differential effect of SG on MCI subjects presumably at different pre-dementia stages of the AD process. MCI patients with brain amyloidosis and neurodegeneration are indeed at higher risk of dementia in the following years. According to the current pathophysiologic model of AD (Jack et al., 2010), they might be at a more advanced disease stage (Prestia et al., 2013). For this reason, a SG effect dependent on single or multiple biomarker positivity could be hypothesized and taken into account for defining optimal SG protocols. Patients with MCI could also be stratify into two groups based on positivity or negativity of biomarkers, in order to investigate whether cognitively impaired subjects devoid of AD pathology might have a greater benefit due to less severe neuronal injury and, consequently, greater brain reserve (Stern, 2009). Finally, it could be interesting to verify if there is an association between biomarkers and methodological parameters cited in the previous subparagraph: for instance, can patients with a single positive biomarker or negativity of biomarkers take advantage from SGs played at lower time intensity (e.g., once at week) or alone at home compared with patients with multiple positive biomarkers or positivity of biomarkers, respectively?

Some studies in AD and MCI patients have shown that MRI and FDG-PET biomarkers may be more sensitive to change than clinical measures, as reported by Caroli et al. (2014) but regulatory agencies have not yet recognized biomarkers as surrogate outcome measures. This cautious approach is due to the requirement that, to be recognized as surrogate outcome measures, biomarker changes should reliably predict detectable clinical changes (Aisen, 2011). Unfortunately, the results of randomized clinical trials with anti-beta amyloid drugs (Abeta vaccine AN1792 and bapineuzumab) have until now shown no clinical efficacy despite a change in biomarkers. On the other hand, use of biomarkers would allow studies with fewer participants, shorter durations, lower costs, and with the possibility to control for the specificity of disease-modifying effect (Morris and Selkoe, 2011; Food and Drug Administration: Draft Guidance for Industry. Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease, 2013). Recent non-pharmacological studies that have incorporated hippocampal atrophy as biomarker outcome have found a disease-modifying benefit of aerobic exercise in early AD over 6 months (Honea et al., 2014), suggesting that similar results could also be found applying physical and cognitive SGs.

Conclusions

If the presumed beneficial effects of SGs will be demonstrated by robust studies, the potential societal impact will be huge considering the very high prevalence of cognitive impairment due to AD, the popularity of video games played by baby-boomers now at risk of dementia, the current lack of effective treatments, and the cost-effectiveness of these enjoyable interventions. Moreover, video games already marketed to older adults for maintaining cognitive health may be seen as a scale up of a prevention program in a high-risk subgroup of the population (Alzheimer's Disease International, 2014). SGs may represent a motivating, low-barrier, engaging and sustainable method to improve or at least delay the decline in specific social, sensory-motor, cognitive and emotional functions of elderly people (Wiemeyer and Kliem, 2012).

References

Abt, C. (1970). *Serious Games*. New York, NY: Viking Press.

Aisen, P. S. (2011). Clinical trial methodologies for disease-modifying therapeutic approaches. *Neurobiol. Aging.* 32, S64–S66. doi: 10.1016/j.neurobiolaging.2011.09.008

Alvarez, J., and Djaouti, D. (2012). *Introduction au Serious Game*. Paris, FR: Question Théoriques.

Alzheimer's Disease International. (2009). *World Alzheimer Report 2009: The Global Prevalence of Dementia.* London: Alzheimer's Disease International.

Alzheimer's Disease International. (2010). *World Alzheimer Report 2010: The Global Economic Impact of Dementia.* London: Alzheimer's Disease International.

Alzheimer's Disease International. (2013). *Policy Brief: The Global Impact of Dementia 2013-2050.* London: Alzheimer's Disease International.

Alzheimer's Disease International. (2014). *World Alzheimer Report 2014: Dementia and Risk Reduction: An Analysis of Protective and Modifiable Factors.* London: Alzheimer's Disease International.

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., and Janowich, J. (2013). Video game training enhances cognitive control in older adults. *Nature* 501, 97–102. doi: 10.1038/nature12486

Bahar-Fuchs, A., Clare, L., and Woods, B. (2013). Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database Syst. Rev.* 6:CD003260. doi: 10.1002/14651858.CD003260

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., and Jones, E. (2011). Alzheimer's disease. *Lancet* 377, 1019–1031. doi: 10.1016/S0140-6736(10)61349-9

BIU. (2014). *Gamer-Statistiken*. Available online at: http://www.biu-online.de/en/facts/market-figures-2013/gamer-statistics/age-distribution.html

Boulay, M., Benveniste, S., Boespug, S., Jouvelot, P., and Rigaud, A. S. (2011). A pilot usability study of MINWii, a music therapy game for demented patients. *Technol. Health Care* 19, 233–246. doi: 10.3233/THC-2011-0628

Caroli, A., Prestia, A., Wade, S., Chen, K., Ayutyanont, N., and Landau, S. M. (2014). Alzheimer disease biomarkers as outcome measures for clinical trials in MCI. *Alzheimer Dis. Assoc. Disord*. doi: 10.1097/WAD.0000000000000071. [Epub ahead of print].

De Gloria, A., Bellotti, F., Berta, R., and Lavagnino, E. (2014). Serious Games for education and training. *Int. J. Serious Game* 1, 1.

Delrieu, J., Ousset, P. J., Voisin, T., and Vellas, B. (2014). Amyloid beta peptide immunotherapy in Alzheimer disease. *Rev. Neurol.* 170, 739–748. doi: 10.1016/j.neurol.2014.10.003

Djaouti, D., Alvarez, J., and Jessel, J. P. (2011). "Classifying serious games: the G/P/S model," in *Handbook of Research on Improving Learning and Motivation through Educational Games: Multidisciplinary Approaches*, ed P. Felicia (Hershey, PA: IGI Global), 118–136.

Doody, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., and Joffe, S. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 370, 311–321. doi: 10.1056/NEJMoa1312889

Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., and Blennow, K. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* 13, 614–629. doi: 10.1016/S1474-4422(14)70090-0

ESA. (2011). *Essential Facts About the Computer and Video Games Industry*. Available online at: http://www.isfe.eu/sites/isfe.eu/files/attachments/esa_ef_2011.pdf

ESA. (2014). *Essential Facts About the Computer and Video Games Industry*. Available online at: http://www.isfe.eu/sites/isfe.eu/files/attachments/esa_ef_2014.pdf

Férnandez-Calvo, B., Rodriguez-Pérez, R., Contador, I., Rubio-Santorum, A., and Ramos, F. (2011). Efficacy of cognitive training programs based on new software technologies in patients with Alzheimer-type dementia. *Psicothema* 23, 44–50.

Food and Drug Administration: Draft Guidance for Industry. Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. (2013). Available online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf. (Accessed: February 24, 2013).

Foster, N. L., Hackett, J. S., White, G., Chenevert, S., Svarvar, P., and Bain, L. (2014). Justifying reimbursement for Alzheimer's diagnostics and treatments: seeking alignment on evidence. *Alzheimers Dement.* 10, 503–508. doi: 10.1016/j.jalz.2014.05.003

Honea, R., Vidoni, E. D., Morris, J., Graves, R., Perea, R. D., and Van Sciver, A. (2014). Aerobic exercise reduces hippocampal atrophy in individuals with early Alzheimer's disease. *Alzheimer's Dement.* 10, P303. doi: 10.1016/j.jalz.2014.04.509

Jack, C. R. Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., and Weiner, M. W. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* 9, 119–128. doi: 10.1016/S1474-4422(09)70299-6

Manning, J. (2004). *The Emblem*. London, UK: Reaktion Books.

Michael, D., and Chen, S. (2005). *Serious Games: Games that Educate, Train and Inform*. Boston, MA: Thomson Course Technology PTR Development.

Morris, J. C., and Selkoe, D. J., (2011). Recommendations for the incorporation of biomarkers into Alzheimer clinical trials: an overview. *Neurobiol Aging.* 1, S1–S3. doi: 10.1016/j.neurobiolaging.2011.09.005

Mosimann, U., Tarnanas, I., Dimitriadis, S., Laskaris, N., Bamidis, P., and Tsolaki, M. (2014). Serious gaming enhances cognitive function in MCI due to Alzheimer's disease. *Alzheimer's Dementia* 10, P922. doi: 10.1016/j.jalz.2014.07.135

Nouchi, R., Taki, Y., Takeuchi, H., Hashizume, H., Akitsuki, Y., and Shigemune, Y. (2012). Brain training game improves executive functions and processing speed in the elderly: a randomized controlled trial. *PLoS ONE* 7:e29676. doi: 10.1371/journal.pone.0029676

Prestia, A., Caroli, A., van der Flier, W. M., Ossenkoppele, R., Van Berckel, B., and Barkhof, F. (2013). Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology* 80, 1048–1056. doi: 10.1212/WNL.0b013e3182872830

Robert, P. H., König, A., Amieva, H., Andrieu, S., Bremond, F., and Bullock, R. (2014). Recommendations for the use of Serious Games in people with Alzheimer's Disease, related disorders and frailty. *Front. Aging Neurosci.* 6:54. doi: 10.3389/fnagi.2014.00054

Rosen, A. C., Sugiura, L., Kramer, J. H., Whiteld-Gabrieli, S., and Gabrieli, J. D. (2011). Cognitive training changes hippocampal function in mild cognitive impairment: a pilot study. *J. Alzheimers Dis.* 26, 349–357. doi: 10.3233/JAD-2011-0009

Salloway, S., Sperling, R., Fox, N. C., Blennow, K., Klunk, W., and Raskind, M. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 23, 322–333. doi: 10.1056/NEJMoa 1304839

Stavros, Z., Fotini, K., and Magda, T. (2010). "Computer based cognitive training for patients with mild cognitive impairment (mci)," in *Proceedings of the 3rd International Conference on Pervasive Technologies Related to Assistive Environments, PETRA ′10* (Petras, RI: ACM), 1–3.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia* 47, 2015–2028. doi: 10.1016/j.neuropsychologia.2009.03.004

Tarnanas, I., Tsolaki, M., Nef, T., M., Müri, R., and Mosimann, U. P. (2014). Can a novel computerized cognitive screening test provide additional information for early detection of Alzheimer's disease? *Alzheimers Dement.* 10, 790–798. doi: 10.1016/j.jalz.2014.01.002

Tomaszewski Farias, S., Cahn-Weiner, D. A., Harvey, D. J., Reed, B. R., Mungas, D., and Kramer, J. H. (2009). Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. *Clin. Neuropsychol.* 23, 446–461. doi: 10.1080/13854040802360558

Wan Shamsuddin, S. N., Valerie, L., and Hassan, U. (2011). Virtual environment design guidelines for elderly people in early detection of dementia. *World Acad. Sci. Eng. Technol.* 5, 1860–1864.

Weybright, E., Dattilo, J., and Rusch, F. (2010). Effects of an interactive video game (Nintendo Wii) on older women with mild cognitive impairment. *Ther. Recreation J.* 44, 271–287.

Wiemeyer, J., and Kliem, A. (2012). Serious games in prevention and rehabilitation – a new panacea for elderly people? *Eur. Rev. Aging Phys. Activ.* 9, 41–50. doi: 10.1007/s11556-011-0093-x

Woods, B., Aguirre, E., Spector, A. E., and Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst. Rev.* 2:CD005562. doi: 10.1002/14651858.CD005562

Yamaguchi, H., Maki, Y., and Takahashi, K. (2011). Rehabilitation for dementia using enjoyable video-sports games. *Int. Psychogeriatr.* 23, 674–676. doi: 10.1017/S1041610210001912

Zinke, K., Zeintl, M., Rose, N. S., Putzmann, J., Pydde, A., and Kliegel, M. (2014). Working memory training and transfer in older adults: effects of age, baseline performance, and training gains. *Dev. Psychol.* 50, 304–315. doi: 10.1037/a0032982

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 22 April 2015
doi: 10.3389/fnagi.2015.00050

Reliability of a novel serious game using dual-task gait profiles to early characterize aMCI

Ioannis Tarnanas[1]*, Sotirios Papagiannopoulos[1], Dimitris Kazis[1], Mark Wiederhold[2], Brenda Widerhold[3] and Magda Tsolaki[1]

[1] 3rd Department of Neurology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2] Division of Cognitive and Restorative Neurology, Virtual Reality Medical Center, San Diego, CA, USA, [3] Virtual Reality Medical Institute, Brussels Life Sciences Incubator, Catholic University's Woluwe Campus, Brussels, Belgium

Background: As the population of older adults is growing, the interest in a simple way to detect characterize amnestic mild cognitive impairment (aMCI), a prodromal stage of Alzheimer's disease (AD), is becoming increasingly important. Serious game (SG) - based cognitive and motor performance profiles while performing everyday activities and dual-task walking (DTW) "motor signatures" are two very promising markers that can be detected in predementia states. We aim to compare the consistency, or conformity, of measurements made by a custom SG with DTW (NAV), a SG without DTW (DOT), neuropsychological measures and genotyping as markers for early detection of aMCI.

Methods: The study population included three groups: early AD ($n = 86$), aMCI ($n = 65$), and healthy control subjects ($n = 76$), who completed the custom SG tasks in three separate sessions over a 3-month period. Outcome measures were neuropsychological data across-domain and within-domain intra-individual variability (IIV) and DOT and NAV latency-based and accuracy-based IIV. IIV reflects a transient, within-person change in behavioral performance, either during different cognitive domains (across-domain) or within the same domain (within-domain). Test–retest reliability of the DOT and NAV markers were assessed using an intraclass correlation (ICC) analysis.

Results: Results indicated that performance data, such as the NAV latency-based and accuracy-based IIV, during the task displayed greater reliability across sessions compared to DOT. During the NAV task-engagement, the executive function, planning, and motor performance profiles exhibited moderate to good reliability (ICC = 0.6–0.8), while during DOT, executive function and spatial memory accuracy profiles exhibited fair to moderate reliability (ICC = 0.3–0.6). Additionally, reliability across tasks was more stable when three sessions were used in the ICC calculation relative to two sessions.

Discussion: Our findings suggest that "motor signature" data during the NAV tasks were a more reliable marker for early diagnosis of aMCI than DOT. This result accentuates the importance of utilizing motor performance data as a metric for aMCI populations where memory decline is often the behavioral outcome of interest. In conclusion, custom

OPEN ACCESS

Edited by:
Valeria Manera, University of Nice Sophia Antipolis, France

Reviewed by:
Cristina Muscio, Fondazione Europea di Ricerca Biomedica, Italy
Pedro Gamito, Lusophone University, Portugal

****Correspondence:***
Ioannis Tarnanas, Gerontechnology and Rehabilitation Group, University of Bern, CH-3010 Bern, Switzerland
gtarnanas@gmail.com

Received: *19 January 2015*
Accepted: *26 March 2015*
Published: *22 April 2015*

Citation:
Tarnanas I, Papagiannopoulos S, Kazis D, Wiederhold M, Widerhold B and Tsolaki M (2015) Reliability of a novel serious game using dual-task gait profiles to early characterize aMCI.
Front. Aging Neurosci. 7:50. doi: 10.3389/fnagi.2015.00050

SG with DTW performance data provide an ecological and reliable approach for cognitive assessment across multiple sessions and thus can be used as a useful tool for tracking longitudinal change in observational and interventional studies on aMCI.

Keywords: mild cognitive impairment, early diagnosis, motor performance, virtual reality, test–retest reliability, Alzheimer's disease

Introduction

Even though a number of risk factors for sporadic Alzheimer's disease (AD), the most common type of dementia, have been discussed (e.g., diagnosis of mild cognitive impairment (MCI), hippocampal atrophy, family history of AD, apolipoprotein-E ε4 allele [APOE-ε4]), one of the most well-documented risk factors for the disease is increasing age (Ferreira et al., 2014; Naj et al., 2014). Neurodegenerative changes such as atrophy, which is characteristic of AD, and occasionally of other dementing diseases such as fronto-temporal lobar dementia (FTLD) or Hippocampal Sclerosis, have a relatively long pre-morbid asymptomatic period (Lindberg et al., 2012a; Pelletier et al., 2013). At the same time, despite the fact that no cognitive symptoms may be obvious during the pre-morbid period, by the time AD is diagnosed, sufficient neuronal injury has occurred such that reversal of the disease is perhaps unlikely (Petersen, 2003; Lindberg et al., 2012b; Lockhart et al., 2012). This has therefore raised considerable interest in the prodromal stage of AD, involving revised criteria for diagnosing an early clinical stage of AD ("MCI due to AD," aMCI or MCI-AD; Dubois and Albert, 2004; Michon, 2009; Sperling et al., 2011) and "Prodromal AD"(Albert et al., 2011) and incorporating biomarkers to increase the certainty of the diagnosis (Dickerson et al., 2013).

The accuracy of early diagnosis for dementia is increasingly important for both therapeutic and scientific investigations. Many of the early-onset dementias are treatable, and the presentation of the common degenerative diseases of late life, such as AD, can be different when presenting in the fifth or sixth decade. The currently available diagnostic tests have moved the field closer to early diagnosis of AD; however, differential diagnosis is broad, and a definitive diagnosis is made only with the development of clinical dementia and the presence of amyloid plaques and neurofibrillary tangles at autopsy (Snowden et al., 2011). An ideal AD biomarker should be able to satisfy the following criteria: the ability to diagnose AD with high sensitivity and specificity as confirmed by the gold standard of autopsy validation, detect early-stage disease, and track the progression of AD and monitor disease progression or therapeutic efficacy (McKhann et al., 2011). This understanding could offer the potential for tailored treatments and a specific diagnosis for both early-onset and late-onset dementia. MCI-AD, or aMCI, is a term used to describe early AD signs that precede functional and cognitive impairment (Sperling et al., 2011) and may be clinically indistinguishable from what is described as "probable AD" (Albert et al., 2011; Dickerson et al., 2013). Epidemiological studies have suggested that the most common form of aMCI is a multiple deficit syndrome with memory impairment and a 10–15% annual risk of conversion to AD (Portet et al., 2006). According to some recent studies, MCI individuals with amnestic syndrome of the hippocampal type (HaMCI), compared to those with the amnestic syndrome of the non-hippocampal type (NHaMCI), are the leading at-risk subgroup of the MCI population for the development of dementia due to AD (Sarazin et al., 2007). However, it is still controversial whether the tests designed to detect hippocampal amnestic syndrome (Duara et al., 2013), such as atrophy of the hippocampus in the CA1 subfield region (Burger, 2010; Fletcher et al., 2014), are superior to other tests for the detection of early-stage dementia (Albert et al., 2011; McKhann et al., 2011). Yet, in addition to the atrophy of hippocampus only in the CA1 subfield region experts recently developed the harmonized protocol for the manual segmentation of the whole hippocampus (Prestia et al., 2013, Alzheimers Dementia). Indeed, after a harmonization effort lasted 4 years and funded by the Alzheimer's Association, world experts converged onto the harmonized segmentation protocol, which. the European Medicines Agency has qualified as an enrichment biomarker to enroll mild and moderate as well as predemented AD subjects in regulatory clinical trials.

Besides the usefulness of cued recall as a diagnostic tool for aMCI and AD (De Jager et al., 2010; Kelemen and Fenton, 2010; Carlesimo et al., 2011; Chechko et al., 2014), emerging evidence has demonstrated the value of walking stability and variability analysis as an early indicator of aMCI and AD (Persad et al., 2008; Gillain et al., 2009; Theill et al., 2011; Montero-Odasso et al., 2012; Muir et al., 2012). More specifically, prospective studies over periods of five and 6 years in cohorts of 427 and 603 older subjects over 70 years of age demonstrated that initial quantitative measures of gait, such as velocity, variability, and frequency can predict the risk of developing dementia (Waite et al., 2005; Verghese et al., 2007; Montero-Odasso et al., 2014). However, the relationship between cognitive function in everyday abilities and gait variables in conditions other than normal walking (NW) is insufficiently understood in people with aMCI. In everyday activities, there are numerous dual-task walking (DTW) situations that require active involvement of the visual system (Al-Yahya et al., 2011). Observing how people walk while they perform a secondary task with a high demand on attention, i.e., a dual-task paradigm, has been used to assess interactions between cognition and gait. Executive function is often implicated in DTW because subjects must walk and adapt to new and/or complex situations that involve working memory, mental inhibition, and mental flexibility. In addition, less efficient executive functions in older adults have shown significant contribution to impairments in spatial memory, especially when spatial interference is high (Holden and Gilbert, 2012).

Another concept that has recently attracted the attention of researchers and clinicians is that of cognitive frailty. Recent work has defined cognitive frailty as a multi-dimensional geriatric syndrome characterized by the simultaneous presence of both physical frailty and cognitive impairment without the presence of a concomitant neurological disease (see Kelaiditi et al., 2013 for a review). Cognitive frailty is viewed as a potential precursor of neurodegenerative processes (Duron et al., 2014). However, few studies have made the link between motor fragility reflected by a reduction in walking velocity and cognitive fragility reflected by an early alteration in executive function and have hypothesized that alteration in motor performance could occur before detection of cognitive impairment (Perrochon et al., 2013).

In a similar vein, recent studies have shown that increased cognitive intra-individual variability (IIV) across accuracy scores from neuropsychological tests, representing different cognitive domains (across-domain IIV), might serve as a biomarker of cognitive frailty occurring before detection of prodromal AD (Kälin et al., 2014). More particularly, latency- (variability across response time performance scores) and accuracy-based IIV (variability across accuracy scores – correct vs. wrong responses) have reportedly been associated with functional decline (Dixon et al., 2007; Morgan et al., 2012), incident dementia (Holtzer et al., 2008), and probable AD (Brewster et al., 2012). A more recent study compared within- and across-domain IIV and APOE genotype between healthy control subjects (HCS), MCI, and AD in a single comparative study and found that within-domain IIV may constitute a cognitive marker for the detection of prodromal AD at the MCI stage, whereas across-domain IIV may detect beginning AD at the MCI stage (Kälin et al., 2014).

In this context, computerized cognitive assessments, such as serious games (SGs), can ideally be applied to detect subtle changes in both DTW and IIV between HCS and aMCI performance profiles (Robert et al., 2014). There is already evidence that SG can be successfully employed for the characterization of episodic and prospective memory profiles in MCI and AD (Werner et al., 2009; Weniger et al., 2011; Plancher et al., 2012) or even early screening for aMCI (Tarnanas et al., 2013, 2014). According to the literature, SG interactions require coordination of information by eliciting medium to high cognitive control, such as inhibition of external stimuli or processing speed (e.g., reaction time at interactive events), which is believed to be affected by aging (De Lillo and James, 2012; Korsch et al., 2014). Very recently, an innovative DTW concept for detecting cognitive impairment eliciting medium to high cognitive control, called the Walking Stroop Carpet, was demonstrated by Perrochon et al. (2013), but to our knowledge, this is the first study reporting on a complex everyday activities SG employing DTW, which might indicate prodromal AD.

The aim of this study was to (1) systematically evaluate the reliability of two SGs—a high cognitive control, requiring inhibition of external stimuli, and planning a virtual day-out task without DTW (DOT) and a high cognitive control, requiring inhibition, navigation task with DTW (NAV)—and (2) explore the stability of test–retest measurements as a factor of the number of SG sessions.

Materials and Methods

Participants

A total of 270 participants (HCS $n = 100$, aMCI $n = 80$, and AD $n = 90$) were considered for analysis from ongoing studies at the 3rd Neurological Clinic of the Aristotle University of Thessaloniki, Greece and from the Greek Association for Alzheimer Disease and Related Disorders (GAADRDs) Memory Clinics, belonging to the 3rd Neurological Clinic of the Aristotle University of Thessaloniki. The study was carried out in accordance with the Declaration of Helsinki, and the participants were recruited from the outpatient population of the GAADRD Memory Clinics or by advertisement in the local media. All subjects had complete cognitive baseline data acquired between January 2010 and April 2013 with written informed consent obtained prior to study participation. From the original HCS sample, 24 subjects were excluded from the analyses due to alcohol abuse ($n = 2$), dropout ($n = 6$), and medication ($n = 16$). Also, 15 aMCI and six early AD subjects were also excluded due to dropout after the initial assessment. Thus, a total of 76 HCS, 65 aMCI, and 86 early AD patients were eligible for the analyses.

Amnestic MCI was diagnosed according to the criteria of Winblad et al. (2004), and all diagnoses were made by a multidisciplinary team under the supervision of an experienced psychiatrist. The diagnosis was made if the patient met the following criteria: (1) memory complaint, (2) abnormal memory for age, (3) normal activities of daily living, (4) normal general cognitive function, and (5) not demented. Structural magnetic resonance imaging (MRI) data were also available in our aMCI cases in order to exclude other conspicuous brain abnormalities that could account for cognitive decline. The diagnosis of AD was done according to the International Working Group (IWG-2) criteria considering three main markers: abnormal neuropsychological assessment, medial temporal atrophy on MRI, and abnormal Abeta42 or tau protein concentrations in the CSF (Dubois et al., 2014). Additionally, all three groups (HC, aMCI, and early AD) were screened for disorders, which could potentially produce cognitive impairment, i.e., depression; psychiatric, neurological, and other diseases. Such subjects were excluded if there were such disorders or medication use potentially affecting cognition. Furthermore, it was ascertained that all participants had normal or corrected to normal vision. All participants but three older adults were right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971).

Neuropsychological and Psychomotor Examination

All subjects were assessed with a standardized neuropsychological test battery. The neuropsychological test battery consisted of multiple tests covering the following cognitive domains: working and episodic memory, executive function, attention/psychomotor processing speed, language, and visual-constructive abilities. The Mini–Mental State Examination (Folstein, 1975) was used to assess global cognitive functioning. For episodic memory, the Grober–Buschke scale was used

(Grober et al., 1988; Carlesimo et al., 2011). Short-term memory and working memory were investigated using a digit span forward test (Ramsay and Reynolds, 1995). Tests of executive functioning included verbal fluency and category fluency (the Set Test; Isaacs and Akhtar, 1972), Stroop (Stirling, 1979), and the TMT B (Tombaugh, 2004). Long term memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT; Rosenberg et al., 1984). We determined impairment if at least one score per domain was 1.5 SD below group means compared to test-specific normative data.

In addition to the neuropsychological examination, participants also completed a baseline psychomotor evaluation in order to exclude physical frailty or other forms of physical disability that might affect the reliability of both DTW and across-domain and within-domain latency- and accuracy-based IIV across SG performance profiles, such as arthritis. The psychomotor examination included a number of simple and complex measures addressing the ability to understand and perform with accuracy specific physical performance tasks. These tasks included the following: (a) "Gait-speed" was measured as the time (to 0.1 s) required for a participant to walk a 4.6-m course at his or her usual pace after starting from a standstill and recorded by stopwatch, and b) the "Finger-Tapping Test" measured both the dominant and non-dominant hand using a computerized screening test, which measured finger tapping speed for a given duration of 10 s.

Quantitative Gait Assessment

We performed a baseline motor evaluation of single-task spontaneous walking for 10 m in a normal environment on an 8-m electronic walkway (GAITRite®, CIR Systems Inc, Sparta, NJ, USA). This tool is equipped with a portable, pressure-sensitive electronic walkway [793 cm × 61 cm × 0.6 cm (L × W × H)] which provides data for both spatial and temporal gait parameters. The simple-task trial consisted of walking the length of the mat at the participant's usual pace. For the dual-task trials, participants walked at their usual pace, with no instruction to prioritize the gait or cognitive task, while doing the following cognitive tasks aloud: (i) counting backward from 100 by ones and (ii) naming animals. To balance and minimize the effects of learning and fatigue, the order of the dual tasks was randomized. Allowing both gait and cognitive tasks to vary provides a better representation of daily living activities, and the reliability of this protocol in people with MCI has been previously established (Montero-Odasso et al., 2009).

SG Hardware Setup

The SG used is patent pending (XtremeVRI AG, Winterthur, Switzerland) and used mobile phone based Augmented Reality (AR) in order to present cognitive tasks and record all behavioral and kinetic responses while the subject navigated the AR environment inside his house (**Figure 1**).

DOT and NAV Tasks

The novel SG used in this study consisted of two modules simulating complex activities of daily living (CADL): the 3D immersive reality day-out complex task without DTW (DOT) and the 3D immersive reality spatial NAV. The DOT was a complex task breakdown followed by a rehearsal exercise of a virtual apartment building fire evacuation drill. The drill included six different scenarios of increasing difficulty, where participants navigated the virtual environment using a first-person perspective and simple hand pointing gestures for forward, backward, and left, and right lateral movement, respectively. They could also use natural finger pointing and grabbing gestures in order to select, pick, drop, and move objects inside the virtual environment and had to complete each within 8 min. All participant movement within the virtual building was recorded at 10 Hz and represented as a series of x, y, z coordinates, with actions annotated and time stamped.

The DOT naturalistic actions script was based on an ordered list of right and wrong actions that was prepared by an occupational psychologist and was used to examine executive function and prospective memory as well as planning and reasoning in a complex emergency routine. The fire evacuation drill setting had six different simulated fire situations (from easy to more difficult) taking place at a virtual apartment block with three levels and five apartments per level. The task put a medium to high load on the cognitive control processes with which older adults prioritize, organize, initiate, and complete a number of

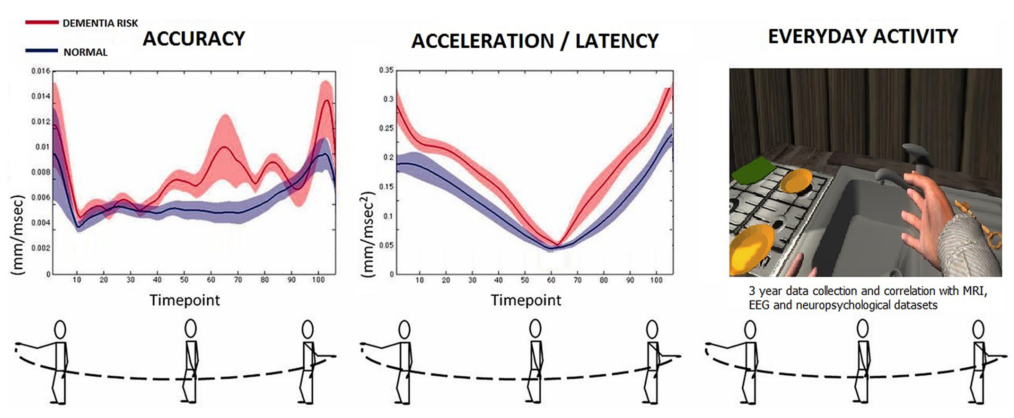

FIGURE 1 | The custom SG with DTW setup.

subroutines (e.g., pick-up the phone and call the fire department, sound the fire-alarm) in order to evacuate safely and in the fastest possible way from an apartment level (e.g., second floor) to the ground area (e.g., determine and gather information on the size of the fire, avoid smoke, avoid wrong actions like using the elevator). In this sense, DOT is a complex activity of daily living, which previous research showed is a valid and reliable indicator of cognitive decline in elderly persons (Tarnanas et al., 2013).

The NAV task took place at the same virtual apartment block but with the player challenged in different aspects of executive function, such as volition, self-awareness, planning, inhibition of dominant response, and external distraction during response control, and dual-task coordination. The goal at difficulty level 1 was to navigate from point A to point B, after the route was demonstrated by a first-person perspective camera walkthrough without iteration. The NAV task took place with six levels of difficulty, with the addition of one more point of destination per difficulty level—for example, level 3 has three points to reach, level 4 has four, etc. Each level had a starting position (start) and an end position (goal) and multiple ways to arrive from start to goal. Participants were asked to make their way from start to goal in the shortest time possible. The NAV task placed a medium to high demand on higher order cognitive control processes, such as following a mental strategy to reach the goal with performance monitoring while inhibiting environmental stressors, such as virtual characters forcing the player to choose a less familiar route or interact with distractors in the virtual environment, a process which typically involves cognitive control.

According to the literature, interactions such as the DOT and NAV tasks, require participants to follow a mental strategy and monitor their performance by eliciting medium to high cognitive control, such as inhibition of external stimuli or processing speed (e.g., reaction time at interactive events; Kelemen and Fenton, 2010). This coordination of information to select appropriate behavioral responses is believed to be affected by aging (Korsch et al., 2014).

The order of participating in either the DOT or NAV tasks was random, and both started after each participant had 5 min to read written instructions detailing the task, virtual building layout, and task rules. Then, participants practiced the virtual environment using gestures to move around the building and completed 3 practice runs involving object collection, button pressing, unlocking the stairwell door with a key code, and folder sorting. This also allowed participants to familiarize themselves with the building. None of the practice runs were used in the main task. The practice session took in total approximately 20 min.

Participants played all difficulty levels of DOT and NAV in a baseline session (Visit 1), again all levels at a 1-month post-baseline session (Visit 2), and finally all levels at a 3-month post-baseline session (Visit 3). A total of three sessions were measured in order to assess test–retest reliability.

Computation of IIV of DOT and NAV Performance

In order to apply IIV computations to the DOT and NAV performance profile data, we first had to categorize the performance profiles into accuracy-based and latency-based data. Since NAV was a more complex task than DOT, we conducted a principal component analysis (PCA) of participants' performance data on the cognitive variables at their initial visit in order to create composite IIV measures. We then used the Spearman's correlations to identify three accuracy- based and three latency-based performance categories, explained bellow, which place medium to high demands on higher order cognitive abilities for both DOT and NAV. Across-domain IIV was calculated with tasks representing different cognitive domains, while within-domain IIV was calculated with tasks representing cognitive control. Additionally, in order to avoid ceiling or floor effects, we added performances from each difficulty level and calculated a total performance profile from all difficulty levels per cognitive domain and category above in order to prevent suppressing variation at the extreme ends of the distribution.

To calculate DOT across-domain accuracy-based IIV, we used accuracy scores from three data categories, each representing a different cognitive domain: (1) spatial memory accuracy measured as the correct route selection, such as the nearest emergency exit or route for the evacuation of the virtual apartment building, according to the memorized virtual building layout; (2) planning accuracy measured as the correct order of subroutines execution, such as first sounding the fire alarm and then calling the fire department; and (3) executive functions accuracy measured as successful subroutines completion, such as sounding the fire alarm.

NAV across-domain accuracy-based IIV was calculated using accuracy scores from three data categories, each representing a different cognitive domain: (1) spatial memory accuracy measured as correct route selection, such as the nearest route for navigating from start to goal, according to the memorized virtual building layout; (2) planning accuracy measured as the correct order of subroutines execution, such as first going to point B and then to point C before goal; and (3) executive functions accuracy measured as successful subroutines completion, such as reaching each point from start to goal.

For calculating DOT within-domain accuracy-based IIV, we used accuracy performance data from three categories, each representing executive functions and eliciting recruitment of cognitive control processes. We calculated: (1) omissions of the subroutines, (2) repetition of the same subroutine, and (3) perseverations of incorrect order while performing the subroutines before completing the given script per difficulty level. According to the literature, virtual reality-based navigation, and interactions, such as the DOT task process, require participants to generate, maintain, and monitor a plan and to select and establish specific responses—therefore, accessing cognitive control (Cushman et al., 2008).

Accordingly, for calculating NAV within-domain accuracy-based IIV, we used accuracy performance data from: (1) omissions of the destination points between start and goal, (2) repetition of the same destination point, and (3) perseverations of incorrect order while navigating to the goal before completing the given script per difficulty level. Participants needed to maintain a goal while inhibiting a routine response in favor of a less familiar one, a process which typically involves cognitive control (West et al., 2002).

The DOT across-domain latency-based IIV was calculated using performance data from the participant's timed response within three data categories, each representing a different cognitive domain: (1) total time to complete the navigation route per difficulty level, according to the memorized virtual building layout; (2) total time to complete the order of emergency evacuation subroutines execution; and (3) time of execution through acceleration data, such as "fast hand pointing gestures," per subroutine completion.

In order to calculate the NAV across-domain latency-based IIV, we used performance data from the participant's timed response at: (1) total time to complete the navigation route per difficulty level; (2) gait frequency at interactive events, such as avoidance of moving obstacles and distractors; and (3) gait parameters such as stride length, distance, and variability of stride while completing the navigation per destination point.

DOT within-domain latency-based IIV was calculated using timed response performance data from the following categories, eliciting recruitment of cognitive control processes: (1) reaction time of "navigation gestures" usage, measured as the time elapsed between the virtual character idle state and the next immediate "direction command"; (2) reaction time of "interaction gestures" usage, measured as the time elapsed between the virtual character idle state and the next immediate interaction response to the virtual environment, such as "open door action"; and (3) reaction time at interactive events, such as avoidance of moving obstacles.

Finally, to calculate NAV within-domain latency-based IIV, we used timed response performance data from the following categories, eliciting recruitment of cognitive control processes during DTW: (1) gait velocity during the navigation, measured as the time elapsed between the virtual character idle state and the next immediate "direction command"; (2) cadence, measured as steps per minute between the virtual character idle state and the next immediate interaction response to the virtual environment, such as "open door action"; and (3) time in double support during interactive events, such as avoidance of distractors and moving obstacles.

Following the work described in recent studies (Nesselroade and Salthouse, 2004; Kälin et al., 2014), we calculated the intra-individual standard deviation (ISD) across each individual's performance profile data in order to compute IIV. Starting from the accuracy-based IIV and the HCS group, we log-transformed performance data in order to achieve normal distribution and multiplied by -1 to adjust for scaling difference. This process generated for HCS standardized residuals representing adjusted accuracy and latency scores with a mean of 0 and variance of ~ 1. We used the General Linear Model to estimate effects associated with age, education, gender, and potential interactions. The model parameters were used to predict accuracy scores in aMCI and early AD subjects. We then calculated standardized residuals for aMCI and early AD subtracting the predicted from the observed accuracy scores and dividing it by the model's SE. Similar to the work of Kälin et al. (2014), we used the intra-individual mean (IIM) across residuals underlying across-domain IIV (across-domain IIM) and across residuals underlying within-domain IIV (within-domain IIM) as covariates in all relevant analyses in order to address the association between ISD and mean performance.

Accordingly, for the latency-based IIV we followed data preparation procedures similar to those of Bielak et al. (2010). We removed the high and low outliers in reaction time from each performance profile category for each participant. We defined high outliers as the individual reaction times that were greater than 3 SD more than the person's mean reaction time and low outliers as individual reaction times less than 3 s. After the outliers were removed, we recalculated mean RT and within-person ISDs for each participant. In order to remove the effect of mean RT from the ISDs, since mean RT is positively associated with variability, and age is associated with slower reaction times (Anstey et al., 2007), we regressed the ISDs on mean RT and collected standardized ISD residuals. Finally, the ISDs of all variables were normally distributed, and we calculated the across-domain IIV and within-domain IIV composite scores of the standardized residuals.

Genotyping Data

We used restriction isotyping to classify participants as either carriers (APOE ε2/ε4, ε3/ε4, and ε4/ε4) or non-carriers of the APOE ε4 allele. A similar approach is also described in another IIV study (Kälin et al., 2014).

Statistics

All analyses were performed as two-tailed tests using the statistical analysis software package PASW 18.0 for Windows. We used univariate analysis of variance (ANOVA) to perform the group comparisons of normally distributed demographic, raw, and adjusted performance data applying Sidak *post hoc* tests correcting for multiple comparisons. Not normally distributed variables were analyzed with Kruskal–Wallis tests followed by Mann–Whitney tests corrected for multiple comparisons, and categorical variables were analyzed with Pearson's chi-square test. Difference in across- and within-domain IIV was analyzed with univariate analyses of covariance (ANCOVA) in order to evaluate group-wise differences with the diagnostic group treated as the main effect. The influences of age, gender, and education as well as across- and within-domain IIM were also used as covariates to control for influences on IIV. To calculate the effect of the IIV type (accuracy- vs. latency-based), we used multivariate analyses of covariance (MANCOVA), and to account for the unbalanced designed we applied Sum of Square Type III. We calculated significant group effects using a Sidak *post hoc* test correcting for multiple comparisons. Finally, all parametric analyses were performed with a significance level of $p < 0.05$, while a significance level of $p < 0.017$ ($0.05/3 = 0.017$) was applied for non-parametric analyses.

Following a recent study (Montero-Odasso et al., 2014), gait variability was calculated as the coefficient of variation for stride time: CV = (SD of stride time/mean stride time) × 100. Gait velocity (cm/s) and stride time variability (CV_{st}, %) were measured during the NAV dual-task trials.

We assessed the test–retest reliability with the intraclass correlation coefficient (ICC) as defined by Shrout and Fleiss (1979). This form of ICC utilizes a two-way ANOVA in which both the SG performance data and participants are treated as random effects to assess reliability at a single point in time. Using this model, test–retest reliability was characterized as excellent (ICC N 0.8), good (ICC 0.6–0.79), moderate (ICC 0.4–0.59), fair (ICC 0.2–0.39), or poor (ICC b 0.2; Kam et al., 2012). We assessed the stability of ICC using three SG data collection sessions by calculating the ICC values from the first two sessions and comparing them to the values from all three sessions.

Results

The baseline demographic details are summarized in **Table 1**, including IIV computations from the baseline neuropsychological performance.

In general we observed a main effect between diagnostic groups and IIV [$F_{(2,225)} = 7.87$; $p = 0.001$; $\eta^2 = 0.07$]. We also observed that IIV in general was influenced by age [$F_{(1,225)} = 4.21$; $p = 0.03$; $\eta^2 = 0.03$] and by IIM, although the effect size was not significant [$F_{(1,225)} = 3.63$; $p = 0.06$; $\eta^2 = 0.02$], but not by education [$F(_{1,225)} = 0.12$; $p = 0.72$; $\eta^2 = 0.00$] or gender [$F_{(1,225)} = 1.78$; $p = 0.27$;

TABLE 1 | Clinical characteristics of the subjects (means with SDs).

Population				
N		227		
Subgroups		**HCS**	**aMCI**	**Early AD**
n		76	65	86
Age (years)		70.06 (13.32)	72.63 (10.05)	76.59 (10.58)
Female		38 (65%)	40 (62%)	54 (63%)
Education		16.1 (6.4)	15.6 (8.0)	8.6 (5.6)
Neuropsychological data				
Global	MMSE	29.1 (0.6)**	27.1 (0.8)**	22.3 (4.2)**
Memory	Free recall†	43.2 (9.1)**	35.6 (10.9)**	22.2 (10.8)**
	RAVLT delayed recall	12.7 (1.8)**	11.0 (3.1)**	9.3 (10.4)*
	Digit span forward	6.0 (2.1)**	5.0 (2.1)**	3.0 (1.9)**
Attention	Stroop trial 3	47.5 (11.1)*	42.1 (13.4)**	28.6 (15.3)**
	TMTB	140.4 (53.3)**	198.4 (91.9)**	220.5 (204.2)**
	Letter fluency	10.5 (2.9)**	8.8 (3.4)**	5.6 (2.8)**
	Category fluency	19.3 (2.9)*	18.8 (2.2)**	16.5 (2.8)**
Psychomotor data				
Gait speed, m/s	Combined	0.95 (0.2)	0.92 (0.2)	0.88 (0.2)
	Women	0.94 (0.2)	0.83 (0.0)	0.77 (0.1)
	Men	1.02 (0.1)	1.01 (0.0)	0.95 (0.6)
Tapping speed dominant, taps/second	Combined	5.88 (0.8)	5.76 (0.8)	5.74 (0.9)
	Women	5.53 (0.7)	5.49 (0.8)	5.43 (0.7)
	Men	6.29 (0.7)	6.21 (0.7)	6.19 (0.7)
Tapping speed non-dominant, taps/second	Combined	5.63 (0.6)	5.61 (0.7)	3.58 (0.7)
	Women	5.41 (0.5)	5.38 (0.6)	5.33 (0.6)
	Men	5.91 (0.6)	5.96 (0.6)	5.90 (0.6)
Baseline gait performance				
Velocity, cm/s	Simple gait	112.9 (15.6)*	96.5 (25.1)*	89.5 (30.4)*
	Counting gait	107.1 (20.7)*	89.3 (22.4)**	70.3 (25.5)**
	Naming animals gait	98.3 (23.3)*	78.6 (23.3)**	69.1 (21.3)**
Stride time variability (CV, %)	Simple gait	2.34 (1.3)*	3.53 (2.3)*	4.11 (2.6)*
	Counting gait	2.80 (0.6)**	4.90 (3.4)**	6.81 (3.3)**
	Naming animals gait	3.99 (2.1)**	5.73 (6.0)**	7.65 (5.0)**
Neuropsychological data IIV				
Across-domain	IIM	0.00 (0.6)**	−1.41 (0.9)**	−2.34 (0.8)**
Within-domain	IIM	0.01 (0.9)**	−0.53 (0.9)**	−1.80 (1.0)**
Across-domain	IIV‡	0.92 (0.6)*	0.96 (0.6)*	1.37 (0.8)**
Within-domain	IIV‡	0.81 (0.6)**	1.12 (0.6)*	1.25 (0.7)**

† *Free recall: sum of the three free recalls.*
‡*Analyses of covariance, means adjusted for gender, age, and education and across- or within-domain IIM.*
*$p < 0.05$, **$p < 0.001$.
HCS, healthy control subjects; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, mini-mental state examination; TMT, trail making test; IIM, intra-individual mean; IIV, intra-individual variability.

$\eta^2 = 0.007$]. Groups did not differ in years of education ($F_{(2,225)} = 1.30, p = 0.33$) or distribution of gender [$\chi^2_{(2)} = 0.29$, $p = 0.89$]. HCS and aMCI did not differ in age [$t_{(225)} = -1.36$, $p = 0.36$].

Accuracy-Based Comparisons Between Across-Domain and Within-Domain IIV

The accuracy-based IIV at both DOT and NAV was not influenced by education [$F_{(1,225)} = 2.41$; $p = 0.13$; $\eta^2 = 0.01$), gender [$F(_{1,225)} = 2.12$; $p = 0.10$; $\eta^2 = 0.01$], or IIM [$F_{(1,225)} = 1.20$; $p = 0.19$; $\eta^2 = 0.01$] but differed among diagnostic groups [$F_{(2,225)} = 5.75$; $p = 0.001$; $\eta^2 = 0.06$] and slightly by age [$F_{(1,225)} = 1.06$; $p = 0.05$; $\eta^2 = 0.02$]. The early AD group revealed in general higher across-domain IIV than both the aMCI group ($p = 0.001$; 95% CI = 0.17–0.88) and HCS group ($p = 0.001$; 95% CI = 0.18–0.99), whereas IIV did not differ significantly between the aMCI and HCS groups ($p = 0.71$; 95% CI = –0.16–0.31). Within-domain IIV was not influenced by age [$F_{(1,225)} = 0.056$; $p = 0.82$; $\eta^2 = 0.00$] but was higher in the early AD group compared to the HCS group ($p = 0.006$; 95% CI = 0.12–0.85) and was not significant between the early AD and the aMCI groups ($p = 0.374$; 95% CI = 0.142–0.582). In addition, we found a strong trend for higher within-domain IIV in the aMCI group than in the HCS group ($p = 0.051$; 95% CI = –0.02–0.27). To avoid statistical issues associated with two missing trials for the DOT group, group-level ISD values were imputed for missing data (<3% of the total data). **Figure 2** summarizes the accuracy-based IIV results.

Latency-Based Comparisons between Across-Domain and Within-Domain IIV

The latency-based IIV at both DOT and NAV was also not influenced by education [$F_{(1,225)} = 2.43$; $p = 0.15$; $\eta^2 = 0.01$], gender [$F_{(1,225)} = 2.21$; $p = 0.13$; $\eta^2 = 0.01$], or IIM [$F_{(1,225)} = 1.19$; $p = 0.20$; $\eta^2 = 0.01$] but differed among diagnostic groups [$F_{(2,225)} = 5.71$; $p = 0.001$; $\eta^2 = 0.06$] and age [$F_{(1,225)} = 1.51$; $p = 0.02$; $\eta^2 = 0.03$]. The across-domain latency-based IIV differed between the early AD and aMCI groups ($p = 0.001$; 95% CI = 0.22–1.07) as well as between the AD and HCS groups ($p = 0.001$; 95% CI = 0.24–1.29) and also between the aMCI and HCS groups ($p = 0.001$; 95% CI = 0.26–1.30). Within-domain latency IIV was found to be higher in the early AD group compared to the aMCI group ($p = 0.001$; 95% CI = 0.19–0.85) and the HCS group ($p = 0.001$; 95% CI = 0.16–0.82) and also between the aMCI and HCS groups ($p = 0.001$; 95% CI = 0.20–0.97). **Figure 3** summarizes the accuracy-based IIV results.

Accuracy-Based IIV vs. Latency-Based IIV

In order to evaluate whether there was a relationship between the accuracy- and latency-based IIV scores and the SG task, a MANCOVA was performed with IIV type (accuracy- or latency-based) and task (DOT and NAV) included as covariates. There was a significant main effect of the IIV type for the group [$F_{(2,225)} = 29.9$; $p = 0.001$; $\eta^2 = 0.41$], but not for task, age, education, or gender.

In addition, ANCOVA was performed in order to calculate a difference score by subtracting within- from across-domain IIV while treating age, education, and gender as covariates. For the accuracy-based IIV, we found only a tendency toward

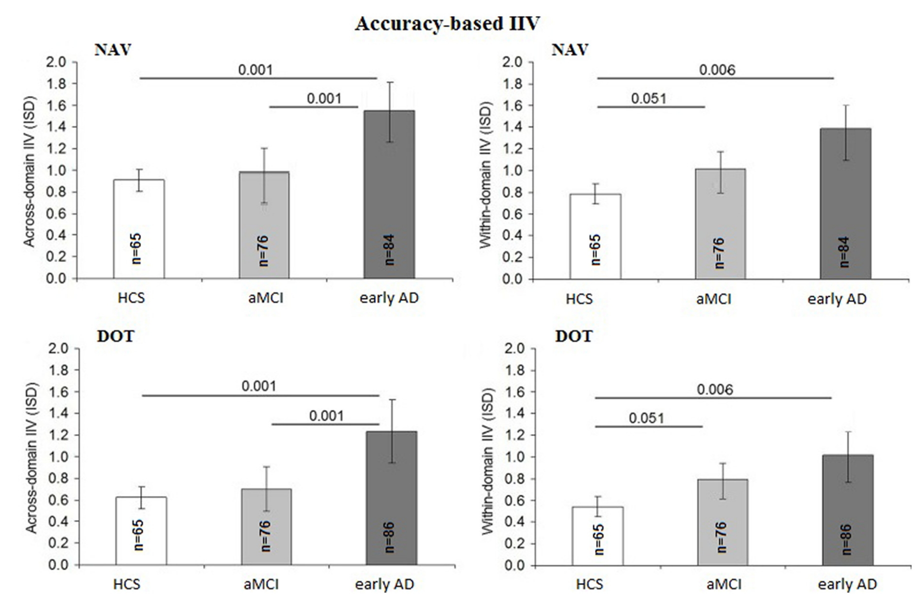

FIGURE 2 | Comparison of accuracy-based intra-individual variability (IIV) scores between diagnostic groups: intra-individual standard deviation (ISD) representing mean across-domain IIV for DOT and NAV as well as mean within-domain IIV for DOT and NAV per diagnostic group (HCS, healthy control subjects; MCI, mild cognitive impairment; AD, Alzheimer's disease). Error bars display 95% confidence interval for the mean with p values based on Sidak *post hoc* tests following analyses of covariance for the comparison of means adjusted for age, years of education and gender as well as mean across-domain performance **(A)** and mean within-domain performance **(B)**, respectively.

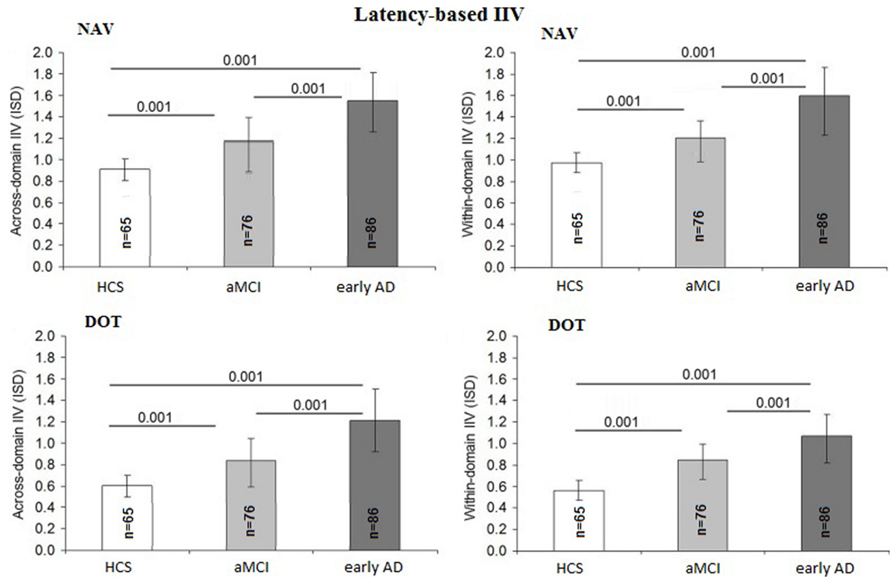

FIGURE 3 | Comparison of latency-based IIV scores between diagnostic groups.

higher across-domain IIV—not within-domain IIV—in each group (HCS: M = 0.21, SD = 0.76; MCI: M = 0.08, SD = 0.81; AD: M = 0.38, SD = 0.95). On the other hand, the latency-based IIV revealed no significant differences between IIV scores across diagnostic groups [$F_{(2,225)} = 4.32$; $p = 0.16$; $\eta^2 = 0.15$].

Associations between IIV, Genotype, and Neuropsychological Tests

Correlations are given in **Table 2**. The relationship between IIV, neuropsychological tests, and APOE status was explored in a subsample with available genotypes. We performed ANCOVAs to compare IIV scores between ε4 carriers and non-carriers within each group by treating gender as a covariate in aMCI. We calculated the general across-domain IIV and found that it did not vary with APOE status in HCS [$F_{(1,75)} = 0.412$; $p = 0.37$; $\eta^2 = 0.003$], MCI [$F_{(1,51)} = 0.316$; $p = 0.54$; $\eta^2 = 0.008$], or AD [$F_{(1,33)} = 0.012$; $p = 0.87$; $\eta^2 = 0.00$]. Similarly, the within-domain IIV did not vary as a function of APOE status in early AD [$F_{(1,33)} = 0.219$; $p = 0.67$; $\eta^2 = 0.01$], but there was a significant effect of APOE status in HCS [$F_{(1,75)} = 4.393$; $p = 0.04$; $\eta^2 = 0.04$] and aMCI [$F_{(1,51)} = 2.399$; $p = 0.05$; $\eta^2 = 0.03$], which indicated increased within-domain IIV in these groups.

Reliability of Performance-Based IIV Data

Figure 4 for the DOT task and **Figure 5** for the NAV task summarize the reliability data. ICC values were calculated using all three SG sessions for both the accuracy- and latency-based IIV of the DOT and NAV tasks. Results showed that, in general, accuracy-based IIV elicits fair to moderate reliability (ICC 0.33–0.57) for both the DOT and NAV tasks. In addition, accuracy-based ICC values increased after all three SG sessions for the DOT task, but the NAV task elicited an average ICC decrease of 0.15 (SEM = 0.04). In contrast, latency-based IIV for both the DOT and NAV tasks exhibited good to excellent reliability measures (ICC 0.69–0.85) after all sessions.

Discussion

A major problem in studying aging is how to separate the effects of aging from disease, and the two most pressing clinical questions relate to etiology and prognosis. In this study, we examined SG with and without DTW performance data and applied across- and within-domain accuracy-based and latency-based IIV measures in order to reliably differentiate between HCS, aMCI, and early AD. Specifically for the SG with DTW, we found increased IIV for both across- and within-domain IIV in early AD vs. HCS, aMCI vs. HSC, and in early AD vs. aMCI, consistent with a recent study (Phillips et al., 2013). In addition, and consistent with the literature on within-domain IIV (Duchek et al., 2009; Schroeter et al., 2012) placing more demands on cognitive control processes, we also found SG with DTW latency-based within-domain IIV being increased in early AD vs. HCS, aMCI vs. HCS, and early AD vs. aMCI, which is found to be a sensitive early marker of cognitive impairment (MacDonald et al., 2012; Kälin et al., 2014). High IIV has been linked to an increased probability that an individual with aMCI will become demented within 2.5 years (Tales et al., 2012).

When one investigates SG-based human navigation—in particular, the strategies implemented in a complex everyday way-finding task—one must also consider the role of vision in walking. In order to maintain a regular walking velocity in the SG, subjects must anticipate visualizing the destination route and process the responses upstream without having to stop. During the NAV task, each way-point had several action points as well as distractors and required several hesitant jerky movements to process them. Using the IIV measures, we were able to verify

TABLE 2 | Cognitive measures per diagnostic group, IIV, and APOE genotype (means with SDs).

Population							
N		161					
Subgroups		**HCS**		**aMCI**		**Early AD**	
n		16	60	34	18	21	12
APOE status		ε4+	ε4−	ε4+	ε4−	ε4+	ε4−
Age (years)		72.6 (12.02)	70.1 (13.21)	74.1 (9.21)	72.7 (9.44)	76.5 (8.83)	77.8 (9.36)
Male		7 (43.7%)	22 (36.6%)	12 (35%)	7 (38.8%)	8 (38%)	6 (50%)
Female		9 (56.3%)	38 (63.4%)	22 (65%)	11 (61.2%)	13 (62%)	6 (50%)
Education		15.1 (5.9)	15.3 (6.0)	14.5 (7.1)	15.1 (7.4)	8.7 (6.0)	9.1 (5.2)
Neuropsychological data							
Global	MMSE	29.3 (1.0)	28.9 (0.8)	26.8 (1.9)	27.3 (1.7)	22.1 (3.5)	22.7 (3.2)
Memory	Free recall†	0.02 (1.1)	−0.01 (1.1)	−0.59 (0.6)	−0.62 (0.7)	−0.49 (1.3)	−0.45 (1.0)
	RAVLT delayed recall†	−0.08 (1.0)	0.06 (0.9)	−2.23 (1.6)	−2.14 (1.5)	−3.88 (1.6)	−3.79 (1.4)
	Digit span forward†	0.35 (1.0)	−0.09 (1.0)	−1.43 (1.0)	−0.99 (1.1)	−2.35 (1.5)	−2.59 (1.1)
Attention	Stroop trial 3†	0.03 (0.9)	0.08 (1.1)	−0.69 (0.9)	−0.37 (1.1)	−2.83 (2.4)	−2.99 (2.0)
	TMTB†	0.61 (1.2)*	−0.08 (1.2)*	0.75 (1.3)*	−0.22 (1.3)*	−1.27 (1.6)	−0.36 (1.5)
	Letter fluency†	0.59 (0.9)*	−0.11 (1.1)*	0.67 (1.1)*	−0.25 (1.4)*	−1.32 (1.5)	−0.24 (1.3)
	Category fluency†	0.57 (1.0)*	−0.09 (1.0)*	0.69 (1.2)*	−0.19 (1.3)*	−1.39 (1.3)	−0.49 (1.3)
IIV							
Across-domain	IIM	0.09 (0.6)	0.01 (0.6)	−1.39 (0.7)	−1.24 (0.6)	−2.38 (1.2)	−2.67 (0.9)
Within-domain	IIM	0.33 (0.7)	−0.10 (0.8)	−0.49 (0.5)	−0.56 (0.9)	−1.91 (1.1)	−1.56 (1.0)
Across-domain	IIV‡	0.81 (0.5)	0.77 (0.6)	1.09 (0.7)	1.23 (0.2)	1.79 (0.6)	1.86 (0.8)
Within-domain	IIV‡	0.56 (0.5)*	−0.18 (0.5)*	0.57 (0.4)*	−0.22 (0.5)*	1.35 (0.8)	1.48 (1.1)

† Data shown are calculated standardized residuals of cognitive test scores for MCI and AD by using parameter estimates for age, education, and gender in HCS.
‡Analyses of covariance, means adjusted for gender, age, education, and across- or within-domain IIM.
**$p < 0.05$.*
HCSs, healthy control subjects; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, mini–mental state examination; TMT, trail making test; IIM, intra-individual mean; IIV, intra-individual variability.

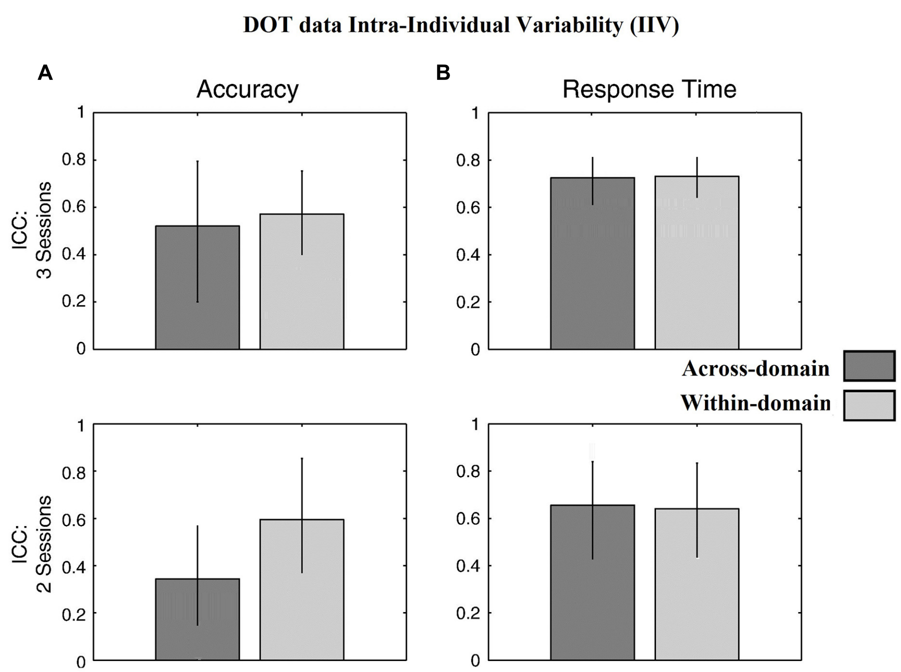

FIGURE 4 | Behavioral results for the DOT task. ICC values from **(A)** accuracy-based and **(B)** latency-based IIV times with 3 and 2 experimental sessions. Error bars represent 95% confidence interval.

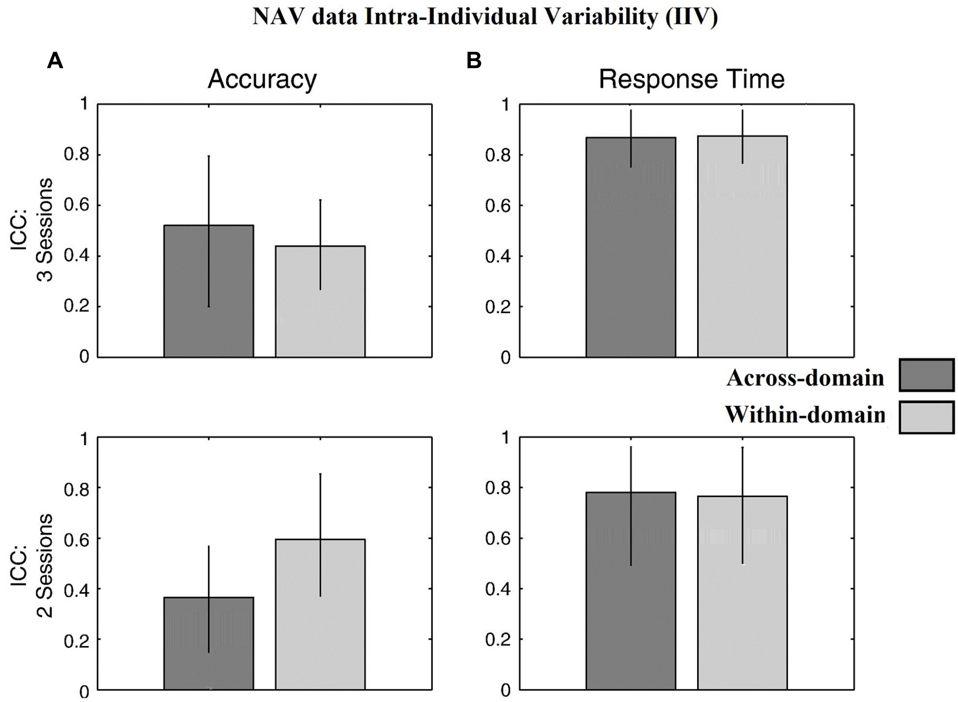

FIGURE 5 | Behavioral results for the NAV task. ICC values from **(A)** accuracy-based and **(B)** latency-based IIV times with 3 and 2 experimental sessions. Error bars represent 95% confidence interval.

that NAV task interference is preserved in dual-task conditions, consistent with other recent studies, i.e., (Perrochon et al., 2013).

The role of vision in gait control during locomotion has been demonstrated by other studies, especially when the environment is enriched with visual information (Chapman and Hollands, 2006, 2007). During NAV, this mechanism triggered a modification in gait parameters, such as a reduction in velocity and frequency, and more so by an increase in double support time. At the same time, others have suggested that elders with reduced cognitive ability have more difficulty identifying the environment, and it is necessary to fixate more to have a maximum of visual information (Di Fabio et al., 2005). In another study, Scherder et al. (2011) demonstrated that one can predict a change in walking control and motor performance in subgroups of patients with dementia pathology using the concept of "last in-first out," —that is, the neuronal circuits that mature late would be the first to deteriorate in neurodegenerative pathology. In that study, subjects with frontotemporal or vascular dementia had difficulties at the motor level in coordinating complex foot movements and planning movements associated with early degeneration of the anterior cingulate cortex and dorsolateral prefrontal cortex. In another study, Gwin et al. (2011) performed an electroencephalogram on a subject walking on DTW and noted activation of the anterior cingulate cortex during placement of the foot, similar to the detection of an error in placing the foot on the floor and correction of its trajectory. During the NAV task, one could imagine that there is a conflict at the level of the anterior cingulate cortex, which simultaneously manages performance of the cognitive task and correct placement of the foot. This conflict at the level of the anterior cingulate cortex could be increased in early AD because this cerebral zone is often prematurely deteriorated in patients with dementia.

We also examined the stability of measurements. Our results found at both the SG accuracy- and latency-based measures an increased IIV, suggesting a breakdown of cognitive control functions early in prodromal AD. More precisely, across- and within-domain accuracy-based IIV differed between each group, underlying the differences in cognitive control required by the DOT and NAV tasks. Consistent with other studies (Kälin et al., 2014), we also found that accuracy-based within-domain IIV was increased in early AD and aMCI vs. HCS and appeared to constitute a reliable marker for the detection of prodromal AD at the MCI stage. We also found that accuracy-based across-domain IIV was increased in early AD vs. aMCI and HCS and may be used to separate early AD from the aMCI stage.

Furthermore, since higher IIV has been found in tasks requiring cognitive control to be influenced by gender, by task-related processing load and processing speed (MacDonald et al., 2009; Phillips et al., 2013; Kofler et al., 2014), previous studies found that MCI subjects who later converted to dementia were found to have higher IIV than non-converters. Consistent with this study and the literature on latency-based within-domain IIV (Duchek et al., 2009; Schroeter et al., 2012) placing more demands on cognitive control processes, we also found latency-based within-domain IIV being increased in early AD vs. HCS, aMCI vs. HCS, and early AD vs. aMCI.

Additionally, we found increased within-domain IIV in HCS and aMCI ε4 carriers vs. non-carriers, whereas there was no ε4-related change in IIV in the early AD group. Contrary to findings reported by others (Duchek et al., 2009; Kälin et al., 2014) who only found an increased latency-based IIV in a cognitive control task in HCS ε4 carriers vs. non-carriers, we also found increased latency-based IIV in aMCI ε4 carriers vs. non-carriers. One reason for our findings might be that, in contrast to the previous studies, we examined the relationship between accuracy- and latency-based intra-individual differences in trial-to-trial variability. Another reason might be that the SG performance data are sensitive enough to detect subtle changes in IIV at both the HCS and aMCI stages. However, such interpretations should be treated with caution as it is already known that the frontal lobe constitutes a brain region that manifests ε4-effects very early in the disease (Filbey et al., 2010). Since the frontal lobe is believed to be the basis of IIV (MacDonald et al., 2009), our findings add evidence to recent studies (Kälin et al., 2014) and further support the relationship between within-domain IIV and APOE status.

In order to assess the reliability of performance data IIV, we analyzed the stability of test–retest measurements for both the DOT and NAV tasks using ICC values. Given that longitudinal change in IIV among accuracy and response time is thought to be particularly important and robust in signaling the risk of cognitive impairment and dementia (Vaughan et al., 2013), this result underscores the importance of utilizing response time data as a metric for memory processes, especially in aMCI populations where memory decline is often the behavioral outcome of interest.

In summary, our results demonstrated that SG with DTW performance profiles data represents another aspect of cognition that underlies age-related differences in cognitively demanding tasks independently of mean reaction time and executive function. Importantly, our findings confirmed that impaired cognitive control processes, especially in terms of latency, as measured with NAV performance profiles, produce stable inconsistencies across IIV in cognitive control-sensitive tasks, and hence can act as a predictor of greater cognitive decline.

Consistent with other studies, we found intra-individual differences in cognitive domains, both cross-sectional as well as longitudinal, which can be used for early detection and intervention. Recently, evidence for a strong association between IIV and frontal gray and white matter integrity changes on MRI scans (volumetric decline, demyelination, and hyperintensities) due to age-related changes in cerebral bold flow, vascular injury, or neurological conditions such as AD (Jackson et al., 2012; Lövdén et al., 2013; Radanovic et al., 2013) support the idea of frontal system disruptions underlying increased IIV in aMCI and early AD.

Our study has strengths but also limitations. One limitation was the small variability of the education profiles of our groups, which were all considered to be highly educated older adults. Although recent studies (Kälin et al., 2014) found no effect between education and IIV, this risk was addressed by treating education and within- and across-domain IIM as covariates in all analyses. Furthermore, the outcome of interest in the present study was the ISD calculated across tasks, and thus we assume the risk to be minimal. Another limitation was the correlation of SG performance profile data with neuropsychological tasks that might not exclusively assess the same cognitive functions. Specifically, the NAV task required motor performance with complex cognitive abilities, such as processing speed, visuoconstruction, and inhibition, among other cognitive control functions. Neuropsychological tasks, such as the TMT, the Letter and Category Fluency task, the Stroop Test, and the RAVLT place fewer demands on cognitive control processes, which might have influenced the significance of our correlations. Finally, the motor performance seen in subjects with aMCI is likely to be linked to early degeneration of the dorsolateral prefrontal cortices as well as the anterior cingulate cortex, and these subjects would be susceptible to progressive dementia pathology, such as frontotemporal and vascular dementia and not only AD. Brain imaging will be used in a future study to confirm or refute this hypothesis.

Despite these limitations, SG with DTW might useful in everyday clinical practice. Compared to other non-invasive biomarkers such as MRI, using SG performance data in clinical practice could optimize the diagnosis of AD at the early stage of the disease and would provide the greatest benefit in terms of cost and risk compared with other techniques. Finally, we suspect that integrating this type of dual-tasking with training programs or physical therapy, in an acute training design, might delay cognitive and motor decline in the elderly. However, further examination using different custom SG tasks in a longitudinal design is needed to provide more specific information about their preventive value.

Author Contributions

For the work described in this manuscript, IT developed and implemented the DAT and NAV system, performed manuscript drafting and statistical analysis. DK performed data collection and analysis. MT and SP performed the recruitment of participants and drafted the Ethical Approval. IT, BD and MD conceived the study and participated in its design, and coordinated the Grant funding. All authors did read and approve the final manuscript.

Acknowledgments

This research was funded by the University of Bern, Serious Game project at the ARTORG Center for Biomedical Engineering Research and the European project PharmaCog (Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development). The Serious Game project started in 2013, and it is one of the most ambitious research projects for the use of serious games in the early screening of dementia and cognitive exercising that can delay the onset of the disease. PharmaCog started at 2010, and it is a partnership of 32 academic and industry actors from seven countries and is one of the most ambitious European projects for tackling bottlenecks in Alzheimer's disease research and drug discovery. We would also like to thank the personnel from the Greek Association for Alzheimer Disease and Related Disorders (GAADRD) Memory Clinics and especially Dr. Anthoula Tsolaki, MD, for their support in data acquisition.

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease. *Alzheimers Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K., and Cockburn, J. (2011). Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 35, 715–728. doi: 10.1016/j.neubiorev.2010.08.008

Anstey, K. J., Mack, H. A., Christensen, H., Li, S.-C., Reglade-Meslin, C., Maller, J., et al. (2007). Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia* 45, 1911–1920. doi: 10.1016/j.neuropsychologia.2006.11.020

Bielak, A. A., Hultsch, D. F., Strauss, E., MacDonald, S. W. S., and Hunter, M. A. (2010). Intraindividual variability is related to cognitive change in older adults: evidence for within-person coupling. *Psychol. Aging* 25, 575–586. doi: 10.1037/a0019503

Brewster, P., Tuokko, H., and MacDonald, S. (2012). Inter-test variability contributes independently to the five-year prediction of Alzheimer's disease in nondemented older adults. *Alzheimers Dement.* 8, 369. doi: 10.1016/j.jalz.2012.05.1010

Burger, C. (2010). Region-specific genetic alterations in the aging hippocampus: implications for cognitive aging. *Front. Aging Neurosci.* 2:140. doi: 10.3389/fnagi.2010.00140

Carlesimo, G. A., Perri, R., and Caltagirone, C. (2011). Category cued recall following controlled encoding as a neuropsychological tool in the diagnosis of Alzheimer's disease: a review of the evidence. *Neuropsychol. Rev.* 21, 54–65. doi: 10.1007/s11065-010-9153-7

Chapman, G. J., and Hollands, M. A. (2006). Evidence for a link between changes to gaze behaviour and risk of falling in older adults during adaptive locomotion. *Gait Posture* 24, 288–294. doi: 10.1016/j.gaitpost.2005.10.002 x

Chapman, G. J., and Hollands, M. A. (2007). Evidence that older adult fallers prioritise the planning of future stepping actions over the accurate execution of ongoing steps during complex locomotor tasks. *Gait Posture* 26, 59–67. doi: 10.1016/j.gaitpost.2006.07.010

Chechko, N., Drexler, E. I., Voss, B., Kellermann, T., Finkelmeyer, A., Schneider, F., et al. (2014). Neural correlates of unsuccessful memory performance in MCI. *Front. Aging Neurosci.* 6:201. doi: 10.3389/fnagi.2014.00201

Cushman, L. A., Stein, K., and Duffy, C. J. (2008). Detecting navigational deficits in cognitive aging and alzheimer disease using virtual reality. *Neurology* 71, 888–895. doi: 10.1212/01.wnl.0000326262.67613.fe

De Jager, C. A., Honey T. E., Birks, J., and Wilcock, G. K. (2010). Retrospective evaluation of revised criteria for the diagnosis of alzheimer's disease using a cohort with post-mortem diagnosis. *Int. J. Geriatr. Psychiatry* 25, 988–997. doi: 10.1002/gps.2448

De Lillo, C., and James, F. C. (2012). Spatial working memory for clustered and linear configurations of sites in a virtual reality foraging task. *Cogn. Process.* 13(Suppl. 1), S243–S246. doi: 10.1007/s10339-012-0448-x

Dickerson, B. C., and Wolk, D., and Alzheimer's Disease Neuroimaging Initiative. (2013). Biomarker-based prediction of progression in MCI: comparison of AD-signature and hippocampal volume with spinal fluid amyloid-B and tau. *Front. Aging Neurosci.* 5:55. doi: 10.3389/fnagi.2013.00055

Di Fabio, R. P., Zampieri, C., Henke, J., Olson, K., Rickheim, D., and Russell, M. (2005). Influence of elderly executive cognitive function on attention in the lower visual field during step initiation. *Gerontology* 51, 94–107. doi: 10.1159/000082194

Dixon, R. A., Garrett, D., Lentz, T. L., MacDonald, S. W. S., Strauss, E., and Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: exploring the roles of speed and inconsistency. *Neuropsychology* 21, 381–399. doi: 10.1037/0894-4105.21.3.381

Duara, R., Loewenstein, D. A., Shen, Q., Barker, W., Varon, D., Greig, M. T., et al. (2013). The utility of age-specific cut-offs for visual rating of medial temporal atrophy in classifying Alzheimer's Disease, MCI and cognitively normal elderly subjects. *Front. Aging Neurosci.* 5:47. doi: 10.3389/fnagi.2013.00047

Dubois, B., and Albert M. L. (2004). Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurol.* 3, 246–248. doi: 10.1016/S1474-4422(04)00710-0

Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo J. L., Blennow, K., et al. (2014). Advancing research diagnostic criteria for Alzheimer's Disease: the IWG-2 criteria. *Lancet Neurol.* 13, 614–629. doi: 10.1016/S1474-4422(14)70090-0

Duchek, J. M., Balota, D. A., Tse, C.-S., Holtzman, D. M., Fagan, A. M., and Goate, A. M. (2009). The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. *Neuropsychology* 23, 746–758. doi: 10.1037/a0016583

Duron, E., Vidal, J. S., Bounatiro, S., Ben Ahmed, S., Seux, M. L., Rigaud, A. S., et al. (2014). Relationships between personality traits, medial temporal lobe atrophy, and white matter lesion in subjects suffering from mild cognitive impairment. *Front. Aging Neurosci.* 6:195. doi: 10.3389/fnagi.2014.00195

Ferreira, D., Perestelo-Pérez, L., Westman, E., Wahlund, L. O., Sarría, A., Serrano-Aguilar, P., et al. (2014). Meta-review of CSF core biomarkers in Alzheimer's disease: the state-of-the-art after the new revised diagnostic criteria. *Front. Aging Neurosci.* 6:47. doi: 10.3389/fnagi.2014.00047

Filbey, F. M., Chen, G., Sunderland, T., and Cohen, R. M. (2010). Failing compensatory mechanisms during working memory in older apolipoprotein e-epsilon4 healthy adults. *Brain Imaging Behav.* 4, 177–188. doi: 10.1007/s11682-010-9097-9

Fletcher, E., Carmichael, O., Pasternak. O., Maier-Hein, K. H., and DeCarli, C. (2014). Early brain loss in circuits affected by alzheimer's disease is predicted by fornix microstructure but may be independent of gray matter. *Front. Aging Neurosci.* 6:106. doi: 10.3389/fnagi.2014.00106

Folstein, M. F., Folstein, S. E., and McHugh. P. R. (1975). Mini-mental state. a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatric Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Gillain, S., Warzee, E., Lekeu, F., Wojtasik, V., Maquet, D., Croisier, J.-L., et al. (2009). The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Ann. Phys. Rehabil. Med.* 52, 453–474. doi: 10.1016/j.rehab.2008.10.004

Grober, E., Buschke, H., Crystal, H., Bang, S., and Dresner, R. (1988). Screening for dementia by memory testing. *Neurology* 38, 900–903. doi: 10.1212/WNL.38.6.900

Gwin, J. T., Gramann, K., Makeig, S., and Ferris, D. P. (2011). Electrocortical activity is coupled to gait cycle phase during treadmill walking. *Neuroimage* 54, 1289–1296. doi: 10.1016/j.neuroimage.2010.08.066

Holden, H. M., and Gilbert, P. E. (2012). Less efficient pattern separation may contribute to age-related spatial memory deficits. *Front. Aging Neurosci.* 4:9. doi: 10.3389/fnagi.2012.00009

Holtzer, R., Verghese, J., Wang, C., Hall, C. B., and Lipton. R. B. (2008). Within-person across-neuropsychological test variability and incident dementia. *JAMA* 300, 823–830. doi: 10.1001/jama.300.7.823

Isaacs, B., and Akhtar, A. J. (1972). The set test: a rapid test of mental function in old people. *Age Ageing* 1, 222–226. doi: 10.1093/ageing/1.4.222

Jackson, J. D., Balota, D. A., Duchek, J. M., and Head, D. (2012). White matter integrity and reaction time intraindividual variability in healthy aging and early-stage Alzheimer disease. *Neuropsychologia* 50, 357–366. doi: 10.1016/j.neuropsychologia.2011.11.024

Kälin, A. M., Pflüger, M., Gietl, A. F., Riese, F., Jäncke, L., Nitsch, R. M., et al. (2014). Intraindividual variability across cognitive tasks as a potential marker for prodromal Alzheimer's disease. *Front. Aging Neurosci.* 6:147. doi: 10.3389/fnagi.2014.00147

Kam, A. C., Sung, J. K., Lee, T., Wong, T. K., and van Hasselt. A. (2012). Clinical evaluation of a computerized self-administered hearing test. *Int. J. Audiol.* 51, 606–610. doi: 10.3109/14992027.2012.688144

Kelaiditi, E., Cesari, M., Canevelli, M., van Kan, G. A., Ousset, P. J., Gillette-Guyonnet, S., et al. (2013). Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J. Nutr. Health Aging* 17, 726–734. doi: 10.1007/s12603-013-0367-2

Kelemen, E., and Fenton, A. A. (2010). Dynamic grouping of hippocampal neural activity during cognitive control of two spatial frames. *PLoS Biol.* 8:e1000403. doi: 10.1371/journal.pbio.1000403

Kofler, M. J., Matt Alderson, R., Raiker, J. S., Bolden, J., Sarver, D. E., and Rapport, M. D. (2014). Working memory and intraindividual variability as neurocognitive indicators in ADHD: examining competing model predictions. *Neuropsychology* 28, 459–471. doi: 10.1037/neu0000050

Korsch, M., Frühholz, S., and Herrmann, M. (2014). Ageing differentially affects neural processing of different conflict types-an fMRI Study. *Front. Aging Neurosci.* 6:57. doi: 10.3389/fnagi.2014.00057

Lindberg, O., Walterfang, M., Looi, J. C., Malykhin, N., Ostberg, P., Zandbelt, B., et al. (2012a). Hippocampal shape analysis in Alzheimer's disease and frontotemporal lobar degeneration subtypes. *J. Alzheimers Dis.* 30, 355–365. doi: 10.3233/JAD-2012-112210

Lindberg, O., Westman, E., Karlsson, S., Ostberg, P., Svensson, L. A., Simmons, A., et al. (2012b). Is the subcallosal medial prefrontal cortex a common site of atrophy in Alzheimer's disease and frontotemporal lobar degeneration? *Front. Aging Neurosci.* 4:32. doi: 10.3389/fnagi.2012.00032

Lockhart, S. N., Mayda, A. B., Roach, A. E., Fletcher, E., Carmichael, O., Maillard, P., et al. (2012). Episodic memory function is associated with multiple measures of white matter integrity in cognitive aging. *Front. Hum. Neurosci.* 6:56. doi: 10.3389/fnhum.2012.00056

Lövdén, M., Schmiedek, F., Kennedy, K. M., Rodrigue, K. M., Lindenberger, U., and Raz, N. (2013). Does variability in cognitive performance correlate with frontal brain volume? *Neuroimage* 64, 209–215. doi: 10.1016/j.neuroimage.2012.09.039

MacDonald, S., Brewster, P., Laukka, E., Fratiglioni, L., and Bäckman, L. (2012). Intraindividual variability across neuropsychological tasks is associated with risk of Alzheimer's disease. *Alzheimers Dement.* 8, P370. doi: 10.1016/j.jalz.2012.05.1016

MacDonald, S. W., Li, S. C., and Bäckman, L. (2009). Neural Underpinnings of within-person variability in cognitive functioning. *Psychol. Aging* 24, 792–808. doi: 10.1037/a0017798

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R. Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Michon, A. (2009). The Concept of mild cognitive impairment: relevance and limits in clinical practice. *Front. Neurol. Neurosci.* 24:12. doi: 10.1159/000197880

Montero-Odasso, M., Casas, A., Hansen, K. T., Bilski, P., Gutmanis, I., Wells, J. L., et al. (2009). Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study. *J. Neuroeng. Rehabil.* 6, 35. doi: 10.1186/1743-0003-6-35

Montero-Odasso, M., Muir, S. W., and Speechley, M. (2012). Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch. Phys. Med. Rehabil.* 93, 293–299. doi: 10.1016/j.apmr.2011.08.026

Montero-Odasso, M., Oteng-Amoako, A., Speechley, M., Gopaul, K., Beauchet, O., Annweiler, C., et al. (2014). The motor signature of mild cognitive impairment: results from the gait and brain Study. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 69, 1415–1421. doi: 10.1093/gerona/glu155

Morgan, E. E., Woods, S. P., and Grant, I. (2012). Intra-individual neurocognitive variability confers risk of dependence in activities of daily living among HIV-seropositive individuals without HIV-associated neurocognitive sisorders. *Arch. Clin. Neuropsychol.* 27, 293–303. doi: 10.1093/arclin/acs003

Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., and Montero-Odasso, M. (2012). Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture* 35, 96–100. doi: 10.1016/j.gaitpost.2011.08.014

Naj, A. C., Jun, G., Reitz, C., Kunkle, B. W., Perry, W., Park, Y. S., et al. (2014). Effects of multiple genetic loci on age at onset in late-onset alzheimer disease. *JAMA Neurol.* 71, 1394–1404. doi: 10.1001/jamaneurol.2014.1491

Nesselroade, J. R., and Salthouse, T. A. (2004). Methodological and theoretical implications of intraindividual variability in perceptual-motor performance. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 59, P49–P55. doi: 10.1093/geronb/59.2.P49

Oldfield, R. C. (1971). The assessment and analysis of handedness: the edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Pelletier, A., Periot, O., Dilharreguy, B., Hiba, B., Bordessoules, M., Pérès K., et al. (2013). Structural hippocampal network alterations during healthy aging: a multi-modal MRI study. *Front. Aging Neurosci.* 5:84. doi: 10.3389/fnagi.2013.00084

Perrochon, A., Kemoun, G., Watelain, E., and Berthoz, A. (2013). Walking stroop carpet: an innovative dual-task concept for detecting cognitive impairment. *Clin. Interv. Aging* 8, 317–28. doi: 10.2147/CIA.S38667

Persad, C. C., Jones, J. L., Ashton-Miller, J. A., Alexander, N. B., and Giordani, B. (2008). Executive function and gait in older adults with cognitive impairment. *J. Gerontol. A Biol. Sci. Med. Sci*. 63, 1350–1355. doi: 10.1093/gerona/63.12.1350

Petersen, R. C. (2003). Mild cognitive impairment clinical trials. *Nat. Rev. Drug Discov*. 2, 646–653. doi: 10.1038/nrd1155

Phillips, M., Rogers, P., Haworth, J., Bayer, A., and Tales, A. (2013). Intra-individual reaction time variability in mild cognitive impairment and Alzheimer's Disease: gender, processing load and speed factors. *PLoS ONE* 8:e65712. doi: 10.1371/journal.pone.0065712

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., and Piolino, P. (2012). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active and passive encoding. *Neuropsychologia* 50, 592–602. doi: 10.1016/j.neuropsychologia.2011.12.013

Portet, F., Ousset, P. J., Visser, P. J., Frisoni, G. B., Nobili, F., Scheltens, P., et al. (2006). Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. report of the MCI working group of the european consortium on Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 77, 714–718. doi: 10.1136/jnnp.2005.085332

Prestia, A., Caroli, A., Herholz, K., Reiman, E., Chen, K., Jagust, W. J., et al. (2013). Diagnostic accuracy of markers for prodromal Alzheimer's disease in independent clinical series. *Alzheimers Dement.* 9, 677–686. doi: 10.1016/j.jalz.2012.09.016

Radanovic, M., Pereira, F. R., Stella, F., Aprahamian, I., Ferreira, L. K., Forlenza, O. V., et al. (2013). White matter abnormalities associated with Alzheimer's disease and mild cognitive impairment: a critical review of MRI studies. *Expert. Rev. Neurother*. 13, 483–493. doi: 10.1586/ern.13.45

Ramsay, M. C., and Reynolds, C. R. (1995). Separate digits tests: a brief history, a literature review, and a reexamination of the factor structure of the test of memory and learning (TOMAL). *Neuropsychol. Rev*. 5, 151–71. doi: 10.1007/BF02214760

Robert, P. H., König, A., Amieva, H., Andrieu, S., Bremond, F., Bullock, R., et al. (2014). Recommendations for the use of serious games in people with Alzheimer's disease, related disorders and frailty. *Front. Aging Neurosci*. 6:54. doi: 10.3389/fnagi.2014.00054

Rosenberg, S. J., Ryan, J. J., and Prifitera, A. (1984). Rey auditory-verbal learning test performance of patients with and without memory impairment. *J. Clin. Psychol.* 40, 785–787. doi: 10.1002/1097-4679(198405)40:3<785::AID-JCLP2270400325>3.0.CO;2-4

Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S., et al. (2007). Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. *Neurology* 69, 1859–1867. doi: 10.1212/01.wnl.0000279336.36610.f7

Scherder, E., Eggermont, L., Visscher, C., Scheltens, P., and Swaab, D. (2011). Understanding higher level gait disturbances in mild dementia in order to improve rehabilitation: 'last in-first out'. *Neurosci. Biobehav. Rev*. 35, 699–714. doi: 10.1016/j.neubiorev.2010.08.009

Schroeter, M. L., Vogt, B., Frisch, S., Becker, G., Barthel, H., Mueller, K., et al. (2012). Executive deficits are related to the inferior frontal junction in early dementia. *Brain* 135(Pt 1), 201–215. doi: 10.1093/brain/awr311

Shrout, P. E., and Fleiss, J. L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychol. Bull*. 86, 420–428. doi: 10.1037/0033-2909.86.2.420

Snowden, J. S., Thompson, J. C., Stopford, C. L., Richardson, A. M., Gerhard, A., Neary, D., et al. (2011). The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. *Brain* 134(Pt 9), 2478–2492. doi: 10.1093/brain/awr189

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7, 280–292. doi: 10.1016/j.jalz.2011.03.003

Stirling, N. (1979). Stroop interference: an input and an output phenomenon. *Q. J. Exp. Psychol*. 31, 121–132. doi: 10.1080/14640747908400712

Tales, A., Leonards, U., Bompas, A., Snowden, R. J., Philips, M., Porter, G., et al. (2012). Intra-individual reaction time variability in amnestic mild cognitive impairment: a precursor to dementia? *J. Alzheimers. Dis.* 32, 457–466. doi: 10.3233/JAD-2012-120505

Tarnanas, I., Schlee, W., Tsolaki, M., Müri1, R., Mosimann, U., and Nef, T. (2013). Ecological validity of virtual reality daily living activities screening for early dementia: longitudinal study. *JMIR Serious Games* 1:e1. doi: 10.2196/games.2778

Tarnanas, I., Tsolaki, M., Nef, T. M., Müri, R., and Mosimann, U. P. (2014). Can a novel computerized cognitive screening test provide additional information for early detection of Alzheimer disease? *Alzheimer Dement.* 10, 790–798. doi: 10.1016/j.jalz.2014.01.002

Theill, N., Martin, M., Schumacher, V., Bridenbaugh, S. A., and Kressig, R. W. (2011). Simultaneously measuring gait and cognitive performance in cognitively healthy and cognitively impaired older adults: the basel motor-cognition dual-task paradigm. *J. Am. Geriatr. Soc.* 59, 1012–1018. doi: 10.1111/j.1532-5415.2011.03429.x

Tombaugh, T. N. (2004). Trail making test A and B: normative data stratified by age and education. *Arch. Clin. Neuropsychol.* 19, 203–214. doi: 10.1016/S0887-6177(03)00039-8

Vaughan, L., Leng, I., Dagenbach, D., Resnick, S. M., Rapp, S. R., Jennings, J. M., et al. (2013). Intraindividual variability in domain-specific cognition and risk of mild cognitive impairment and dementia. *Curr. Gerontol. Geriatr. Res.* 2013, 495793. doi: 10.1155/2013/495793

Verghese, J., Wang, C., Lipton, R. B., Holtzer, R., and Xue, X. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *J. Neurol. Neurosurg. Psychiatry* 78, 929–35. doi: 10.1136/jnnp.2006.106914

Waite, L. M., Grayson, D. A., Piguet, O., Creasey, H., Bennett, H. P., and Broe., G. A. (2005). Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the sydney older persons study. *J. Neurol. Sci.* 229–230, 89–93. doi: 10.1016/j.jns.2004.11.009

Weniger, G., Ruhleder, M., Lange, C., Wolf, S., and Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia* 49, 518–27. doi: 10.1016/j.neuropsychologia.2010.12.031

Werner, P., Rabinowitz, S., Klinger, E., Korczyn, A. D., and Josman, N. (2009). Use of the virtual action planning supermarket for the diagnosis of mild cognitive impairment: a preliminary study. *Dement. Geriatr. Cogn. Disord.* 27, 301–309. doi: 10.1159/000204915

West, R., Murphy, K. J., Armilio, M. L., Craik, F. I., and Stuss, D. T. (2002). Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain Cogn.* 49, 402–419. doi: 10.1006/brcg.2001.1507

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J. Intern. Med.* 256, 240–46. doi: 10.1111/j.1365-2796.2004.01380.x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 20 May 2015
doi: 10.3389/fnagi.2015.00088

Detecting early egocentric and allocentric impairments deficits in Alzheimer's disease: an experimental study with virtual reality

Silvia Serino[1]*, *Francesca Morganti*[2], *Fabio Di Stefano*[3] *and Giuseppe Riva*[1,4]

[1] Applied Technology for Neuro-Psychology Lab, Istituto Auxologico Italiano, Milan, Italy, [2] Department of Human and Social Sciences, University of Bergamo, Bergamo, Italy, [3] Ospedale Castelli Verbania, Verbania, Italy, [4] Department of Psychology, Università Cattolica del Sacro Cuore, Milan, Italy

OPEN ACCESS

Edited by:
Valeria Manera, University of Nice Sophia Antipolis, France

Reviewed by:
Johannes Schröder, Section of Geriatric Psychiatry at the University of Heidelberg, Germany
Ioannis Tarnanas, University of Bern, Switzerland

***Correspondence:**
Silvia Serino, Applied Technology for Neuro-Psychology Lab, Istituto Auxologico Italiano, Via Magnasco, 2 20149 Milan, Italy
s.serino@auxologico.it

Received: *01 December 2014*
Paper pending published: *21 January 2015*
Accepted: *01 May 2015*
Published: *20 May 2015*

Citation:
Serino S, Morganti F, Di Stefano F and Riva G (2015) Detecting early egocentric and allocentric impairments deficits in Alzheimer's disease: an experimental study with virtual reality. Front. Aging Neurosci. 7:88. doi: 10.3389/fnagi.2015.00088

Several studies have pointed out that egocentric and allocentric spatial impairments are one of the earliest manifestations of Alzheimer's Disease (AD). It is less clear how a break in the continuous interaction between these two representations may be a crucial marker to detect patients who are at risk to develop dementia. The main objective of this study is to compare the performances of participants suffering from amnestic mild cognitive impairment (aMCI group), patients with AD (AD group) and a control group (CG), using a virtual reality (VR)-based procedure for assessing the abilities in encoding, storing and syncing different spatial representations. In the first task, participants were required to indicate on a real map the position of the object they had memorized, while in the second task they were invited to retrieve its position from an empty version of the same virtual room, starting from a different position. The entire procedure was repeated across three different trials, depending on the object location in the encoding phase. Our finding showed that aMCI patients performed significantly more poorly in the third trial of the first task, showing a deficit in the ability to encode and store an allocentric viewpoint independent representation. On the other hand, AD patients performed significantly more poorly when compared to the CG in the second task, indicating a specific impairment in storing an allocentric viewpoint independent representation and then syncing it with the allocentric viewpoint dependent representation. Furthermore, data suggested that these impairments are not a product of generalized cognitive decline or of general decay in spatial abilities, but instead may reflect a selective deficit in the spatial organization Overall, these findings provide an initial insight into the cognitive underpinnings of amnestic impairment in aMCI and AD patient exploiting the potentiality of VR.

Keywords: virtual reality, egocentric representation, allocentric representation, mild cognitive impairment, Alzheimer's disease

Introduction

Given the rise in life expectancy and concomitant growth of the aging population (aged 65 and over), the prevalence of dementia is expected to increase dramatically. It is estimated that the number of the elderly affected by Alzheimer's disease (AD), which is the most common type of dementia, will reach 115.4 million by 2050 (Prince et al., 2013). Accordingly, the identification of early indicators of cognitive decline in the elderly is becoming a worldwide health policy priority. In parallel with continuous research of well-validated biomarkers of AD processes, cognitive assessment continues to provide reliable cognitive indicators that are crucial for better definition, for both early and differential diagnosis, for improving the design of clinical trials, and for offering the chance of prevention treatments. The early impairment in episodic memory is traditionally considered the first sign of AD (Weintraub et al., 2012). Episodic memory is the ability to encode, store and then retrieve personal past events characterized by a specific time and place ("what," "where," and "when"), and with a reference to the individual themselves as participants of those events (Tulving, 1985, 2001, 2002). Indeed, the core feature of episodic memory is the *autonoetic consciousness*, namely the subjective and conscious experience of mentally reliving an event (Tulving, 2001). From a cognitive standpoint, this first-person perspective is the default mode for information processing, and corresponds to egocentric spatial representations (Vogeley et al., 2004). There are two types of spatial representations, defined on the basis of the reference used to encode and store spatial information: egocentric and allocentric representations (Paillard, 1991; Klatzky, 1998).

Egocentric spatial representations are constituted by subject-to-object spatial relations, since spatial information is acquired and processed using the self as the reference (self-centered). These transient spatial representations are integrated in posterior parietal area 7a (Zipser and Andersen, 1988; Pouget and Sejnowski, 1992; Lester and Dassonville, 2014). On the other hand, allocentric spatial representations are constituted by object-to-object spatial relations, since spatial information is stored using objects and/or environmental features as reference (world-centered). Hippocampal place cells are supposed to be responsible for the long-term storage of the allocentric representations of space (O'Keefe and Dostrovsky, 1971; Ono et al., 1993; Ekstrom et al., 2003).

Starting from the role of the hippocampus in providing a spatial scaffold to bind all neocortical representations related to a specific event (O'Keefe and Nadel, 1978; Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1998), the spatial mechanism underlying episodic retrieval has been modeled in the well-known Boundary Vector Model (Burgess et al., 2001; Byrne et al., 2007). According to this model, a retrieval cue (for example, a particular song associated with a meaningful life episode) may evoke the entire past event: the retrieved content includes the spatial scaffold of this past event (i.e., its spatial context), encoded as allocentric representation in the hippocampal regions (i.e., the distances of event elements, which are independent of the individual). Although allocentric, this hippocampal representation is translated into an egocentric representation (i.e., the distances of event elements to the left or right of or ahead of the individual). In this perspective, the difficulty in encoding and storing egocentric and allocentric spatial representations may become a useful cognitive marker of AD. A recent systematic review of allocentric and egocentric abilities in AD showed that there is a prevalence of allocentric deficit both in amnestic mild cognitive impairment (aMCI) and AD patients (Serino et al., 2014). In addition, two selected studies pointed out a more specific cognitive impairment in the translation between the egocentric and allocentric representations (Morganti et al., 2013; Pai and Yang, 2013). These findings underlined that, from the earliest stages of AD, there is a significant degeneration centered in the hippocampus and interconnected areas. Indeed, earliest AD-related neuropathologic changes (i.e., neurofibrillary tangles and amyloid plaques) usually begin in the medial temporal lobe and related areas, especially the hippocampus (Braak and Braak, 1991, 1996; Dickson, 1997; Thal et al., 2000; Alafuzoff et al., 2008). On the other hand, from a cognitive point of view, this review observed a more complex spatial deficit involving the ability to encode and store an allocentric hippocampal representation and, then, to translate it to the egocentric parietal representation. To explain the presence of both allocentric and translation impairments from the earliest stages of AD, Serino and Riva (2013) proposed that early damage in the hippocampus may provoke a break in the mental frame syncing between different spatial representations and, then impair both spatial and episodic retrieval. Indeed, Behrendt (2013) recently proposed a distinction between two types of allocentric representations: the *allocentric view-point dependent representation*, namely an allocentric representation of the scene toward which the individual orients; and the *allocentric view-point independent representation*, namely a complete abstract object-to-object allocentric representation of the scene. From a neurobiological perspective, within the hippocampus there are two regions responsible for the storing of allocentric information, region CA3 and region CA1 (Robertson et al., 1998; Rolls, 2007). More precisely, the dentate gyrus projects to region CA3, which encodes an allocentric viewpoint dependent representation. Then, region CA3 projects, through the Schaffer collaterals, to region CA1, which stores an allocentric viewpoint independent representations. In this perspective, the mental frame syncing may be defined as the ability in the synchronization between these two allocentric spatial representations that is useful for an effective retrieval (Serino and Riva, 2013; Serino et al., 2014). Indeed, when we retrieve an experienced environment and/or a past event, first, we have to encode and memorize an abstract structure of the spatial scene, including all of the relevant objects and their reciprocal relationships (allocentric viewpoint-independent representation). Second, we have to impose a specific viewpoint on this abstract allocentric scene (allocentric viewpoint-dependent representation), to ease its translation into a first-perspective egocentric representation. When there is a break in this process, as it is assumed to happen in AD, the retrieved content may lack coherence.

Virtual reality (VR) appears to be a useful tool to detect early impairment in the ability to encode, store and sync different spatial representations. Besides the opportunity for controlled and secure testing environments (for a review, see Bohil et al., 2011), with VR it is possible to systematically change the retrieval viewpoint with respect to the view-point in the encoding phase. This strategy, known as "virtual disorientation," induces interference in the egocentric representation and forces the use of long-term allocentric representation (Bosco et al., 2008).

Based on these premises, the main objective of this study is to explore the cognitive underpinnings of spatial impairments in AD using a VR-based procedure specifically designed for evaluating the abilities to encode, use and sync different spatial representations. To achieve this general aim, we will compare the performances of elderly participants suffering from aMCI, patients with AD, and a control group (CG), using both a traditional standard neuropsychological assessment of spatial functions and this VR-based procedure. First, we assumed, in line with the available literature, that both aMCI patients and AD patients will show severe spatial deficits.

Second, based on the "mental frame syncing hypothesis," we assumed that there are differences between the three groups in our VR-based procedure. Specifically, we argued that AD patients would show a break in the syncing between different spatial representations.

Materials and Methods

Participants

A total of 45 participants allocated to three groups were included in the study: 15 AD patients (AD group), 15 aMCI patients (aMCI group), and 15 cognitively healthy individuals (CG). Demographic and clinical characteristics are reported in **Table 1**.

Individuals for AD group were recruited from the clinically diagnosed outpatients of the Ospedale Castelli Verbania in Verbania (Italy). These diagnoses were made by the clinical geriatric staff using the criteria of the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984).

Individuals for the aMCI group were recruited from different social senior centers located in Lombardy (Italy). They met the criteria for an amnestic single-domain form of MCI as defined by Petersen (2004), including the presence of a subjective memory complaint; the objective evidence of memory impairment [as assessed by the Short Story Recall call (Spinnler and Tognoni, 1987)]; preserved general cognitive function as assessed by mini mental state examination (MMSE; Folstein et al., 1975); preserved activities of daily living as reported by formal and/or informal caregiver, and the absence of dementia [as assessed by the Milan Overall Dementia Rating Scale (MODA; Brazzelli et al., 1994)]. To verify if the aMCI patients were impaired only on declarative memory functioning, together with their MMSE scores (individuals in this group were required to have a MMSE score > 24, indicating no severe cognitive impairment), we administered the Milan Overall Dementia Rating Scale [MODA, (Brazzelli et al., 1994)] to exclude the presence of dementia and significant impairments in other cognitive domains. Only patients with a score > 63/100, which corresponds to a mild degree of cognitive impairment, and with a performance resulting <1.5 standard deviations below normative norms on the Short Story Recall (Spinnler and Tognoni, 1987), were included in this study.

The CG was recruited from a panel of volunteers. They were eligible to take part in the study if they were over 65 years of age and had no history of traumatic brain injury or any other neurological illness, that may affect brain structures. Individuals in this group were required to have a MMSE score > 27.

Participants did not receive money as reward for the participation to the study and gave their written content for the inclusion in the study, which was approved by the Ethical Committee of Università Cattolica del Sacro Cuore di Milano.

Traditional Spatial Neuropsychological Assessment

To evaluate the spatial abilities of the study's participants, the following standard neuropsychological tests were administered. Scores obtained from these neuropsychological tests were corrected for age, education level, and gender according to Italian normative data where needed.

Corsi Block Test

The Corsi Block Test (Corsi, 1972; Spinnler and Tognoni, 1987) was used to measure short-term spatial memory (Corsi Span) and long-term spatial memory (Corsi Supraspan). Stimuli consisted of a random array of wooden blocks spread out on a wooden base, placed between the experimenter and the participant. In the Corsi Span, the participants are invited to tap

TABLE 1 | Demographic and clinical information.

	Group		
Test or variable	**aMCI group[1]**	**AD group[1]**	**CG[1]**
Male	11	11	9
Female	4	4	6
Total	15	15	15
Years of age[2]	77.53 (5.52)	82.93 (5.61)	73.87 (7.38)
Years of education[2]	7.73 (4.48)	6.60 (3.83)	12.27 (3.88)
Duration of disease (months)[2]	–	25.62 (10.45)	–
MMSE[2,3]	22.46 (1.95)	23.06 (1.50)	27.52 (1.48)

[1]*amnestic mild cognitive impairment group (aMCI group); Alzheimer's Disease group (AD group); control group (CG).*
[2]*Values are shown as mean (SD).*
[3]*Mini Mental State Examination (MMSE; Folstein et al., 1975).*

a sequence of wooden blocks in the same order as the researcher, with increasing span length on each trial. In the Corsi Supraspan, the researcher proposed a sequence of nine blocks to be repeated for several trials.

Money Road Map

The Money Road Map is used to evaluate spatial navigation abilities (Money et al., 1965). In this test, the participants were given a map of a small town on which was drawn a route taken by a traveler. The route had 32 turns with left–right intersections. The participants had to imagine themselves traveling along this route to decide whether a right or left turn was demanded at the intersections. No time limit was imposed and the maximum score is 32 points.

Manikin's Test

The Manikin's Test (Ratcliff, 1979) was used to evaluate general mental rotation abilities. The participants were given 32 sheets showing a "little man" from different perspectives who holds a ball. Participants were required to evaluate in which hand the little man was holding the ball. No time limit was imposed and the maximum score is 32 points.

The Judgment of Line Orientation

The Judgment of Line Orientation (Benton et al., 1978) was used to assess visuo-spatial skills. Participants were given 30 sheets showing pairs of target lines positioned above a reference figure containing 11 lines arranged in a semicircle and numbered from 1 to 11. They were required to identify their angular positions in relation to the reference figure. No time limit was imposed and the maximum score is 30 points.

Apparatus and Stimuli

A virtual room was created as test environment. It included two objects (namely, a plant and a stone) and an arrow drawn on the floor, which pointed to the North and represented the start of the navigation (see **Figure 1**).

As explained later in the procedure, the participants were instructed to memorize the position of the plant, that varied across three different trials. In the first trial (Trial 1), the object in the learning phase was on the East side, in the second trial (Trial 2) the object was on the West side, in the third trial (Trial 3) the object was on the South side. For the retrieval phase, two different tasks were developed. In the first task (Task 1), participants were asked to indicate the position of the object on a real map, namely, a retrieval with spatial allocentric information independent of point of view. In the second task (Task 2), participants were asked to enter an empty version of the same virtual room. The participants had to indicate the position of the plant, starting from the position of the other object, namely, a retrieval without any spatial allocentric information. In this task, the participants changed their points of view from those they had in the learning phase. As posited by Bosco et al. (2008), this strategy induced interference in the egocentric representation of the object with respect to participants' view (i.e., "virtual disorientation"). To indicate the position of the plant, this technique forced the participants to refer to their allocentric viewpoint-independent representation and sync it with the allocentric viewpoint-dependent representation. In both tasks, the accuracy of spatial location is the dependent variable [0 = no answer; 1 = very poor answer, for example, choosing the same side of the retrieval, namely the North; 2 = poor answer, for example, choosing the opposite side of the virtual room (i.e., choosing the southern side when the object in the learning phase was in the northern part); 3 = medium answer, for example bad left–right discrimination (i.e., the eastern part of the virtual room, when the object in the learning phase was in the western side); 4 = correct answer)].

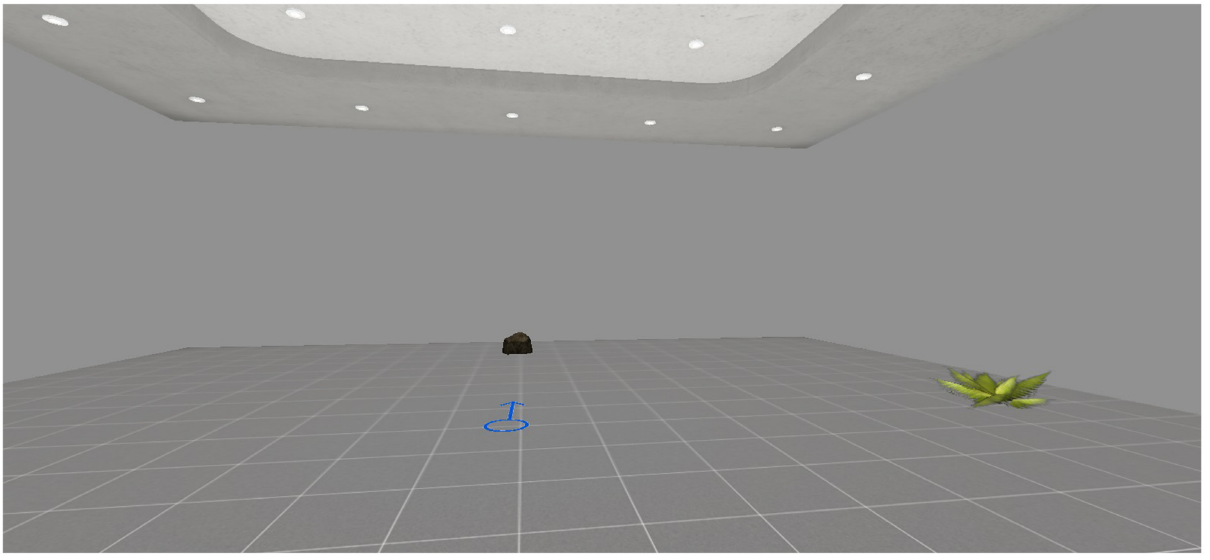

FIGURE 1 | In the encoding phase, participants were asked to memorize the position of the plant starting from the arrow.

From a technical point of view, this VR-based procedure for assessing the abilities to encode, use and sync different spatial representations was created using NeuroVirtual 3D, a recent extension of the software NeuroVR (Riva et al., 2011; Cipresso et al., 2014), which is a free VR platform for creating virtual environments, useful for neuropsychological assessment and neurorehabilitation.

Procedure

Before starting the experimental procedure, each participant was provided with written information about the study and was asked to sign the informed consent form to participate in the study. Then, all participants were required to complete the neuropsychological tests described above. At the start of the experimental session, the participants were seated in front of a horizontally placed 15″ monitor. The monitor screen was placed at a distance of 50 cm from the body plane. The virtual environments were rendered using a portable computer (ACER ASPIRE with CPU Intel® Core™i5 with graphic processor NVidia GeForce GT 540M, 1024 × 768 resolution). The participants also had a gamepad (Logitech Rumble F510), which allowed them to explore and to interact with the environment. After an initial training in VR technology, the experimental procedure was initiated, consisting of an encoding phase, which was followed by the retrieval phase in two different tasks, i.e., Task 1 and Task 2. In the encoding phase, starting from the center of the virtual room (i.e., indicated by the presence of the arrow), each participant was instructed to memorize the position of the plant. In Task 1, the participants were given a real map and invited to retrieve the position of the plant they had memorized in the learning phase, and sign that position with a pen. This real map was a full aerial view of the virtual room. In Task 2, the participants entered the virtual room from the position of the other object (i.e., the stone), and were invited to retrieve the position of the plant they had discovered in the learning phase. They were instructed to stop when they were sure that they had the correct position (i.e., where the plant had been). The order of the presentation of the conditions was randomized for each participant. As explained before, in the Trial 1, the plan was on the East side, in the Trial 2 the object was on the West side, and in the Trial 3 the object was on the South side. The order of the presentation of the trials was randomized for each participant. There was no time limit. Then, all participants were required to indicate the position of the object in the two tasks.

Data Analysis

First, to investigate differences in the traditional spatial neuropsychological tests, a series of analysis of variance with the LSD *post hoc* comparisons were computed with Group ("aMCI group" vs. "AD group" vs. "CG") as between variable. Then, differences in the accuracy of the spatial location for Task 1 and Task 2 were calculated using two repeated measure analyses of variance: Trials ("Trial 1" vs. "Trial 2" vs. "Trial 3") as within factors and Group ("aMCI group" vs. "AD group" vs. "CG") as between factor. For these analyses that were conducted, the Greenhouse-Geisser test statistic was used when the assumption of sphericity was violated. Pairwise comparisons (with Bonferroni's adjustment) and simple contrasts were computed to compare significant differences.

In addition, a series of linear multiple regression analyses were carried out to determine whether a combination of traditional neuropsychological tests (MMSE, Money Road Map, Corsi Block Test – Span, Corsi Block Test- Supraspan, Manikin's Test, The Judgment of Line Orientation) were associated with performance on the VR-procedure.

For all analyses, determination of significance was based on $\alpha = 0.05$.

Results and Discussion

Data were entered into Microsoft Excel and analyzed using SPSS version 18 (Statistical Package for the Social Sciences–SPSS for Windows, Chicago, IL, USA).

One patient from the aMCI group was excluded from the analyses of the Corsi Block Test -Supraspan and the Judgment of Line Orientation due to unfinished tasks.

A series of analysis of variance with the LSD *post hoc* comparisons were computed with Group ("aMCI group" vs. "AD group" vs. "CG") as between variable to investigate differences in the traditional spatial neuropsychological tests. In regard to the Corsi Block Test – Span, findings showed significant differences between groups [$F(2,42) = 5.174, p < 0.05, \eta_p^2 = 0.198$]. Post-hoc comparisons showed that the AD group had significantly poor short-term spatial mnestic abilities ($M = 4.38$, SD = 0.83) when compared with the CG ($M = 5.167$, SD = 0.62, $p < 0.01$). As concerns the Corsi Block Test – Supraspan, results indicated significant differences between groups [$F(2,41) = 13.138$, $p < 0.001$, $\eta_p^2 = 0.391$]. Post-hoc comparisons showed that the CG had better long-term mnestic spatial abilities ($M = 13.33$, SD = 5.86) both when compared with the aMCI group ($M = 7.96$, SD = 3.77 $p < 0.01$) and AD group ($M = 5.54$, SD = 2.32 $p < 0.001$).

Regarding the Money Road Map, results showed significant differences between groups [$F(2,43) = 3.48, p < 0.05, \eta_p^2 = 0.142$]. Specifically, *post hoc* comparisons showed that the AD group showed weak spatial navigation abilities ($M = 16.73$, SD = 5.60) when compared with the CG ($M = 7.96$, SD = 3.77, $p < 0.05$).

In relation to Manikin's Test, findings indicated significant differences between groups [$F(2,42) = 23.42$, $p < 0.001$, $\eta_p^2 = 0.527$]. Specifically, *post hoc* comparisons showed that the AD group had weak mental rotation abilities ($M = 17.07$, SD = 3.05) when compared with the CG ($M = 28.73$, SD = 3.55, $p < 0.001$). Moreover, it was noted that the AD group performed significantly more poorly compared to the aMCI group ($M = 23.13$, SD = 6.63, $p < 0.01$).

Finally, as concerns the Judgment of Line Orientation, findings showed significant differences between groups [$F(2,41) = 26.79$, $p < 0.001$, $\eta_p^2 = 0.567$]. *Post hoc* comparisons showed that the AD group had very poor visuo-spatial abilities ($M = 6.33$, SD = 5.46) both when compared with the aMCI group ($M = 16.57$, SD = 7.77 $p < 0.01$) and CG ($M = 21.73$, SD = 3.82 $p < 0.001$). Moreover, mean scores of the aMCI group were significantly higher ($p < 0.001$) when compared with those of the AD group.

On one side, these data indicated that AD patients had severe deficits on all spatial functions analyzed. On the other side, it was noted that the performance of aMCI group is similar to AD patients for almost all the traditional neuropsychological tests considered. Specifically, AD patient are more impaired in mental rotation abilities and in visuo-spatial functions when compared to aMCI group. **Table 2** summarizes findings from spatial neuropsychological tests.

As concerns data from the VR-based procedure, two repeated measure analyses of variance were carried out. One patient from the aMCI group was excluded from the analyses due to unfinished tasks.

First of all, to investigate differences in the accuracy of the spatial location for Task 1, a repeated measure analysis of variance was computed: Trials ("Trial 1" vs. "Trial 2" vs. "Trial 3") as within factors and Group ("aMCI group" vs. "AD group" vs. "CG") as between factor. No significant effect of Group was found, i.e., there were no absolute significant differences between groups in the ability to retrieve spatial allocentric information independent of point of view. The main effects of Trial [$F(1,82) = 18.09$, $p \leq 0.001$, $\eta_p^2 = 0.306$] were significant. Specifically, simple contrasts indicated that the average scores were significantly lower in the third trials, when compared to the first trial [$F(1,41) = 17.73$, $p < 0.001$, $\eta_p^2 = 0.302$], and to the second trial [$F(1,41) = 27.02$, $p < 0.001$, $\eta_p^2 = 0.394$]. The third trial may be more difficult since the object is presented at the South of the virtual room in the encoding phase, requiring a 180° spatial rotation to find it. Finally, a significant effect was found of the interaction Trials X Group [$F(4,82) = 4.40$, $p < 0.01$, $\eta_p^2 = 0.177$]. As shown by simple contrasts, aMCI patients performed significantly more poorly in the third trial when compared to CG [$F(2,41) = 4.81$, $p < 0.01$, $\eta_p^2 = 0.190$] and to AD group [$F(2,41) = 5.03$, $p < 0.01$, $\eta_p^2 = 0.197$].

Second, to investigate differences in the accuracy of the spatial location for Task 2, another repeated measure analysis of variance was conducted: Trials ("Trial 1" vs. "Trial 2" vs. "Trial 3") as within factors and Group ("aMCI group" vs. "AD group" vs. "CG") as between factor.

The main effect of Group was found [$F(2,41) = 2.41$, $p < 0.05$, $\eta_p^2 = 0.161$]. Specifically, *post hoc* comparisons indicated that AD patients performed more poorly ($M = 2.71$, SD = 1.57) when compared with the CG ($M = 3.33$, SD = 1.57, $p < 0.05$). This means that AD patients showed very weak abilities in retrieving the position of the object without allocentric spatial information. Moreover, results indicated significant differences within Trials [$F(2,1,517) = 8.48$, $p < 0.01$, $\eta_p^2 = 0.177$]. As for the Task 1, the Trial 3 appeared to be the most difficult. Specifically, simple contrasts indicated that the average scores were significantly lower in the Trial 3 when compared to the Trial 1 [$F(1,41) = 19.37$, $p < 0.01$, $\eta_p^2 = 0.321$] and to the Trial 2 [$F(1,41) = 6.16$, $p < 0.01$, $\eta_p^2 = 0.131$]. No significant interaction effect Trials X Group was found, i.e., all groups performed worse in the Trial 3.

Table 3 summarizes mean scores obtained by participants in both tasks.

Finally, a series of linear multiple regression analyses, including all participants, with the accuracy of spatial location for both tasks in each trials as the dependent variable, and general cognitive functioning (MMSE) and traditional Money Road Map, Corsi Block Test – Span, Corsi Block Test-Supraspan, Manikin's Test, The Judgment of Line Orientation) as independent variables, were carried out. All independent variables were entered singularly into the model using the 'enter' method. Results revealed that these neuropsychological tests in combination with each other did not predict impairment in the ability to retrieve spatial allocentric information independent of point of view, not in the Trial 22 ($R^2 = 0.141$, $p = 0.561$), nor in the Trial 2 ($R^2 = 104$, $p = 0.743$), nor in the Trial 3 ($R^2 = 0.305$, $p = 0.71$).

As concerns findings from the second tasks, results showed that these neuropsychological tests in combination with each other predict impairment in the ability to retrieve the position of the object without allocentric spatial information only in the Trial 2 ($R^2 = 0.375$, $p < 0.05$) and in the Trial 3 ($R^2 = 0.381$, $p < 0.05$), but not in the Trial 1 ($R^2 = 0.279$, $p = 0.743$). However, findings revealed that there are only two significant predictors of performance in the third trial of the Task 2, namely, the scores

TABLE 2 | Analysis of variance results of mean scores obtained by participants divided into the three groups at the spatial neuropsychological tests.

	Group						*Post hoc* comparisons[3]		
	aMCI group[1]	AD group[1]	CG[1]	*F*	*P*[3]	η_p^2	aMCI group[1] vs. AD group[1]	aMCI group[1] vs. CG[1]	CG[1] vs. AD group[1]
Corsi Block Test- Span[2]	4.73 (0.50)	4.38 (0.83)	5.16 (0.62)	5.17	**	0.198	N.S.	N.S	**
Corsi Block Test-Supraspan[2]	7.96 (3.77)	5.54 (2.32)	13.33 (5.86)	13.13	***	0.391	N.S.	**	***
Money Rood Map[2]	16.73 (5.63)	16.80 (3.09)	21.20 (6.59)	3.48	*	0.142	N.S.	N.S.	**
Manikin's Test[2]	23.13 (6.63)	17.07 (3.05)	28.73 (3.55)	23.42	***	0.527	**	**	***
Judgment of Line Orientation[2]	16.57 (7.77)	6.33 (5.46)	21.73 (3.82)	26.79	***	0.567	*	***	***

[1]*amnestic mild cognitive impairment group (aMCI group); Alzheimer's Disease group (AD group); control group (CG).*
[2]*Values are shown as mean (SD).*
[3]**$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; N.S., non-significant.*

TABLE 3 | Mean scores obtained by participants divided into the three groups at the virtual-reality based procedure for evaluating abilities in encoding, using and syncing spatial representations.

	Task	Trial	Mean	SD
aMCI group[1]	Task 1	First trial	3.89	0.01
	Task 1	Second trial	3.86	0.36
	Task 1	Third trial	2.57	0.93
	Task 2	First trial	3.13	0.51
	Task 2	Second trial	2.93	0.79
	Task 2	Third trial	2.07	0.96
AD group[1]	Task 1	First trial	3.53	0.73
	Task 1	Second trial	3.87	0.51
	Task 1	Third trial	2.93	1.03
	Task 2	First trial	3.13	0.51
	Task 2	Second trial	2.93	0.79
	Task 2	Third trial	2.07	0.96
CG[1]	Task 1	First trial	3.73	1.03
	Task 1	Second trial	3.73	0.45
	Task 1	Third trial	3.60	0.82
	Task 2	First trial	3.33	1.11
	Task 2	Second trial	3.60	0.50
	Task 2	Third trial	3.07	1.43

[1]*amnestic mild cognitive impairment group (aMCI group); Alzheimer's Disease group (AD group); control group (CG).*

on the Money Road Map ($B = -0.389$, $t = -2.140$, $p < 0.05$) and the scores on the Manikin's Test ($B = -0.687$, $t = 2.774$, $p < 0.01$). These two tests, indeed, evaluate respectively the ability in the spatial navigation, which requires the cognitive ability to correctly retrieve the position of the object in large environment, and the mental rotation ability, which is fundamental in the Trial 3, since it required a 180° spatial rotation to memorize the object.

Together, these data suggested that the impairments in the encoding, using and syncing between different spatial representations are not a product of generalized cognitive decline (as measured with the MMSE) or of general decay in spatial abilities, but instead may reflect a selective deficit in spatial organization.

Conclusion

It is well known that spatial memory deficits characterize the cognitive profile of AD patients (Iachini et al., 2009; Gazova et al., 2012; Lithfous et al., 2013). These spatial impairments manifest themselves in several episodes of topographical disorientation, which were reported in both AD outpatients (McShane et al., 1998) and AD patients residing in a community (Pai and Jacobs, 2004). What is still under debate in scientific literature are the cognitive underpinnings of spatial memory deficits in AD, and the relationship with early impairment in the episodic memory.

If spatial memory can be defined as the ability to encode and store information from our surrounding in egocentric and allocentric representations (O'Keefe and Nadel, 1978), how can deficits in the relationships between these representations become a crucial early indicators of cognitive decline? Within this research field, the current study is aimed at comparing the performances of elderly participants suffering from amnestic MCI, AD patients and a CG, using a VR-based procedure for assessing the ability to encode, use and sync different spatial representations.

First, in line with previous research and clinical evidence mentioned, our results confirmed that AD patients were impaired in the traditional neuropsychological evaluation of spatial functions when compared with the CG. Specifically, it was observed that the cognitive profile of aMCI group is very similar to AD patients for almost all the spatial traditional neuropsychological tests considered. Since the introduction of the clinical criteria in the late 1990s (Petersen et al., 1999), the concept of MCI has been used both in clinical and in research settings to identify individuals in the early stages of cognitive impairment. In particular, amnestic MCI patients are more likely to develop AD when compared with cognitively healthy age-matched individuals (Mitchell and Shiri-Feshki, 2009).

As concerns results from the VR-based procedure, our findings showed that in both tasks all groups performed more poorly in the Trial 3 (i.e., the plant is at the southern side of the virtual room during the encoding phase), which may be more difficult since it required a 180° spatial rotation to memorize the object. On one side, our finding showed that aMCI patients, compared with cognitively healthy controls and AD patients, performed significantly more poorly in the Trial 3 of Task 1. In the Trial 3 of the task, aMCI patients showed a specific deficit in the ability to encode and store an allocentric viewpoint independent representation, since this task asked participants to retrieve the position of the object on a real map. On the other side, our findings from Task 2 indicated that AD patients, compared with cognitively healthy controls, had a specific impairment in syncing the allocentric viewpoint independent representation with the allocentric viewpoint dependent representation. As previously explained, Task 2 may evaluate a more complex spatial ability since participants are required to indicate the position of the object in an empty virtual room without any spatial allocentric information, starting from another point of view. Thus, this task forced the participants to refer to their stored allocentric viewpoint-independent representation and sync it with the allocentric viewpoint-dependent representation. Finally, our results suggested that the impairments in the encoding, using and syncing between different allocentric representations are not a product of generalized cognitive decline (as assessed with the MMSE) or of general decay in spatial abilities, but instead may reflect selective deficits in the spatial organization.

In sum, according to the "mental frame syncing" hypothesis (Serino and Riva, 2013, 2014), our data indicated the presence of a deficit in storing an allocentric viewpoint independent representation in aMCI patients. Then, a profound deficit was found in AD patients in the storage of an allocentric viewpoint independent representation and, consequently, in its synchronization with the allocentric viewpoint dependent representation. From a neurobiological perspective, Padurariu et al. (2012) have recently showed that decrease of hippocampal neuronal density in AD is more prominent, especially in the CA1 and CA3 hippocampal areas. As previously explained, these early neurodegenerative processes significantly impair the neural network that is presumed to be crucial for storing and syncing allocentric representations. The synchronization between the allocentric viewpoint independent representation and the viewpoint dependent representation permits a coherent spatial framework, which is crucial for an effective spatial and episodic retrieval (Serino and Riva, 2014). Moreover, on the basis of the most recent theories of episodic memory, several cognitive and neural processes work in parallel to support the aforementioned "mental time travel" from past to present and future (for a review, see Roediger et al., 2007). Specifically, a number of studies have shown that when individuals remember the past or imagine the future, a comparable level of activation occurs in the medial temporal and frontal lobes, the posterior cingulate, the retrosplenial cortex, and the lateral parietal area (Okuda et al., 2003; Addis et al., 2007, 2009; Buckner and Carroll, 2007; Botzung et al., 2008; Spreng et al., 2009; Viard et al., 2011; Eichenbaum, 2013). Within a wider theoretical account, Buckner and Carroll (2007) theorized that the so-called default network (which includes the above mentioned area of activation) serves as "self-projection," with the ability to shift perspective from the immediate present to alternative perspectives. In addition to the default network's role in remembering the past and imagining the future (i.e., episodic memory) and simulating another viewpoint for successfully orienting in space (i.e., spatial memory and navigation), this includes the ability to conceive the viewpoint of others [i.e., "theory of mind" (TOM)]. An interesting systematic review showed that recent evidence underlined the existence of impairment in the most complex TOM tasks in AD, but it is still unclear whether a TOM deficit is linked to global cognitive dysfunctions or to a specific dysfunction in the episodic memory system (Moreau et al., 2013). According to Frith and de Vignemont (2005), in the egocentric viewpoint, the others are represented in relation to the self, while in the allocentric perspective, the others' mental states are represented independently from the self. However, there is no empirical evidence of the underlying cognitive mechanism that supports this process, and what happens if there is an impairment. It would be interesting, as a future challenge, to investigate if a deficiency in the storage of an allocentric viewpoint independent representation and, then, in its syncing with the allocentric viewpoint dependent representation, which affects the possibility to create a coherent scaffold for an effective retrieval of our experiences, may also explain the difficulty in the cognitive translocation of our current viewpoint in other viewpoints.

The findings of this study are interesting and valuable, but there are some limitations. First, one limitation of our study is the difference between the patients and CGs in terms of age and years of educations. Scores obtained from spatial neuropsychological battery were corrected for age and education level according to Italian normative data where needed, but the findings from VR-based procedure must be viewed according to this potential limit. Second, in relation to the use of virtual tools the neuropsychological evaluation of cognitive function, it would also be useful to assess the patient's perception of usability (for example, difficulties during the experience in using the joystick). However, it is interesting to note that only one patient from the aMCI group did not complete the task. Third, it would be crucial to carry out a longitudinal study to investigate the progression from a deficit in storing allocentric viewpoint independent representation deficit to a more subtle impairment in the synchronization between different allocentric representations across time in the same sample of patients.

In conclusion, although preliminary, these findings provide an initial insight on the cognitive underpinnings of mnestic impairment in aMCI and AD patients. A more precise evaluation of cognitive abilities exploiting the potentiality of VR would offer also the chance to detect subtle deficits in early stages of AD.

Acknowledgments

This study was partially supported by the research project "VRehab. Virtual Reality in the Assessment and TeleRehabilitation of Parkinson's Disease and Post-Stroke Disabilities" (RF-2009-1472190) and by the research project Tecnologia Positiva e Healthy Aging (Positive Technology and Healthy Aging) (Grant D.3.2., 2014). FM was supported by the Department of Human and Social Sciences, University of Bergamo (Grant 2013).

References

Addis, D. R., Pan, L., Vu, M. A., Laiser, N., and Schacter, D. L. (2009). Constructive episodic simulation of the future and the past: distinct subsystems of a core brain network mediate imagining and remembering. *Neuropsychologia* 47, 2222–2238. doi: 10.1016/j.neuropsychologia.2008.10.026

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377. doi: 10.1016/j.neuropsychologia.2006.10.016

Alafuzoff, I., Arzberger, T., Al-Sarraj, S., Bodi, I., Bogdanovic, N., Braak, H., et al. (2008). Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium. *Brain Pathol.* 18, 484–496. doi: 10.1111/j.1750-3639.2008.00147.x

Behrendt, R. P. (2013). Conscious experience and episodic memory: hippocampus at the crossroads. *Front. Psychol.* 4:304. doi: 10.3389/fpsyg.2013.00304

Benton, A. L., Varney, N. R., and Hamsher, K. S. (1978). Visuospatial judgment: a clinical test. *Arch. Neurol.* 35, 364–367. doi: 10.1001/archneur.1978.00500300038006

Bohil, C. J., Alicea, B., and Biocca, F. A. (2011). Virtual reality in neuroscience research and therapy. *Nat. Rev. Neurosci.* 12, 752–762. doi: 10.1038/nrn3122

Bosco, A., Picucci, L., Caffo, A. O., Lancioni, G. E., and Gyselinck, V. (2008). Assessing human reorientation ability inside virtual reality environments: the effects of retention interval and landmark characteristics. *Cogn. Process.* 9, 299–309. doi: 10.1007/s10339-008-0210-6

Botzung, A., Denkova, E., and Manning, L. (2008). Experiencing past and future personal events: functional neuroimaging evidence on the neural bases of mental time travel. *Brain Cogn.* 66, 202–212. doi: 10.1016/j.bandc.2007.07.011

Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 82, 239–259. doi: 10.1007/bf00308809

Braak, H., and Braak, E. (1996). Evolution of the neuropathology of Alzheimer's disease. *Acta Neurol. Scand.* 94, 3–12. doi: 10.1111/j.1600-0404.1996.tb05866.x

Brazzelli, M., Capitani, E., Della Sala, S., Spinnler, H., and Zuffi, M. A. (1994). Neuropsychological instrument adding to the description of patients with suspected cortical dementia: the Milan overall dementia assessment. *J. Neurol. Neurosurg. Psychiatry* 57, 1510–1517. doi: 10.1136/jnnp.57.12.1510

Buckner, R. L., and Carroll, D. C. (2007). Self-projection and the brain. *Trends Cogn. Sci.* 11, 49–57. doi: 10.1016/j.tics.2006.11.004

Burgess, N., Becker, S., King, J. A., and O'Keefe, J. (2001). Memory for events and their spatial context: models and experiments. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1493–1503. doi: 10.1098/rstb.2001.0948

Byrne, P., Becker, S., and Burgess, N. (2007). Remembering the past and imagining the future: a neural model of spatial memory and imagery. *Psychol. Rev.* 114, 340–375. doi: 10.1037/0033-295x.114.2.340

Cipresso, P., Serino, S., Pallavicini, F., Gaggioli, A., and Riva, G. (2014). NeuroVirtual 3D: a Multiplatform 3D Simulation System for Application in Psychology and Neuro-Rehabilitation. *Virtual Augment. Real. Serious Games Healthc. 1* 68, 275–286. doi: 10.1007/978-3-642-54816-1_15

Corsi, P. M. (1972). *Human Memory and the Medial Temporal Region of the Brain.* Ph.D. thesis, McGill University, Montreal, QC.

Dickson, D. W. (1997). The pathogenesis of senile plaques. *J. Neuropathol. Exp. Neurol.* 56, 321–339. doi: 10.1097/00005072-199704000-00001

Eichenbaum, H. (2013). Memory on time. *Trends Cogn. Sci.* 17, 81–88. doi: 10.1016/j.tics.2012.12.007

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., et al. (2003). Cellular networks underlying human spatial navigation. *Nature* 425, 184–188. doi: 10.1038/nature01964

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Frith, U., and de Vignemont, F. (2005). Egocentrism, allocentrism, and Asperger syndrome. *Conscious. Cogn.* 14, 719–738. doi: 10.1016/j.concog.2005.04.006

Gazova, I., Vlcek, K., Laczó, J., Nedelska, Z., Hyncicova, E., Mokrisova, I., et al. (2012). Spatial navigation—a unique window into physiological and pathological aging. *Front. Aging Neurosci.* 4:16. doi: 10.3389/fnagi.2012.00016

Iachini, I., Iavarone, A., Senese, V. P., Ruotolo, F., and Ruggiero, G. (2009). Visuospatial memory in healthy elderly, AD and MCI: a review. *Curr. Aging Sci.* 2, 43–59. doi: 10.2174/1874609810902010043

Klatzky, R. L. (1998). "Allocentric and egocentric spatial representations: definitions, distinctions, and interconnections," in *Spatial Cognition. An Interdisciplinary Approach to Representing and Processing Spatial Knowledge*, eds C. Freksa and C. Habel (Heidelberg: Springer), 1–17. doi: 10.2174/1874609810902010043

Lester, B. D., and Dassonville, P. (2014). The role of the right superior parietal lobule in processing visual context for the establishment of the egocentric reference frame. *J. Cogn. Neurosci.* 26, 2201–2209. doi: 10.1162/jocn_a_00636

Lithfous, S., Dufour, A., and Després, O. (2013). Spatial navigation in normal aging and the prodromal stage of Alzheimer's disease: insights from imaging and behavioral studies. *Ageing Res. Rev.* 12, 201–213. doi: 10.1016/j.arr.2012.04.007

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34, 939–939. doi: 10.1212/WNL.34.7.939

McShane, R., Gedling, K., Keene, J., Fairburn, C., Jacoby, R., and Hope, T. (1998). Getting lost in dementia: a longitudinal study of a behavioral symptom. *Int. Psychogeriatr.* 10, 253–260. doi: 10.1017/S1041610298005365

Mitchell, A. J., and Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr. Scand.* 119, 252–265. doi: 10.1111/j.1600-0447.2008.01326.x

Money, I., Alexander, D., and Walker, H. T. (1965). *Manual: A Standardized Road-Map Test of Direction Sense*. Baltimore, MD: Johns Hopkins Press.

Moreau, N., Viallet, F., and Champagne-Lavau, M. (2013). Using memories to understand others: the role of episodic memory in theory of mind impairment in Alzheimer disease. *Ageing Res. Rev.* 12, 833–839. doi: 10.1016/j.arr.2013.06.005

Morganti, F., Stefanini, S., and Riva, G. (2013). From allo-to egocentric spatial ability in early Alzheimer's disease: a study with virtual reality spatial tasks. *Cogn. Neurosci.* 4, 171–180. doi: 10.1080/17588928.2013.854762

Moscovitch, M., and Nadel, L. (1998). Consolidation and the hippocampal complex revisited: in defense of the multiple-trace model. *Curr. Opin. Neurobiol.* 8, 297–300. doi: 10.1016/s0959-4388(98)80155-4

Nadel, L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* 7, 217–227. doi: 10.1016/s0959-4388(97)80010-4

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res.* 34, 171–175. doi: 10.1016/0006-8993(71)90358-1

O'Keefe, J., and Nadel, L. T. (1978). *The Hippocampus as Cognitive Map*. Oxford: Oxford University Press.

Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Tanji, K., Suzuki, K., et al. (2003). Thinking of the future and past: the roles of the frontal pole and the medial temporal lobes. *Neuroimage* 19, 1369–1380. doi: 10.1016/S1053-8119(03)00179-4

Ono, T., Nakamura, K., Nishijo, H., and Eifuku, S. (1993). Monkey hippocampal neurons related to spatial and nonspatial functions. *J. Neurophysiol.* 70, 1516–1516.

Padurariu, M., Ciobica, A., Mavroudis, I., Fotiou, D., and Baloyannis, S. (2012). Hippocampal neuronal loss in the CA1 and CA3 areas of Alzheimer's disease patients. *Psychiatr. Danub.* 24, 152–158. doi: 10.1016/j.neurobiolaging.2014.08.005ů4.85

Pai, M. C., and Jacobs, W. J. (2004). Topographical disorientation in community-residing patients with Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 19, 250–255. doi: 10.1002/gps.1081

Pai, M. C., and Yang, Y. C. (2013). Impaired translation of spatial representation in young onset Alzheimer's disease patients. *Curr. Alzheimer Res.* 10, 95–103. doi: 10.2174/1567205011310010013

Paillard, J. (1991). *Brain and Space*. Oxford: Oxford Science Publications.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194. doi: 10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.* 56, 303–308. doi: 10.1001/archneur.56.3.303

Pouget, A., and Sejnowski, T. J. (1992). A distributed common reference frame for egocentric space in the posterior parietal cortex. *Behav. Brain Sci.* 15, 787–788.

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., and Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 9, 63.e2–75.e2. doi: 10.1016/j.jalz.2012.11.007

Ratcliff, G. (1979). Spatial thought, mental rotation and the right cerebral hemisphere. *Neuropsychologia* 17, 49–54. doi: 10.1016/0028-3932(79)90021-6

Riva, G., Gaggioli, A., Grassi, A., Raspelli, S., Cipresso, P., Pallavicini, F., et al. (2011). NeuroVR 2-A free virtual reality platform for the assessment and treatment in behavioral health care. *Stud. Health Technol. Inform.* 163, 493–495.

Robertson, R. G., Rolls, E. T., and Georges-François, P. (1998). Spatial view cells in the primate hippocampus: effects of removal of view details. *J. Neurophysiol.* 79, 1145–1156.

Roediger, H. L., Dudai, Y., and Fitzpatrick, S. M. (2007). *Science of Memory: Concepts*. Oxford: Oxford University Press. doi: 10.1093/acprof:oso/9780195310443.001.0001

Rolls, E. T. (2007). An attractor network in the hippocampus: theory and neurophysiology. *Learn. Mem.* 14, 714–731. doi: 10.1101/lm.631207

Serino, S., Cipresso, P., Morganti, F., and Riva, G. (2014). The role of egocentric and allocentric abilities in Alzheimer's disease: a systematic review. *Ageing Res. Rev.* 16, 32–44. doi: 10.1016/j.arr.2014.04.004

Serino, S., and Riva, G. (2013). Getting lost in Alzheimer's disease: a break in the mental frame syncing. *Med. Hypotheses* 80, 416–421. doi: 10.1016/j.mehy.2012.12.031

Serino, S., and Riva, G. (2014). What is the role of spatial processing in the decline of episodic memory in Alzheimer's disease? The "mental frame syncing" hypothesis. *Front. Aging Neurosci.* 6:33. doi: 10.3389/fnagi.2014.00033

Spinnler, H., and Tognoni, G. (1987). Standardizzazione e taratura Italiana di test neuropsicologici. *Ital. J. Neurol. Sci.* 6(Suppl. 8), 1–20.

Spreng, R. N., Mar, R. A., and Kim, A. S. N. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *J. Cogn. Neurosci.* 21, 489–510. doi: 10.1162/jocn.2008.21029

Thal, D. R., Rüb, U., Schultz, C., Sassin, I., Ghebremedhin, E., Del Tredici, K., et al. (2000). Sequence of Aβ protein deposition in the human medial temporal lobe. *J. Neuropathol. Exp. Neurol.* 59, 733–748.

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi: 10.1037/h0080017

Tulving, E. (2001). Episodic memory and common sense: how far apart? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1505–1515. doi: 10.1098/rstb.2001.0937

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi: 10.1146/annurev.psych.53.100901.135114

Viard, A., Chetelat, G., Lebreton, K., Desgranges, B., Landeau, B., de La Sayette, V., et al. (2011). Mental time travel into the past and the future in healthy aged adults: an fMRI study. *Brain Cogn.* 75, 1–9. doi: 10.1016/j.bandc.2010.10.009

Vogeley, K., May, M., Ritzl, A., Falkai, P., Zilles, K., and Fink, G. (2004). Neural correlates of first-person perspective as one constituent of human self-consciousness. *J. Cogn. Neurosci.* 16, 817–827. doi: 10.1162/089892904970799

Weintraub, S., Wicklund, A. H., and Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb. Perspect. Med.* 2:a006171. doi: 10.1101/cshperspect.a006171

Zipser, D., and Andersen, R. A. (1988). A back-propagation programmed network that simulates response properties of a subset of posterior parietal neurons. *Nature* 331, 679–684. doi: 10.1038/331679a0

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

MINI REVIEW
published: 12 May 2015
doi: 10.3389/fnagi.2015.00080

A succinct overview of virtual reality technology use in Alzheimer's disease

Rebeca I. García-Betances, María Teresa Arredondo Waldmeyer, Giuseppe Fico and María Fernanda Cabrera-Umpiérrez*

Life Supporting Technologies (LifeSTech), ETSI Telecomunicaciones, Universidad Politécnica de Madrid, Madrid, Spain

We provide a brief review and appraisal of recent and current virtual reality (VR) technology for Alzheimer's disease (AD) applications. We categorize them according to their intended purpose (e.g., diagnosis, patient cognitive training, caregivers' education, etc.), focus feature (e.g., spatial impairment, memory deficit, etc.), methodology employed (e.g., tasks, games, etc.), immersion level, and passive or active interaction. Critical assessment indicates that most of them do not yet take full advantage of virtual environments with high levels of immersion and interaction. Many still rely on conventional 2D graphic displays to create non-immersive or semi-immersive VR scenarios. Important improvements are needed to make VR a better and more versatile assessment and training tool for AD. The use of the latest display technologies available, such as emerging head-mounted displays and 3D smart TV technologies, together with realistic multi-sensorial interaction devices, and neuro-physiological feedback capacity, are some of the most beneficial improvements this mini-review suggests. Additionally, it would be desirable that such VR applications for AD be easily and affordably transferable to in-home and nursing home environments.

Keywords: Alzheimer's disease, mild cognitive impairment, cognitive rehabilitation, virtual reality, virtual environments

OPEN ACCESS

Edited by:
Valeria Manera, University of Nice Sophia Antipolis, France

Reviewed by:
Pascale Piolino, University Paris Descartes, France
Silvia Serino, I.R.C.C.S Istituto Auxologico Italiano, Italy

****Correspondence:***
Rebeca I. García-Betances, Life Supporting Technologies (LifeSTech), ETSI Telecomunicaciones, Universidad Politécnica de Madrid, Av. Complutense s/n, Madrid 28040, Spain
rgarcia@lst.tfo.upm.es

Received: *30 January 2015*
Accepted: *26 April 2015*
Published: *12 May 2015*

Citation:
García-Betances RI, Arredondo Waldmeyer MT, Fico G and Cabrera-Umpiérrez MF (2015) A succinct overview of virtual reality technology use in Alzheimer's disease. Front. Aging Neurosci. 7:80. doi: 10.3389/fnagi.2015.00080

Virtual Reality Technology

Recent brain plasticity theories and findings about the nervous system's ability to reconstruct cellular synapses as a result of interaction with enriched environments, have spurred new research about memory rehabilitation. Consequently, non-invasive non-pharmacological cognitive rehabilitation (CR) interventions have gained increasing attention in recent years (Cotelli et al., 2012; García-Betances et al., 2014).

Since the introduction of the use of computers for psychological testing over a quarter of a century ago (Riva, 1997), several studies have emphasized the use of virtual environments (VEs) and their ecological validity for neuropsychological assessments (Spooner and Pachana, 2006; Campbell et al., 2009; Tarnanas et al., 2013; Parsons, 2015). VEs have been traditionally defined as "interactive, virtual image displays enhanced by special processing and by non-visual display modalities ... to convince users that they are immersed in a synthetic space" (Ellis, 1994). Several software technologies have been introduced into dementia care to assist patients and their families by providing memory aids and educational support (García-Betances et al., 2014). Virtual reality (VR), a recent branch of Information and Communications Technology (ICT), has been suggested for use in some areas of neuropsychology (Rizzo et al., 2001; Schultheis et al., 2002; Rizzo and Kim, 2005; Coyle et al., 2014; Lesk et al., 2014; Shah et al., 2015). Treatment of phobias, stress, and anxiety are characteristic examples of current VR applications in psychotherapy (Esteves and Vidal, 2004; Riva, 2005; Gregg and Tarrier, 2007; Hartanto et al., 2014; McCann et al., 2014; Paliokas et al., 2014; Smahaj and Prochazka, 2014; Fornells-Ambrojo et al., 2015). Other helpful medical uses of VR are surgical training, post-stroke intervention, musculoskeletal recovery, pain mitigation, etc. (Haque and Srinivasan, 2006; Gervasi et al., 2010; Snyder et al., 2011; Imam and Jarus, 2014; Lohse et al., 2014; Pompeu et al., 2014; Trost and Parsons, 2014; Tsoupikova et al., 2015).

Emerging VR applications today address the challenge of diagnosis and cognitive training of mild cognitive impairment (MCI) and dementia patients, concentrating on navigation and orientation, face recognition, cognitive functionality, and other instrumental activities of daily living (IADL) (Jekel et al., 2015). VR exposes cognitively impaired patients to computer-generated VEs providing a sensation of "presence" or "being there," for the patient to interact with in a multisensory fashion through quasi-naturalistic real-life-like stimuli. Using several perception aspects of psychophysics, mainly visual, tactile, and kinesthetic perceptual sensations, VR offers the possibility of performing activities, tasks, and tests in a VE adaptable to various characteristics and needs of individual patients (Riva, 1997; Baus and Bouchard, 2014; García-Betances et al., 2014). A characteristic of VR, very helpful for Alzheimer's disease (AD) applications, is the high interaction level that is possible to achieve in a safe VE. Depending on the specific type of VE, patients may interact from egocentric or allocentric points of view (Weniger et al., 2011). The role of egocentric and allocentric abilities in AD have been recently reviewed by Serino et al. (2014). The devices and stimuli used determine the level of interaction. A growing number of devices is available today for interaction (e.g., joysticks, gloves, surfaces, etc.), as well as for stimuli presentation in VEs [e.g., screens, 3D head-mounted displays (HMDs), audio headsets, speakers, etc.].

Slater et al. (2009) described the concept of the level of immersion offered by a VR system by referring to the "fidelity" to real-world sensory experience offered by the system's displays and tracking in all sensory modalities. Some features of VR systems are most significant when characterizing the immersion level (Slater et al., 2009; Ma and Zheng, 2011; Baus and Bouchard, 2014). They may be reduced to four main types: (a) number of stimulated senses, (b) quantity and level of interactions, (c) synthetic stimuli fidelity, and (d) system's ability to isolate the user from external stimuli.

Based on the above considerations, three basic levels of system immersion may be defined: (1) non-immersive; (2) semi-immersive; and (3) fully-immersive. In a non-immersive system, the patient interacts with the VE using conventional graphic workstations (PC monitor, keyboard, and mouse) (Costello, 1997; Ma and Zheng, 2011). Virtual tasks played as serious videogames even when displayed on 2D screens are considered for the purpose of this review as "non-immersive" VR, irrespective of the perspective used to look at the scene, whether be it an overhead view or a first-person view, commonly referred to as survey and route perspectives (Markováa et al., 2015). Other more dedicated devices, such as joysticks or gamepads may substitute the mouse. A semi-immersive VR system typically consists of more sophisticated graphics, with larger flat surface displays to present the visual VE (Ma and Zheng, 2011). A fully-immersive VE might consist of huge surrounding projection surfaces, or preferably of 3D displays, such as HMDs, that virtually place the patient inside the VE for the highest level of immersion (Costello, 1997; Baus and Bouchard, 2014).

Immersion plays a crucial role on the subjective sense of "presence." "Presence" refers to the experience of felling "being there," that is, how well the VE truly represents a real-world situation, instead of being a simple video viewing experience. "Presence" is strongly related to immersion, since increasing the immersion level induces a higher intensity of the subjective sense of "presence" experienced by the patient (Slobounov et al., 2015). The sense of presence intensity experienced by the patients while performing the required tasks, substantially affects the ensuing behavioral responses (Slobounov et al., 2015). A detailed comparative study of the effect of fully-immersive 3D stereoscopic VEs versus less immersive 2D presentations on brain functions and subsequent behavioral outcomes in VR experiments has been recently published by Slobounov et al. (2015). Health and safety implications of VR use must be taken into serious consideration (Nichols and Patel, 2002), especially when intended for AD patients. Cyber-sickness, a visually induced motion sickness (VIMS) reaction (Keshavarz et al., 2015) that could arise during or after immersion in a VE depending on the level of immersability, should be a matter of concern in clinical settings (Bohil et al., 2011). The possible occurrence and intensity of virtual reality induced sickness symptoms and effects (VRISE) appears to be dependent upon the level of immersion. Experiments have been conducted to comparatively evaluate VRISE in four VR immersion conditions: HMD, PC display, projection screen, and reality theater. In general, higher prevalence of VRISE was found the more immersive the environment is, although a high subject variability was also found (Sharples et al., 2008).

This mini-review does not pretend to be an exhaustive account of all existing applications of VR for AD, rather, it only aims to illustrate, through representative state of the art examples of the most significant types of VR applications, the advantages of using VR for developing a new class of tools in support of the diagnostic assessment of and cognitive training in AD.

Literature Review Methodology

The overall followed methodology may be divided into two phases: (1) literature search and selection of relevant work and (2) categorization of the selected works. The first phase consisted of an initial computer-based on-line non-systematic literature search, conducted in several high-profile databases, such as: PubMed, Web of Knowledge, IEEExplore, ScienceDirect, and Google Scholar. Only peer-reviewed journal articles in English were considered. Because of conciseness, and considering the relative novelty of the field, the search was limited to years from 2000 to the present. However, a few pre-2000 specific articles were included by reason of their outstanding relevance. VR technology studies and applications related to AD assessment and cognitive intervention were searched for using the following search terms, and combinations thereof: VR, VEs, virtual game, AD, cognitive impairment, CR, and cognitive training.

References cited by the initially retrieved articles became a secondary source for manual selection, and included whenever they contributed significant new information. In addition to the most relevant recent studies of VR applications that involve AD patients, some others aimed at healthy elderly people were included because of their comparative value. Articles dealing with MCI patients were also included since such impairment is often a transition from healthy aging to AD. We excluded those studies and applications in which the devices used to interact with the VE were not clearly described. A few articles whose full-text was not easily accessible were also excluded.

The second methodological phase consisted of categorizing, for later systematic study, the retrieved VR studies and application works, according to the predefined classification schematically portrayed in **Figure 1**.

Categorization of VR Applications Used in AD

The potential usefulness and exceptional opportunities of VR systems as valuable ICT tools to assess and train patients in the early stages of AD has been already ascertained by several studies (Schultheis et al., 2002; Gregg and Tarrier, 2007; Déjos et al., 2011; Cotelli et al., 2012; Man et al., 2012; Yamaguchi et al., 2012). For analytical purposes, it seems convenient to classify VR systems according to some functional criteria, as follows: (1) intended purpose (e.g., assessment and diagnosis, cognitive training, patient education, caregivers' training, etc.); (2) impairment feature it is focused on (e.g., spatial impairment, memory deficit, etc.); (3) methodology employed (e.g., tasks, games, or activities); (4) kind of VE (e.g., desktop, goggles-and-gloves, large screen, virtual room, etc.); and (5) type of interaction technique (e.g., full-immersive, semi-immersive, non-immersive, and passive or active interaction, etc.). **Figure 1** presents the schematic representation of such classification.

The pursuit of future advances beyond current VR applications for AD state of the art will benefit from a broad awareness of recent and ongoing VR developments. Such understanding essentially consists of scrutinizing and comparing design and operation specificities that aim to fulfill the intended purpose of particular AD applications, such as the techniques of patient interaction. A useful starting point, particularly regarding design methodology type and immersion level, is **Table 1**, which lists representative current VR applications for AD and briefly classifies them according to their intended purpose and interaction technique.

Intended Purpose

We have identified three main types of planned goals among the reviewed recent and current VR systems. They may be described as: (1) assessment and diagnosis; (2) cognitive training or therapy; and (3) caregivers' training. An additional purpose was proposed by Riva et al. (2009) regarding the use of VR systems for designing new tools. They developed "NeuroVR," an open-source VR platform for assessment and treatment in clinical psychology and neuroscience which allows non-expert users, such as therapists and researchers, to adapt pre-existing VEs to specific clinical or experimental settings needs (Riva et al., 2011). Intended purposes of the recent or current VR applications for AD reviewed here are indicated in **Table 1**.

Focal Aspects

Recent research has focused on certain specific aspects of AD cognitive impairment features that are generally deemed to be most relevant for VR diagnostic and training purposes. For the sake of the present mini-review, they may be roughly summarized as follows: (1) attention (Kalová et al., 2005; Anguera et al., 2013); (2) executive functions (Yeh et al., 2012; Tarnanas et al., 2013); (3) memory, comprising: non-verbal episodic memory, allocentric and egocentric spatial memory, temporal order memory, prospective memory, short-term, and working memory, etc. (Kalová et al., 2005; Burgess et al., 2006; Optale et al., 2010; Weniger et al., 2011;

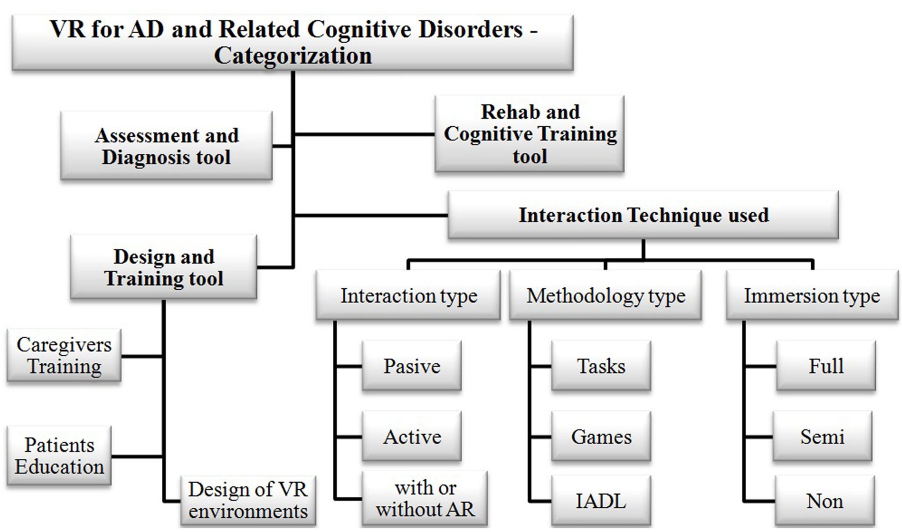

FIGURE 1 | Categorization of VR technology applications for AD.

TABLE 1 | Recent and current VR applications for AD, classified according to the kind of intended purpose and the type of methodological technique used for interaction.

VR technology application and/or reference	Participants/users	Focus feature	Intended purpose	Interaction technique used					
				Methodology type			Immersion type		
				Tasks	Games	IADL	Full	Semi	Non
Kalová et al. (2005)	11 early-AD; 27 subjective problems with memory and concentration; 10 healthy controls	Sequential ordering of places, allothetic orientation, spatial navigation, non-verbal episodic memory	**Assessment and diagnosis**	X				X	X
Burgess et al. (2006)	1 early-AD with topographical disorientation; 4 healthy controls	Allocentric spatial memory. Topographical disorientation		X					X
Hort et al. (2007)	21 probable AD; 11 amnestic MCI single domain; 18 amnestic MCI multiple domain; 7 non-amnestic MCI; 8 subjective memory complaints; 26 healthy controls	Spatial memory. Spatial navigation: allocentric and egocentric navigation		X				X	
Lange et al. (2007)	30 mild dementia Alzheimer's type; 30 healthy controls	Visuospatial and wayfinding orientation		X					X
Cushman et al. (2008)	12 MCI; 14 early-AD; 35 young normal controls; 26 older normal controls	Navigational performance		X					X
Van Schaik et al. (2008)	30 mild to moderate dementia	Evaluation of outdoor environments				X		X	
Zakzanis et al. (2009)	8 healthy young adults; 7 older adults with psychiatric or neurological disorders (2 with probable AD)	Spatial navigation. Spatial memory		X			X		
Laczó et al. (2009, 2010a, 2010b, 2011, 2012)	Amnestic and non-amnestic MCI	Spatial navigation. Hippocampal and non-hippocampal memory impairment		X				X	
Optale et al. (2010)	36 elderly with presence of memory deficits (Verbal Story Recall Test)	Improve memory functions		X			X		
Weniger et al. (2011)	29 amnestic MCI; 29 healthy controls	Egocentric and allocentric memory		X					X
Bellassen et al. (2012)	16 mild AD; 11 frontotemporal lobar degeneration; 24 normal aging	Spatiotemporal navigation. Temporal order memory		X					X
Nedelska et al. (2012)	23 amnestic MCI; 19 mild and moderate AD; 14 healthy controls	Allocentric spatial navigation		X				X	
VREAD, Shamsuddin et al. (2012)	31 healthy elderly and with MCI	Diagnosis of MCI. Cognitive performance. Topographical disorientation		X	X				X
Yeh et al. (2012)	60 senile dementia; 30 healthy controls	Executive functions and memory		X		X	X	X	
Widmann et al. (2012)	15 with AD; 31 healthy controls	Spatial and verbal memory		X				X	
Plancher et al. (2012)	15 amnesic MCI; 15 early to moderate AD; 21 healthy older adults	Episodic memory		X					X
VR-DOT, Tarnanas et al. (2013)	2013: 65 amnestic MCI; 68 mild AD; 72 healthy controls. 2014: 134 with MCI; 75 healthy controls	Executive function. Prospective memory				X		X	
VRAM, Lee et al. (2014)	20 amnestic MCI; 20 mild AD; 20 normal controls	Spatial working memory		X					X
Allain et al. (2014)	24 with AD; 31 healthy elderly controls	IADL functioning		X		X			X
Jebara et al. (2014)	64 young adults; 64 elderly adults	Episodic memory		X				X	

(Continued)

TABLE 1 | Continued

VR technology application and/or reference	Participants/users	Focus feature	Intended purpose	Interaction technique used					
				Methodology type			Immersion type		
				Tasks	Games	IADL	Full	Semi	Non
Hofmann et al. (2003)	9 with AD; 9 with major depressive episode; 10 healthy controls	Psychomotor slowing, strategic and critical thinking, cognitive flexibility, problem solving, spatial orientation, delayed recall, long-term memory	**Cognitive training/ therapy**	X		X			X
Cognimat, Buss (2009)	6–8 early-AD; 4 healthy controls	Train spatial orientation and working memory		X		X			X
PREVIRNEC, Tost et al. (2009)	Patients with neuropsychological disorders	ADL training		X					X
eGaming, Bartolome et al. (2012)	Patients with neurodegenerative disorders	Cognitive and memory functions			X				X
NeuroRacer, Anguera et al. (2013)	Healthy young and older adults	Enhances cognitive control		X					X
BrightArm, Burdea et al. (2013)	3 with dementia	Cognitive rehabilitation of advanced dementia			X				X
IVIRAGE, Chapoulie et al. (2014)	13 healthy elderly adults	Reminiscence therapy		X				X	
O'Connor et al. (2014)	7 dementia caregivers	On-line support group	**Caregivers' training**		X				X

Bellassen et al., 2012; Shamsuddin et al., 2012; Yeh et al., 2012; Burdea et al., 2013; Tarnanas et al., 2013; Jebara et al., 2014; Lee et al., 2014; Serino and Riva, 2015); (4) orientation, specifically: allothetic, visuospatial, wayfinding, spatial navigation, topographical disorientation, etc. (Kalová et al., 2005; Burgess et al., 2006; Hort et al., 2007; Lange et al., 2007; Cushman et al., 2008; Zakzanis et al., 2009; Nedelska et al., 2012); and also (5) executive functions and IADL (Hofmann et al., 2003; Van Schaik et al., 2008; Buss, 2009; Yeh et al., 2012; Tarnanas et al., 2013, 2014; Allain et al., 2014; Jekel et al., 2015). The justification of the importance of these specific cognitive aspects of AD may be found in the cited references.

Some approaches look at more than one of the above mentioned aspects for better assessment. Examples of this combined focus are: Kalová et al. (2005), Burgess et al. (2006), Hort et al. (2007), Cushman et al. (2008), Laczó et al. (2009), Zakzanis et al. (2009), Weniger et al. (2011), Bellassen et al. (2012), Nedelska et al. (2012), Plancher et al. (2012), and Shamsuddin et al. (2012), likewise, a combination of more than one aspect may be used for more effective training tools (Buss, 2009; Anguera et al., 2013). Frequently, memory and attention are combined with navigation, because navigational impairment is a common manifestation of AD that implies disorders of spatial cognition, spatial memory, and orientation. For example, Bellassen et al. (2012) assessed temporal order memory, as acquired through active navigation (spatiotemporal navigation), to design a sensitive behavioral non-verbal marker of mild AD. Lee et al. (2014) evaluated spatial memory in amnestic MCI (aMCI) patients from results of a virtual route learning environment-labeled virtual radial arm maze (VRAM).

Interaction Techniques

User interaction with VEs and scenarios might involve several methodological modalities. It could consist of playing serious games or performing different tasks or activities (e.g., IADL). Here, we refer to "tasks" and "activities" in reference to VR systems for AD, the term "task" specifically means a particular action that is intended, designed, and established to improve a specific cognitive function, while "activities" involve performing high-level sustained cognitive actions and processes such as: eating, bathing, dressing, shopping, etc. Furthermore, the term "game" refers to activities that are defined by rules and any type of user engagement. Most current VR systems for assessment and diagnosis of AD are based on performing tasks, such as navigation or memorization. Moreover, current VR systems for cognitive training concentrate on performing activities that are related to IADL, such as: cooking, driving, shopping, etc. It has been recently demonstrated that the use of a familiar image-based VE can stimulate recollections of autobiographical memory in healthy elderly subjects (Benoit et al., 2015). The fact that episodic autobiographical memory is impaired in early stages of AD (Seidl et al., 2011), suggests that using such type of VR systems may be helpful for reminiscence rehabilitation of AD patients. **Table 1** classifies the reviewed VR systems in terms of the methodology utilized for user interaction.

Recent progress in augmented reality (AR) indicates that this technology will probably become another useful ICT tool for AD. This form of mixed reality enhances a non-synthetic real environment by superimposing some synthetic elements into the users' perception of that reality (Baus and Bouchard, 2014). In contrast to VR system users, who are exposed to VEs (immersive or not), users of AR applications face real physical locations, upon which AR systems introduce additional virtual elements. Some AR applications have been developed in recent years for medically related purposes, such as phobia therapy (Botella et al., 2005; Wrzesien et al., 2014), and for assessment and treatment of psychological disorders (Giglioli et al., 2015). A few researchers have conducted appraisals of AR applications for cognitive training and rehabilitation of AD patients (Quintana and Favela, 2013). Some examples are the GenVirtual (Correa et al., 2007), BuildAR (Al-Khafaji et al., 2013), and ARCube (Boletsis and Mccallum, 2014).

Conclusion

We have presented a glimpse at VR applications for diagnostic assessment and cognitive training in MCI and AD. Instead of presenting an exhaustive account of all VR applications currently available, this mini-review has focused on representative state of the art examples of the most significant types, which we have classified into specific categories to aid in their systematic scrutiny. This analysis reveals that most VR applications for AD do not offer today VEs with sufficient levels of immersion or interaction, but simpler non-immersive or semi-immersive VR scenarios.

The present general tendency to develop personalized ICT-based healthcare applications (PMC – Personalized Medicine Coalition, 2014), together with the considerable recent advances in sensor, VR, and 3D technologies, highlights the urgency of continuing the improvement of existing early stage medical VR applications. The improvements should translate in better VR-based applications for AD, with more immersive VEs, based on the latest innovative technologies available (e.g., novel HMDs, 3D smart televisions, etc.). The incorporation of emerging display and interactive technologies will enable innovative designs and implementations of more effective and versatile supportive VR applications for diagnosis and cognitive training of AD patients.

We suggest that future developments of VR cognitive assessment and training applications for MCI and AD should prioritize the specificity of the particular needs of AD patients and their symptoms' evolution. VR platform designs must be able to incorporate emerging know-how and techniques, not only to better fulfill the intended specific purposes of VR applications for AD, but also to equip those future applications with adequate capacity to supply assistive support to clinicians and caregivers, to significantly contribute to the improvement of the quality of life of MCI and AD patients and their families. Advances in this field should also contemplate providing easy transfer of the applications in a simple and affordable way into in-home and nursing home environments.

Furthermore, a vital feature that could make an important impact on future VR applications for AD usefulness is the capacity to timely gather and transmit relevant information (García-Betances et al., 2014). Such information should consist, not only of ongoing patient performance data, but also of pertinent psycho-physiological data, such as heart rate variability, respiration, ECG, EEG, etc., and any other multimodal information useful for affective (emotional) state recognition (García-Betances et al., 2015) and cognitive stress detection (McDuff et al., 2014). This data gathering feature should also include immediately accessible real-time feedback, to enable computer as well as specialist controlled intervention during the course of the session. Collected data would provide valuable up-to-date information about the patient's performance evolution, adherence to training and rehabilitation routines, as well as about synchronous physiological reactions of the patient. This feedback capacity could prove to be a valuable tool for implementing other future closed-loop applications, and also become a source of reliable data to build systematic and robust knowledge bases that are indispensable for advancing analytical research and future development.

Acknowledgments

We would like to thank the consortia of Horizon2020 EU projects "MIAMI-MD" and "PD_Manager" for their valuable contributions to the systematic conceptualization of neuropsychological knowledge used in this study.

References

Al-Khafaji, N. J., Al Shaher, M. A., Al-Khafaji, M. J., and Ahmed Asmail, M. A. (2013). "Use buildAR to help the Alzheimer's disease patients," in *The Int Conf on E-Technologies and Business on the Web (EBW2013)* (Bangkok: SDIWC digital library), 280–284.

Allain, P., Foloppe, D. A., Besnard, J., Yamaguchi, T., Etcharry-Bouyx, F., Le Gall, D., et al. (2014). Detecting everyday action deficits in Alzheimer's disease using a nonimmersive virtual reality kitchen. *J. Int. Neuropsychol. Soc.* 20, 468–477. doi:10.1017/S1355617714000344

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., et al. (2013). Video game training enhances cognitive control in older adults. *Nature* 501, 97–101. doi:10.1038/nature12486

Bartolome, N. A., Zapirain, B. G., and Mendez, A. (2012). "Innovative system for cognitive brain enhancement and language disorders treatment using a virtual reality environment," in *17th Int. Conf. CGAMES* (Louisville, KY: IEEE), 120–124.

Baus, O., and Bouchard, S. (2014). Moving from virtual reality exposure-based therapy to augmented reality exposure-based therapy: a review. *Front. Hum. Neurosci.* 8, 112. doi:10.3389/fnhum.2014.00112

Bellassen, V., Igloi, K., Cruz, L., Dubois, B., and Rondi-Reig, L. (2012). Temporal order memory assessed during spatiotemporal navigation as a behavioral cognitive marker for differential Alzheimer's disease diagnosis. *J. Neurosci.* 32, 1942–1952. doi:10.1523/JNEUROSCI.4556-11.2012

Benoit, M., Guerchouche, R., Petit, P.-D., Chapoulie, E., Manera, V., Chaurasia, G., et al. (2015). Is it possible to use highly realistic virtual reality in the elderly? A feasibility study with image-based rendering. *Neuropsychiatr. Dis. Treat.* 11, 557–563. doi:10.2147/NDT.S73179

Bohil, C. J., Alicea, B., and Biocca, F. A. (2011). Virtual reality in neuroscience research and therapy. *Nat. Rev. Neurosci.* 12, 752–762. doi:10.1038/nrn3122

Boletsis, C., and Mccallum, S. (2014). Augmented reality cube game for cognitive training: an interaction study. *Stud. Health Technol. Inform.* 200, 81–87. doi:10.3233/978-1-61499-393-3-81

Botella, C. M., Juan, M. C., Baños, R. M., Alcañiz, M., Guillen, V., and Rey, B. (2005). Mixing realities? An application of augmented reality for the treatment of cockroach phobia. *Cyberpsychol. Behav.* 8, 162–171. doi:10.1089/cpb.2005.8.162

Burdea, G., Rabin, B., Rethage, D., Damiani, F., Hundal, J. S., and Fitzpatrick, C. (2013). "BrightArm™ therapy for patients with advanced dementia: a feasibility study," in *2013 ICVR* (Philadelphia, PA: IEEE), 208–209.

Burgess, N., Trinkler, I., King, J., Kennedy, A., and Cipolotti, L. (2006). Impaired allocentric spatial memory underlying topographical disorientation. *Rev. Neurosci.* 17, 239–251. doi:10.1515/REVNEURO.2006.17.1-2.239

Buss, B. (2009). *Virtual Reality Training System for Patients with Dementia*. Zürich: ETH, Swiss Federal Institute of Technology, Institute of Neuroinformatics.

Campbell, Z., Zakzanis, K. K., Jovanovski, D., Joordens, S., Mraz, R., and Graham, S. J. (2009). Utilizing virtual reality to improve the ecological validity of clinical neuropsychology: an FMRI case study elucidating the neural basis of planning by comparing the Tower of London with a three-dimensional navigation task. *Appl. Neuropsychol.* 16, 295–306. doi:10.1080/09084280903297891

Chapoulie, E., Guerchouche, R., Petit, P. D., Chaurasia, G., Robert, P., and Drettakis, G. (2014). "Reminiscence therapy using image-based rendering in VR," in *2014 IEEE VR* (Minneapolis, MN: IEEE), 45–50.

Correa, A. G. D., de Assis, G. A., do Nascimento, M., Ficheman, I., and de Deus López, R. (2007). "GenVirtual: an augmented reality musical game for cognitive and motor rehabilitation," in *2007 Virtual Rehabilitation* (Venice: IEEE), 1–6.

Costello, P. J. (1997). "Health and safety issues associated with virtual reality – a review of current literature," in *Advisory Group on Computer Graphics, Technical Report Series*. Available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.6.3025&rep=rep1&type=pdf

Cotelli, M., Manenti, R., Zanetti, O., and Miniussi, C. (2012). Non-pharmacological intervention for memory decline. *Front. Hum. Neurosci.* 6, 46. doi:10.3389/fnhum.2012.00046

Coyle, H., Traynor, V., and Solowij, N. (2014). Computerized and virtual reality cognitive training for individuals at high risk of cognitive decline: systematic review of the literature. *Am. J. Geriatr. Psychiatry* 23, 335–359. doi:10.1016/j.jagp.2014.04.009

Cushman, L. A., Stein, K., and Duffy, C. J. (2008). Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality. *Neurology* 71, 888–895. doi:10.1212/01.wnl.0000326262.67613.fe

Déjos, M., Sauzéon, H., Falière, A., and N'Kaoua, B. (2011). Naturalistic assessment of spatial cognition disorders in Alzheimer's disease using virtual reality. *Ann. Phys. Rehabil. Med.* 54, e90. doi:10.1016/j.rehab.2011.07.696

Ellis, S. R. (1994). What are virtual environments? *IEEE Comput. Graph. Appl.* 14, 17–22. doi:10.1109/38.250914

Esteves, R., and Vidal, L. (2004). The acceptance of virtual reality devices for cognitive rehabilitation: a report of positive results with schizophrenia. *Comput. Methods Programs Biomed.* 73, 173–182. doi:10.1016/S0169-2607(03)00066-X

Fornells-Ambrojo, M., Freeman, D., Slater, M., Swapp, D., Antley, A., and Barker, C. (2015). How do people with persecutory delusions evaluate threat in a controlled social environment? A qualitative study using virtual reality. *Behav. Cogn. Psychother.* 43, 89–107. doi:10.1017/S1352465813000830

García-Betances, R., Fico, G., Salvi, D., OTTaviano, M., and Arredondo, M. T. (2015). On the convergence of affective and persuasive technologies in computer-mediated health-care systems. *Human Technol.* (in press).

García-Betances, R., Jiménez-Mixco, V., Arredondo, M. T., and Cabrera-Umpiérrez, M. F. (2014). Using virtual reality for cognitive training of the elderly. *Am. J. Alzheimers Dis. Other Demen.* 30, 49–54. doi:10.1177/1533317514545866

Gervasi, O., Magni, R., and Zampolini, M. (2010). Nu! Reha VR: virtual reality in neuro tele-rehabilitation of patients with traumatic brain injury and stroke. *Virtual Real.* 14, 131–141. doi:10.1007/s10055-009-0149-7

Giglioli, I. A. C., Pallavicini, F., Pedroli, E., Serino, S., and Giuseppe Riva, G. (2015). Augmented reality: a brand new challenge for the assessment and treatment of psychological disorders, review article. *Comput. Math. Methods Med.* Article ID: 862942 (in press).

Gregg, L., and Tarrier, N. (2007). Virtual reality in mental health: a review of the literature. *Soc. Psychiatry Psychiatr. Epidemiol.* 42, 343–354. doi:10.1007/s00127-007-0173-4

Haque, S., and Srinivasan, S. (2006). A meta-analysis of the training effectiveness of virtual reality surgical simulators. *IEEE Trans. Inf. Technol. Biomed.* 10, 51–58. doi:10.1109/TITB.2005.855529

Hartanto, D., Kampmann, I. L., Morina, N., Emmelkamp, P. G. M., Neerincs, M. A., and Brinkman, W. P. (2014). Controlling social stress in virtual reality environments. *PLoS ONE* 9:e92804. doi:10.1371/journal.pone.0092804

Hofmann, M., Rosler, A., Schwarz, W., Muller-Spahn, F., Krauchi, K., Hock, C., et al. (2003). Interactive computer-training as a therapeutic tool in Alzheimer's disease. *Compr. Psychiatry* 44, 213–219. doi:10.1016/S0010-440X(03)00006-3

Hort, J., Laczo, J., Vyhnalek, M., Bojar, M., Bures, J., and Vlcek, K. (2007). Spatial navigation deficit in amnestic mild cognitive impairment. *Proc. Natl. Acad. Sci. U.S.A.* 104, 4042–4047. doi:10.1073/pnas.0611314104

Imam, B., and Jarus, T. (2014). Virtual reality rehabilitation from social cognitive and motor learning theoretical perspectives in stroke population. *Rehabil. Res. Pract.* 2014, 540–594. doi:10.1155/2014/594540

Jebara, N., Orriols, E., Zaoui, M., Berthoz, A., and Piolino, P. (2014). Effects of enactment in episodic memory: a pilot virtual reality study with young and elderly adults. *Front. Aging Neurosci.* 6, 338. doi:10.3389/fnagi.2014.00338

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., et al. (2015). Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review. *Alzheimers Res. Ther.* 7, 17–20. doi:10.1186/s13195-015-0099-0

Kalová, E., Vlček, K., Jarolímová, E., and Bureš, J. (2005). Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: corresponding results in real space tests and computer tests. *Behav. Brain Res.* 159, 175–186. doi:10.1016/j.bbr.2004.10.016

Keshavarz, B., Riecke, B. E., Hettinger, L. J., and Campos, J. L. (2015). Vection and visually induced motion sickness: how are they related? *Front. Psychol.* 6, 472. doi:10.3389/fpsyg.2015.00472

Laczó, J., Andel, R., Vlcek, K., Matoska, V., Vyhnalek, M., Tolar, M., et al. (2011). Spatial navigation and APOE in amnestic mild cognitive impairment. *Neurodegener. Dis.* 8, 169–177. doi:10.1159/000321581

Laczó, J., Andel, R., Vlcek, K., Vyhnalek, M., Magerova, H., Varjassyova, A., et al. (2010a). Spatial navigation deficits predict Alzheimer's disease in patients with amnestic mild cognitive impairment: a 3-year follow-up study. *Eur. J. Neurol.* 17, 44.

Laczó, J., Andel, R., Vyhnalek, M., Vlcek, K., Magerova, H., Varjassyova, A., et al. (2010b). Human analogue of the Morris water maze for testing subjects at risk of Alzheimer's disease. *Neurodegener. Dis.* 7, 148–152. doi:10.1159/000289226

Laczó, J., Andel, R., Vyhnalek, M., Vlcek, K., Magerova, H., Varjassyova, A., et al. (2012). From Morris water maze to computer tests in the prediction of Alzheimer's disease. *Neurodegener. Dis.* 10, 153–157. doi:10.1159/000333121

Laczó, J., Vlček, K., Vyhnálek, M., Vajnerová, O., Ort, M., Holmerová, I., et al. (2009). Spatial navigation testing discriminates two types of amnestic mild cognitive impairment. *Behav. Brain Res.* 202, 52–59. doi:10.1016/j.bbr.2009.03.041

Lange, B. S., Rizzo, A., Astur, R., and Parsons, T. (2007). Virtual reality visuospatial and wayfinding assessment for mild dementia of the Alzheimer's type. *Alzheimers Dementia* 3, S135. doi:10.1016/j.jalz.2007.04.178

Lee, J. Y., Kho, S., Yoo, H. B., Park, S., Choi, J. S., Kwon, J. S., et al. (2014). Spatial memory impairments in amnestic mild cognitive impairment in a virtual radial arm maze. *Neuropsychiatr. Dis. Treat.* 10, 653–660. doi:10.2147/NDT.S58185

Lesk, V. E., Shamsuddin, S. N. W., Elizabeth, R., Walters, E. R., and Ugail, H. (2014). Using a virtual environment to assess cognition in the elderly. *Virtual Real.* 18, 271–279. doi:10.1007/s10055-014-0252-2

Lohse, K. R., Hilderman, C. G. E., Cheung, K. L., Tatla, S., and Van der Loos, H. F. M. (2014). Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. *PLoS ONE* 9:e93318. doi:10.1371/journal.pone.0093318

Ma, M., and Zheng, H. (2011). Virtual reality and serious games in healthcare. *Adv. Comput. Intell. Paradigms Healthcare* 6, 169–192. doi:10.1007/978-3-642-17824-5_9

Man, D. W. K., Chung, J. C. C., and Lee, G. Y. Y. (2012). Evaluation of a virtual reality-based memory training programme for Hong Kong Chinese older adults with questionable dementia: a pilot study. *Int. J. Geriatr. Psychiatry* 27, 513–520. doi:10.1002/gps.2746

Markováa, H., Laczóa, J., Andeld, R., Horta, J., and Vlcek, K. (2015). Perspective taking abilities in amnestic mild cognitive impairment and Alzheimer's disease. *Behav. Brain Res.* 281, 229–238. doi:10.1016/j.bbr.2014.12.033

McCann, R. A., Armstrong, C. M., Skopp, N. A., Edwards-Stewart, A., Smolenski, D. J., June, J. D., et al. (2014). Virtual reality exposure therapy for the treatment of anxiety disorders: an evaluation of research quality. *J. Anxiety Disord.* 28, 625–631. doi:10.1016/j.janxdis.2014.05.010

McDuff, D., Gontarek, S., and Picard, R. (2014). "Remote measurement of cognitive stress via heart rate variability," in *36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 26–30 Aug. 2014* (Chicago, IL: IEEE), 2957–2960. doi:10.1109/EMBC.2014.6944243

Nedelska, Z., Andel, R., Laczo, J., Vlcek, K., Horinek, D., Lisy, J., et al. (2012). Spatial navigation impairment is proportional to right hippocampal volume. *Proc. Natl. Acad. Sci. U.S A.* 109, 2590–2594. doi:10.1073/pnas.1121588109

Nichols, S., and Patel, H. (2002). Health and safety implications of virtual reality: a review of empirical evidence. *Appl. Ergon.* 33, 251–271. doi:10.1016/S0003-6870(02)00020-0

O'Connor, M. F., Arizmendi, B. J., and Kaszniak, A. W. (2014). Virtually supportive: a feasibility pilot study of an online support group for dementia caregivers in a 3D virtual environment. *J. Aging Stud*. 30, 87–93. doi:10.1016/j.jaging.2014.03.001

Optale, G., Urgesi, C., Busato, V., Marin, S., Piron, L., Priftis, K., et al. (2010). Controlling memory impairment in elderly adults using virtual reality memory training: a randomized controlled pilot study. *Neurorehabil. Neural Repair* 24, 348–357. doi:10.1177/1545968309353328

Paliokas, I., Tsakiris, A., Vidalis, A., and Tzovaras, D. (2014). "Sense of presence and metacognition enhancement in virtual reality exposure therapy in the treatment of social phobias and the fear of flying," in *Proceedings of the VAMR 2014* (Springer International Publishing), 316–328. doi:10.1007/978-3-319-07464-1_30

Parsons, T. D. (2015). "Ecological validity in virtual reality-based neuropsychological assessment," in *Encyclopedia of Information Science and Technology, Third Edition*, ed. M. Khosrow-Pour (Hershey, PA: Information Science Reference), 1006–1015. doi:10.4018/978-1-4666-5888-2.ch095

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., and Piolino, P. (2012). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active and passive encoding. *Neuropsychologia* 50, 592–602. doi:10.1016/j.neuropsychologia.2011.12.013

PMC – Personalized Medicine Coalition. (2014). *The Case for Personalized Medicine*, 4th Edn. Available at: http://www.personalizedmedicinecoalition.org/Resources/Publications

Pompeu, J. E., Alonso, T. H., Masson, I. B., Pompeu, S. M. A. A., and Torriani-Pasin, C. (2014). The effects of virtual reality on stroke rehabilitation: a systematic review. *Motricidade* 10, 111–122. doi:10.6063/motricidade.10(4)0.3341

Quintana, E., and Favela, J. (2013). Augmented reality annotations to assist persons with Alzheimer's and their caregivers. *Pers. Ubiquitous Comput.* 17, 1105–1116. doi:10.1007/s00779-012-0558-6

Riva, G. (1997). Virtual reality as assessment tool in psychology. *Stud. Health Technol. Inform.* 44, 71–79. doi:10.3233/978-1-60750-888-5-71

Riva, G. (2005). Virtual reality in psychotherapy: review. *Cyberpsychol. Behav.* 8, 220–240. doi:10.1089/cpb.2005.8.220

Riva, G., Carelli, L., Gaggioli, A., Gorini, A., Vigna, C., Corsi, R., et al. (2009). NeuroVR 1.5-A free virtual reality platform for the assessment and treatment. *Stud. Health Technol. Inform.* 142, 268–270. doi:10.3233/978-1-58603-964-6-268

Riva, G., Gaggioli, A., Grassi, A., Raspelli, S., Cipresso, P., Pallavicini, F., et al. (2011). NeuroVR 2 – a free virtual reality platform for the assessment and treatment in behavioral health care. *Stud. Health Technol. Inform.* 163, 493–495. doi:10.3233/978-1-60750-706-2-493

Rizzo, A., and Kim, G. J. (2005). ASWOT analysis of the field of virtual reality rehabilitation and therapy. *Presence (Camb)* 14, 119–146. doi:10.1162/1054746053967094

Rizzo, A. A., Buckwalter, J. G., McGee, J., Bowerly, T., van der Zaag, C., Neumann, U., et al. (2001). Virtual environments for assessing and rehabilitating cognitive/functional performance: a review of project's at the USC Integrated Media Systems Center. *Presence* 10, 359–374. doi:10.1162/1054746011470226

Schultheis, M. T., Himelstein, J., and Rizzo, A. R. (2002). Virtual reality and neuropsychology: upgrading the current tools. *J. Head Trauma Rehabil.* 17, 379–394. doi:10.1097/00001199-200210000-00002

Seidl, U., Lueken, U., Thomann, P. A., Geider, J., and Schroder, J. (2011). Autobiographical memory deficits in Alzheimer's disease. *J. Alzheimers Dis.* 27, 567–574. doi:10.3233/JAD-2011-110014

Serino, S., Pietro Cipresso, P., Morganti, F., and Riva, G. (2014). The role of egocentric and allocentric abilities in Alzheimer's disease: a systematic review. *Ageing Res. Rev.* 16, 32–44. doi:10.1016/j.arr.2014.04.004

Serino, S., and Riva, G. (2015). How different spatial representations interact in virtual environments: the role of mental frame syncing. *Cogn. Process.* 16, 191–201. doi:10.1007/s10339-015-0646-4

Shah, L. B. I., Torres, S., Kannusamy, P., Chng, C. M. L., He, H. G., and Klainin-Yobas, P. (2015). Efficacy of the virtual reality-based stress management program on stress-related variables in people with mood disorders: the feasibility study. *Arch. Psychiatr. Nurs.* 29, 6–13. doi:10.1016/j.apnu.2014.09.003

Shamsuddin, S. N. W., Ugail, H., Lesk, V., and Walters, E. (2012). "VREAD: a virtual simulation to investigate cognitive function in the elderly," in *Int Conf Cyberworlds*, Darmstadt. doi:10.1109/CW.2012.37

Sharples, S., Cobb, S., Moody, A., and Wilson, J. R. (2008). Virtual reality induced symptoms and effects (VRISE): comparison of head mounted display (HMD), desktop and projection display systems. *Displays* 29, 58–69. doi:10.1016/j.displa.2007.09.005

Slater, M., Lotto, B., Arnold, M. M., and Sanchez-Vives, M. V. (2009). How we experience immersive virtual environments: the concept of presence and its measurement. *Annuario de Psicología* 40, 193–210.

Slobounov, S. M., Ray, W., Johnson, B., Slobounov, E., and Newell, K. M. (2015). Modulation of cortical activity in 2D versus 3D virtual reality environments: an EEG study. *Int. J. Psychophysiol.* 95, 254–260. doi:10.1016/j.ijpsycho.2014.11.003

Smahaj, J., and Prochazka, R. (2014). Virtual reality as alternative for anxiety disorders treatment. *Cesk. Psychol.* 58, 571–579. doi:10.1002/da.20734

Snyder, C. W., Vandromme, M. J., Tyra, S. L., Porterfield, J. R., Clements, R. H., and Hawn, M. T. (2011). Effects of virtual reality simulator training method and observational learning on surgical performance. *World J. Surg.* 35, 245–252. doi:10.1007/s00268-010-0861-1

Spooner, D. M., and Pachana, N. A. (2006). Ecological validity in neuropsychological assessment: a case for greater consideration in research with neurologically intact population. *Arch. Clin. Neuropsychol.* 21, 327–337. doi:10.1016/j.acn.2006.04.004

Tarnanas, I., Schlee, W., Tsolaki, M., Müri, R., Mosimann, U., and Nef, T. (2013). Ecological validity of virtual reality daily living activities screening for early dementia: longitudinal study. *JMIR Serious Games* 1, e1. doi:10.2196/games.2778

Tarnanas, I., Tsolaki, M., Nef, T., Müri, R. M., and Mosimann, U. P. (2014). Can a novel computerized cognitive screening test provide additional information for early detection of Alzheimer's disease? *Alzheimers Dement.* 10, 790–798. doi:10.1016/j.jalz.2014.01.002

Tost, D., Grau, S., Ferre, M., Garcia, P., Tormos, J. M., Garcia, A., et al. (2009). "PREVIRNEC: a cognitive telerehabilitation system based on virtual environments," in *Int Conf Vir Rehab* (Haifa: IEEE), 87–93. doi:10.1109/ICVR.2009.5174211

Trost, Z., and Parsons, T. D. (2014). Beyond distraction: virtual reality graded exposure therapy as a treatment for pain-related fear and disability in chronic pain. *J. Appl. Biobehav. Res.* 19, 106–126. doi:10.1111/jabr.12021

Tsoupikova, D., Stoykov, N. S., Corrigan, M., Thielbar, K., Vick, R., Li, Y., et al. (2015). Virtual immersion for post-stroke hand rehabilitation therapy. *Ann. Biomed. Eng.* 43, 467–477. doi:10.1007/s10439-014-1218-y

Van Schaik, P., Martyr, A., Blackman, T., and Robinson, J. (2008). Involving persons with dementia in the evaluation of outdoor environments. *Cyberpsychol. Behav.* 11, 415–424. doi:10.1089/cpb.2007.0105

Weniger, G., Ruhleder, M., Lange, C., Wolf, S., and Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia* 49, 518–527. doi:10.1016/j.neuropsychologia.2010.12.031

Widmann, C. N., Beinhoff, U., and Riepe, M. W. (2012). Everyday memory deficits in very mild Alzheimer's disease. *Neurobiol. Aging* 33, 297–303. doi:10.1016/j.neurobiolaging.2010.03.012

Wrzesien, M., Alcañiz, M., Botella, C., Burkhardt, J.-M., Breton, L. J., and Rodríguez, O. A. (2014). A pilot evaluation of a therapeutic game applied to small animal phobia treatment. *Seripus Games Dev. Appl.* 8778, 10–20. doi:10.1007/978-3-319-11623-5_2

Yamaguchi, T., Foloppe, D. A., Richard, P., Richard, E., and Allain, P. (2012). A dual-modal virtual reality kitchen for (Re)learning of everyday cooking activities in Alzheimer's disease. *Precence* 21, 43–57. doi:10.1162/PRES_a_00080

Yeh, S. C., Tsai, C. F., Chen, Y. C., and Rizzo, A. (2012). "An innovative virtual reality system for mild cognitive impairment: diagnosis and evaluation," in *IEEE EMBS Conf IECBES* (Langkawi: IEEE), 23–27.

Zakzanis, K., Quintin, G., Graham, S., and Mraz, R. (2009). Age and dementia related differences in spatial navigation within an immersive virtual environment. *Med. Sci. Monit.* 15, CR140–CR150.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

CORRECTION
published: 14 December 2015
doi: 10.3389/fnagi.2015.00235

Corrigendum: A succinct overview of virtual reality technology use in Alzheimer's disease

Rebeca I. García-Betances, María Teresa Arredondo Waldmeyer, Giuseppe Fico and María Fernanda Cabrera-Umpiérrez*

Life Supporting Technologies (LifeSTech), ETSI Telecomunicaciones, Universidad Politécnica de Madrid, Madrid, Spain

Keywords: Alzheimer's disease, mild cognitive impairment, cognitive rehabilitation, virtual reality, virtual environments

A corrigendum on

A succinct overview of virtual reality technology use in Alzheimer's disease
by García-Betances, R. I., Arredondo Waldmeyer, M. T., Fico, G., and Cabrera-Umpiérrez, M. F. (2015). Front. Aging Neurosci. 7, 80. doi: 10.3389/fnagi.2015.00080

Due to a misunderstanding, the "last name" of the main author of reference: Giglioli et al., 2015, is a two-word name "Chicchi Giglioli" and not "Giglioli." Consequently, reference Giglioli et al., 2015 should read:

Chicchi Giglioli, I. A., Pallavicini, F., Pedroli, E., Serino, S., and Giuseppe Riva, G. (2015). Augmented reality: a brand new challenge for the assessment and treatment of psychological disorders, review article. *Comput. Math. Methods Med.* Article ID: 862942.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Edited and reviewed by:
Valeria Manera, University of Nice Sophia Antipolis, France

****Correspondence:***
Rebeca I. García-Betances
rgarcia@lst.tfo.upm.es

Received: *20 November 2015*
Accepted: *30 November 2015*
Published: *14 December 2015*

Citation:
García-Betances RI, Arredondo Waldmeyer MT, Fico G and Cabrera-Umpiérrez MF (2015) Corrigendum: A succinct overview of virtual reality technology use in Alzheimer's disease. Front. Aging Neurosci. 7:235. doi: 10.3389/fnagi.2015.00235

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 17 December 2014
doi: 10.3389/fnagi.2014.00338

Effects of enactment in episodic memory: a pilot virtual reality study with young and elderly adults

Najate Jebara[1,2,3], Eric Orriols[2,3], Mohamed Zaoui[1], Alain Berthoz[1]* and Pascale Piolino[2,3,4]*

[1] *UMR 7152 CNRS, Collège de France, Paris, France*
[2] *Institut de Psychologie, Université Paris Descartes, Paris, France*
[3] *INSERM U894, Centre de Psychiatrie et Neurosciences, Paris, France*
[4] *Institut Universitaire de France, Paris, France*

Edited by:
Valeria Manera, University of Nice Sophia Antipolis, France

Reviewed by:
Giuseppe Riva, Istituto Auxologico Italiano, Italy
Ioannis Tarnanas, University of Bern, Switzerland
Rebeca Isabel Garcia Betances, Universidad Politecnica de Madrid, Spain

****Correspondence:***
Pascale Piolino, Université Paris-Descartes, Lab. Mémoire et Cognition, UMR 894 INSERM, 2 TER rue d'Alésia, Paris 75014, France
e-mail: pascale.piolino@parisdescartes.fr;
Alain Berthoz, UMR 7152 CNRS, LPPA, Collège de France, 11 Place Marcelin Berthelot, Paris 75005, France
e-mail: alain.berthoz@college-de-france.fr

None of the previous studies on aging have tested the influence of action with respect to the degree of interaction with the environment (active or passive navigation) and the source of itinerary choice (self or externally imposed), on episodic memory (EM) encoding. The aim of this pilot study was to explore the influence of these factors on feature binding (the association between what, where, and when) in EM and on the subjective sense of remembering. Navigation in a virtual city was performed by 64 young and 64 older adults in one of four modes of exploration: (1) *passive condition* where participants were immersed as passengers of a virtual car [no interaction, no itinerary control (IC)], (2) *IC* (the subject chose the itinerary, but did not drive the car), (3) *low*, or (4) *high navigation control* (the subject just moved the car on rails or drove the car with a steering-wheel and a gas pedal on a fixed itinerary, respectively). The task was to memorize as many events encountered in the virtual environment as possible along with their factual (what), spatial (where), and temporal (when) details, and then to perform immediate and delayed memory tests. An age-related decline was evidenced for immediate and delayed feature binding. Compared to passive and high navigation conditions, and regardless of age-groups, feature binding was enhanced by low navigation and IC conditions. The subjective sense of remembering was boosted by the IC in older adults. Memory performance following high navigation was specifically linked to variability in executive functions. The present findings suggest that the decision of the itinerary is beneficial to boost EM in aging, although it does not eliminate age-related deficits. Active navigation can also enhance EM when it is not too demanding for subjects' cognitive resources.

Keywords: episodic memory, binding, aging, virtual reality, everyday memory, action, decision, events memory

INTRODUCTION

Episodic memory (EM) contains specific events of one's life and enables humans to travel back in personal time to re-experience events. Retrieval depends on the successful "recollection" of the features of the original event, such as the time, place, people, emotional, and idiosyncratic as well as sensorimotor aspects of that event (Tulving, 2002). Much of what people remember in everyday life refers to actions they carried out in a complex environment. For instance, during the recall of a walk in the streets of a city, several components are associated in EM: *what* happened (e.g., "meeting Charles"), and the corresponding items referring to *elements* (buildings, people) of the environment; perceptual features (*details*); internal feelings, thoughts; spatial ("*where*"); and temporal ("*when*") situation and also self-performed actions. The process of integrating the core content (*what happened*) with other contextual features of an event into a cohesive memory representation is a key feature of EM, and is designated as "*binding*." This mechanism makes it possible to form connections that give a memory its specificity and distinctiveness (Johnson et al., 1993; Naveh-Benjamin, 2000; Hommel, 2004; Van Asselen et al., 2006; Kessels et al., 2007; Mitchell and Johnson, 2009).

Older adults often have difficulty retrieving specific events from their personal past, providing general information instead (Levine et al., 2002; Piolino et al., 2002, 2006, 2010; Martinelli et al., 2013). Moreover, in laboratory settings, they show difficulty in learning new items (Albert, 1994; Luo and Craik, 2008), and in determining in which experimental context they had encoded a previously encountered item [see Johnson et al. (1993) for review]. The memory for spatial context (Kessels et al., 2007) as well as for temporal context (Fabiani and Friedman, 1997) declines with age. Elderly people generally perform better on tests of item memory than on tests that require feature binding (Spencer and Raz, 1995; Chalfonte and Johnson, 1996; Mitchell et al., 2000; Kessels et al., 2007; Mitchell and Johnson, 2009). These deficits have been mainly associated with age-related effects on both the *associative* and *strategic* components of EM (Moscovitch, 1992; Shing et al., 2008; Piolino et al., 2010). The associative component refers to binding mechanisms based on the medial temporal lobe including the hippocampus (Zimmer et al., 2006). The strategic component refers to cognitive control processes based on prefrontal regions that monitor memory functions at both encoding and retrieval (Simons and Spiers, 2003).

One way to improve EM in laboratory settings is to give older participants encoding instructions that favor the link between a content and its context (Naveh-Benjamin et al., 2004, 2005; Glisky and Kong, 2008) or to add an environmental support at encoding that can serve as a compensatory strategy for deficient memory processing [see Glisky (2001), Naveh-Benjamin et al. (2002), and Luo and Craik (2008) for reviews]. One encoding strategy that has been considered as one of the most effective in recent decades is the enactment effect that consists in enhancing memory by linking implicitly or explicitly the information to be remembered with personal actions (Engelkamp et al., 1994; Engelkamp, 1998; Zimmer and Cohen, 2001; Earles and Kersten, 2002; Earles et al., 2004; Madan and Singhal, 2012).Typically, in action memory paradigms, memory for actions is enhanced if they are actually performed during encoding [subject-performed task (SPT)], compared to verbal encoding, even in older adults (Feyereisen, 2009). The mechanisms responsible for the enactment effect are still under debate. Some authors consider that the multimodal nature of a "movement" may reinforce item-specific information by enriching its encoding specificity, thereby acting as an additional retrieval cue (Engelkamp, 1998), while others argue that the benefit of action is due to the involvement of self goal-directed activities rather than motor activities *per se* (Kormi-Nouri, 1995). As action is always embedded in an intention to interact with the environment, rather than just a movement (Berthoz, 2003), acting in accordance with a decision therefore seems to benefit memory performances by improving the distinctiveness of mnesic traces (Viard et al., 2011; Voss et al., 2011).

Virtual reality is now considered as particularly relevant to test cognition in naturalistic and controlled situations with different levels of immersion (Bohil et al., 2011; Mueller et al., 2012; Zawadzki et al., 2013). Strong concordance with real-world abilities is a notable benefit of virtual reality (VR) technology (Schultheis et al., 2002; Plancher et al., 2010, 2012). Because the critical purpose of VR is to allow users to carry out cognitive and sensorimotor activities while being immersed in an artificial world (Schultheis et al., 2002; Fuchs et al., 2006), VR appears as a good tool to investigate the enactment effect on EM in complex situations (Brooks et al., 1999; Sauzéon et al., 2011; Plancher et al., 2012). Yet, VR-based research has long been used to study large-scale spatial skills in young (e.g., Maguire et al., 1997; Carassa et al., 2002; Lambrey et al., 2008; Galati et al., 2010; Iglói et al., 2010; Barra et al., 2012; Gras et al., 2013) and older adults (Lövden et al., 2005; Iaria et al., 2009; Moffat, 2009; Head and Isom, 2010; Bohbot et al., 2012; Klencklen et al., 2012; Gyselinck et al., 2013; Taillade et al., 2013), rather than the memory of complex episodes. While there has been a substantial amount of VR research on spatial learning comparing active vs. passive navigation, contradictory results have been reported, with some studies showing a positive effect of active navigation (Brooks et al., 1999; Péruch and Wilson, 2004; Wallet et al., 2011; Plancher et al., 2012), others reporting no benefits (Wilson, 1999; Gaunet et al., 2001; Foreman et al., 2005; Plancher et al., 2008), or even a negative effect (Sandamas and Foreman, 2003; Taillade et al., 2013).

In the domain of VR-based EM study, several researchers have used virtual immersion to assess item memory (e.g., objects) (Parsons and Rizzo, 2008; Sauzéon et al., 2011; Widman et al., 2012), or item memory in association with contextual information (e.g., the character, the location, and the moment associated with each object) (Burgess et al., 2001, 2002; Rauchs et al., 2008; Plancher et al., 2010, 2012, 2013). For instance, using a simulation of the California Verbal Learning Test in a virtual apartment (HOMES test), Arvind-Pala et al. (2014) confirmed poor recall, but better recognition, and intact clustering and proactive interference effects for item memory in older adults. In another study investigating age-related EM deficits of real-life events encountered in a virtual town, Plancher et al. (2010) showed that older adults recalled poorer episodic bindings compared to younger adults, regardless of the mode of encoding (intentional or incidental). Interestingly, some VR-based studies investigated the benefit of active navigation (compared to passive navigation) on subsequent EM performances. For instance, comparing participants assigned to a free active navigation using a joystick with participants in a passive condition, Brooks et al. (1999) found that the active condition improved the recall of spatial layout, but not the recall of objects seen during navigation. The authors attributed the benefit of action to an additional motor trace that increases specificity of the memory, but argued that it was limited to aspects of the virtual environment (VE) that are directly targeted by the interaction (here the spatial layout). More recently, Sauzéon et al. (2011) found that EM for objects placed in the rooms of two virtual apartments (HOMES test) was enhanced by active compared to passive navigation. Active participants had better item-specific measures such as learning and recognition, compared to passive participants, and they made fewer false recognitions. A similar beneficial effect of active navigation was reported by Plancher et al. (2012) in aging. Active navigation as a driver of a car, compared to passive navigation as a passenger, in the same participants, boosted feature binding (what–where–when) in healthy elderly participants and in patients with mild cognitive impairment and to a lesser extent in patients with Alzheimer's disease. Nevertheless, there was a negative effect of active navigation on recall of perceptual details associated to elements (e.g., a car accident). Overall, the benefit of active navigation was assumed to result from the enrichment of item-specific processing (Sauzéon et al., 2011; Plancher et al., 2012, 2013), and the appropriateness of perceptive-motor traces at encoding for a specific memory task (Brooks et al., 1999; Wallet et al., 2011), while the detriment could depend on the level of complexity of the active navigation (Gaunet et al., 2001; Wilson and Peruch, 2002; Wolbers and Hegarty, 2010; Plancher et al., 2012). In some cases, active navigation might require additional cognitive resources that are not fully available for the encoding process, leading to a detrimental effect on some aspects of EM.

According to some authors (Wilson, 1999; Bakdash et al., 2008; Chrastil and Warren, 2012), the inconsistent results concerning the active–passive effect during virtual navigation on subsequent memory might be due to discrepancies in the experimental designs, notably with regard to the manipulation of control differing in terms of sensorimotor stimulation and its confounding effects with psychological activity (planning, decision-making, and attention). In this line of research, Bakdash et al. (2008) demonstrated in young adults that spatial performance was comparable when the VE was learned with decision-making in the absence of motor control or decision-making and motor control, but was much worse when only motor control was present. They concluded that decision-making is an essential cognitive process in active navigation that impacts spatial memory. A more recent VR-based EM study aspired to disentangle these two components of action on items and spatial memory in young adults (Plancher et al., 2013). It was found that both conditions enhanced subsequent spatial memory compared to passive navigation, but motor interaction produced worse memory for items, unlike decision-making.

In continuity with these two previous studies, the objective of the present one was to test how different components of action control at encoding (active navigation and decision) may influence feature binding EM performance (item plus context) and effect of aging. We used a computer-based simulation to manipulate the degree of interaction at encoding, and investigate subsequent EM in groups of young and older adults in: (1) a passive condition (where the subject was just immersed as the passenger of a car, i.e., no active navigation, no decision); (2) an itinerary condition (the subject was immersed as a passenger and chose the itinerary but did not drive the car); (3) a low active navigation condition (the subject moved the car on rails, but the itinerary was fixed); and (4) a high active navigation condition [the subject drove the car using the usual driving mode (a steering-wheel and pedals), but the itinerary was fixed]. The latter two navigation conditions differed in the degree of interactive sensorimotor engagement, but more especially they differed in the degree of executive/attentional load. On the one hand, higher navigation control adds sensorimotor interaction, which could help EM, but it also makes driving more complex in the VE, requiring a higher level of attentiveness (Blankertz et al., 2010) and thus could be detrimental for EM, especially in older adults. It has been shown that age-related memory differences after active navigation are mediated by executive functions (Taillade et al., 2013). On the other hand, the low navigation condition involves lower sensorimotor interaction, but it also adds an environmental support at encoding (driver assistance) that could compensate for deficient memory processing (Craik, 1986; Luo and Craik, 2008). Finally, given that the itinerary control (IC) condition involved only right/left decisions, it was assumed that this condition would engage the same amount of cognitive resources as the low active navigation condition. We thus mainly expected: (1) a large decline with aging for feature binding EM performance; (2) a beneficial effect for both age-groups of IC and low active navigation conditions, in comparison with the passive and the high active navigation conditions; and (3) a possible reduction of age-related decline in the decision and low active navigation conditions.

MATERIALS AND METHODS

PARTICIPANTS

One hundred twenty-eight volunteers, 64 young, and 64 elderly adults (32 males and 32 females in each group, mean age 27 years, ranging from 19 to 40 years old for the young adults and a mean age of 65 years, ranging from 52 to 78 years old for the older adults) took part in the study. All had normal or corrected-to-normal vision and had a driving license. They provided written informed consent, and were paid for their participation. The local ethical committee of the CNRS approved the experimental protocol. Volunteers were divided into 4 groups of 16 in each age-group. All participants were tested individually and in only one condition.

All participants were unmedicated, living at home, and screened for absence of history of alcohol or substance abuse, head trauma, major disease affecting brain function, depression (BFS self-rating mood scale, Von Zerssen et al., 1974), and abnormal general cognitive functioning as assessed by the Mini Mental Scale (Folstein et al., 1975). Lastly, both age-groups were matched according to their verbal abilities and crystallized intelligence as assessed by the Mill Hill test (Deltour, 1993; a multiple-choice synonym vocabulary test).

BRIEF COGNITIVE ASSESSMENT

To assess that general cognitive abilities were well matched across participants assigned to the four conditions, they were screened using a brief battery assessing cognitive functions that comprised: (1) The verbal and visual memory subscales of the clinical memory scale MEM-III (Wechsler, 2000). In the verbal memory subscale, participants heard a story and had to memorize its content. They then underwent immediate and delayed recalls. In the visual memory subscale, participants were asked to memorize pictures of visual scenes with different people doing different things. They then had to recall the elements making up the scene together with their spatial location, immediately and after a delay. We recorded two global scores, one of verbal memory (out of 50) and the other of visual memory (out of 64); (2) Working memory was assessed by computerized forward visuo-spatial span and short-term feature binding span (Picard et al., 2012). In the latter task, participants had to memorize increasingly long strings of objects associated with a specific spatial context (area of a grid) after having mentally associated the picture of an object displayed below the grid with its location in the grid according to a color code. We recorded a mean score of the two span tasks. (3) The Trail-Making Test (Lezak et al., 2004) was used as a measure of shifting. A score was computed by subtracting the response time for part A from part B. The results are presented in **Table 1**. Finally, the older participants were also screened for their subjective memory complaints (CDS, McNair and Kahn, 1983).

EXPERIMENTAL VR EPISODIC MEMORY ASSESSMENT (VR–EM TEST)

Material

A virtual town (see an example of a view, **Figure 1A**) was built with Virtools Dev. 3.0 (www.virtools.com) and was projected via a PC (DELL PRECISION M6300) on a large SONY screen (Resolution 1932*1080) covering 66° of the visual field in a first-person perspective. The VE was projected 150 cm in front of the participants who were seated in a comfortable chair at the center of the screen.

To develop a full measure of EM retrieval, a rich virtual town was created by the Memory and Cognition laboratory at Paris-Descartes University (EditoMem and SimulMem). It was composed of buildings, people, cars, different typical objects of a town (barriers, lampposts, etc.), and several intersections (where participants could decide or were constrained to turn left or right) and background noise of the city. EM was solicited by an environment composed of 16 different scenes, such as the supermarket, the post office, the town hall, a car accident, representing the main

Table 1 | Description of the population as a function of age and experimental condition.

	Experimental conditions								ANOVAs		
	Passive (1)		**Itinerary control (2)**		**Low navigation control (3)**		**High navigation control (4)**		**Group effect**	**Condition effect**	**Interaction**
	YA	**OA**	**YA**	**OA**	**YA**	**OA**	**YA**	**OA**	**F(1,120)**	**F(3,120)**	**F(3,120)**
Participants (*N*)	16 (8F; 8M)	16 (8F; 8M)	16 (8F; 8M)	16 (8F; 8M)	16 (8F; 8M)	16 (8F; 8M)	16 (8F; 8M)	16 (8F; 8M)			
Age	25.68 (2.91)	64.18 (6.67)	25.25 (4.66)	65.68 (6.94)	24.00 (2.55)	65.62 (5.77)	28.25 (6.76)	65.18 (8.02)	1452.95***	0.71	1.00
									$\eta^2 = 0.92$	$\eta^2 = 0.01$	$\eta^2 = 0.02$
Mill Hill	36.12 (2.87)	37.75 (6.67)	32.91 (4.14)	35.87 (5.84)	36.31 (5.34)	37.00 (5.44)	33.93 (5.16)	34.81 (5.64)	5.27*	1.72	0.37
									$\eta^2 = 0.04$	$\eta^2 = 0.04$	$\eta^2 = 0.00$
CDS	–	43.35 (21.01)	–	40.50 (14.55)	–	46.75 (17.33)	–	39.60 (18.87)		0.35	
										$\eta^2 = 0.01$	
Verbal memory	29.93 (4.89)	23.43 (8.35)	28.50 (6.42)	24.31 (5.95)	32.18 (5.60)	23.37 (5.84)	27.81 (5.30)	24.81 (7.30)	21.18***	1.09	0.68
									$\eta^2 = 0.15$	$\eta^2 = 0.02$	$\eta^2 = 0.01$
Visual memory	86.32 (14.50)	53.12 (22.86)	84.50 (20.30)	56.00 (23.14)	91.50 (15.91)	57.43 (13.51)	82.68 (22.25)	53.56 (17.81)	85.12***	0.64	0.17
									$\eta^2 = 0.41$	$\eta^2 = 0.01$	$\eta^2 = 0.00$
Working memory	12.44 (1.99)	9.62 (2.18)	11.43 (1.63)	9.94 (2.20)	12.81 (1.47)	9.12 (1.41)	11.00 (1.59)	9.31 (1.78)	57.43***	1.76	2.56
									$\eta^2 = 0.32$	$\eta^2 = 0.04$	$\eta^2 = 0.06$
Executive functions (TMT B-A, sec)	17.00 (10.65)	30.82 (16.72)	26.18 (10.41)	37.83 (27.47)	17.02 (6.18)	29.04 (16.86)	24.12 (13.99)	46.95 (37.93)	18.22***	1.16	0.50
									$\eta^2 = 0.13$	$\eta^2 = 0.02$	$\eta^2 = 0.01$

****p < 0.001, **p < 0.01, *p < 0.05.*

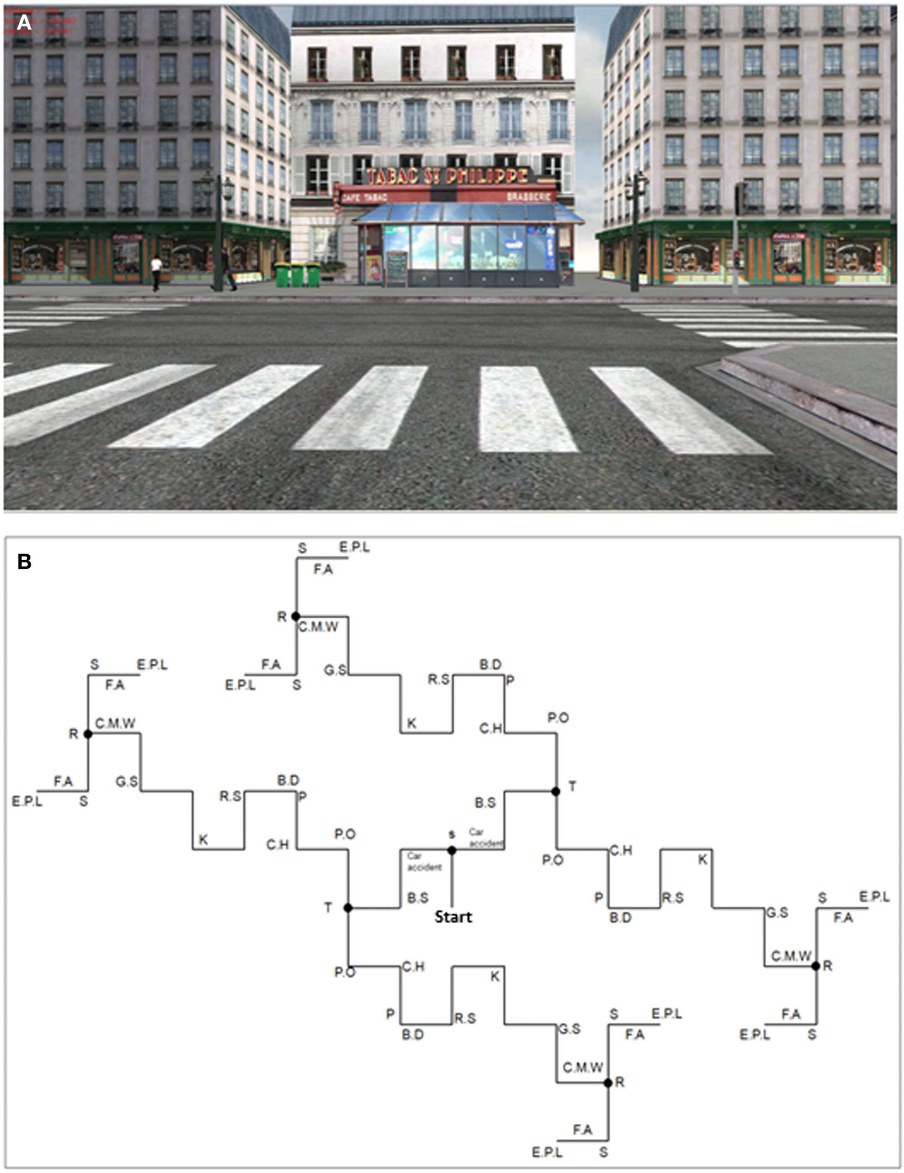

FIGURE 1 | Example of a screenshot (A) and map of the virtual town with main elements located on the map (B). Since the environment was built symmetrically, wherever "itinerary choice" participants turned they always saw the same elements. S, supermarket; car accident; B.S, bus stop; T, tobacco shop; P.O, post-office; C.H, city hall; P, public parking lot; B.D, business district; R.S, road safety sign; K, kebab shop; G.S, grocery store; C.M.W, two cars in the middle of the road; R, restaurants; S, train station; F.A, action against famine sign; E.P.L, external parking lot.

landmarks and salient events, each scene comprising prominent associated elements (e.g., a man in a suit walking in front of the post office). The scenes were mainly located at the intersections when the participants were stopped at the traffic lights (for 5 s) or in the middle of the road (e.g., the car accident). The saliency of scenes and associated elements was validated based on our previous VR studies in young and older adults (Plancher et al., 2010, 2012, 2013). Importantly, the virtual town was built symmetrically (see **Figure 1B**) so that regardless of the direction taken by the subjects at the intersection (either a left or a right turn), they saw the same thing.

The material used for the driving was composed of a steering-wheel allowing control of the vehicle inside the VE, and the pedals allowing participants to control speed.

Procedure

Participants were tested individually. The experimenter was present and depending on the condition, sat either alongside or behind the participant (see the "Experimental conditions" section below).

Before the test session, the participants underwent a training session in an empty environment (with only streets), in order to familiarize them with the equipment and the VE with a different spatial layout from that of the town subsequently used for the test. The objectives of this training session were twofold: to provide participants with an initial experience of a VE, and to familiarize them with control of the virtual car. The training session lasted until participants felt familiar with the equipment; they were free to navigate anywhere in the training period.

Participants were then requested to explore the experimental environment by active or passive navigation (as the driver or passenger of a virtual car). Subjects were encouraged to pay attention to as much detail as possible (i.e., details, spatial locations, and temporal order) of the different scenes/events encountered during their navigation ("What," "Where," and "When"), since they would subsequently undergo a memory test (intentional encoding). An example of a scene not presented in the experiment was shown as a picture before the exploration, to ensure that the participants understood what they had to memorize. They were randomly assigned to one of the four conditions:

(1) A "passive" condition (memorize without driving or choosing the itinerary) where each participant was just a passenger while the experimenter drove the car. The visual information displayed to each passive subject was the same as that of a subject who interacted with the environment. This condition served as a baseline condition compared to the three "active" experimental conditions requiring different processes (itinerary or navigation control) (see **Figure 2**).
(2) An "IC" condition (memorize and choose the itinerary without driving) was tested. Participants were passengers of the car and could choose the direction (left or right), by verbal instructions to the experimenter, at each intersection. This condition required participants to interact with the VE just at a purely cognitive "decisional" level. In the following two conditions, participants were "physically active" as driver of the car, but they were requested to follow a given itinerary (indicated by the experimenter).
(3) A "Low Navigation Control (LNC)" condition (memorize and move the car on rails) in which each participant could displace the car on rails, manipulating only the pedals (a gas pedal to control the speed and a brake pedal to stop). Pressing the pedals controlled the speed but there was no enactment of the movement associated with the direction (such as turning the steering-wheel).
(4) A "High Navigation Control (HNC)", condition (memorize and drive) similar to ordinary driving in which each participant drove as in real-life, manipulating a steering-wheel and pedals. He/she could interact with the environment by pressing pedals for speed control of the vehicle and by turning the steering-wheel to control the direction of the vehicle trajectory in the virtual town.

Finally, in order to better standardize subjects' attention to different features of the environment in the different conditions (i.e., more time spent viewing this or that detail), each participant was informed that he/she would be stopped at each set of traffic lights until it changed to green (5 s). In the navigation conditions, participants were instructed to stop and restart their car at each traffic light. Driving speed was limited so that participants could neither drive above a set speed nor stop anywhere in the town apart from traffic lights.

VR episodic memory assessment (VR–EM test)

After exploring the virtual town, all participants underwent a series of memory tests previously validated in VR–EM studies comparing young and older adults after immersion in a VE (Plancher et al., 2010, 2012).

Free recall test. Immediately after the navigation, the participants were asked to verbally report the elements of the scenes/events encountered during their navigation (what) and indicate for each of them the different components (for 10 min):

– To test the memory of the content information ("what"), they were asked to try and remember each scene/event with associated elements and to give the most salient "*details*" accompanying these elements [e.g., "I saw a car crash between a *yellow* car and a *blue* car (event), a woman with a *blue t-shirt* witnessed the accident (salient element)"].
– For each scene/event previously recalled, the participants were requested to report its location from their viewpoint and if they had turned to the left or to the right after seeing it. They had to situate each scene roughly either at the beginning, the middle, or the end of the circuit, and then to report their temporal order to test the sequential order in which they met them. This allowed us to obtain information about the association between the visual perception of the scene and the spatial egocentric "where" and temporal "when" components.
– At the end of free recall, the Remember/Know paradigm (Tulving, 1985; Gardiner, 2001) was proposed asking participants if they remembered (or just knew) the details of their navigation. They were asked to provide the intensity of their sense of remembering (using an analogical scale from 0 to 5, corresponding respectively to no re-experiencing and to very vivid re-experiencing) and then to provide some additional vivid specific details such as thoughts and feelings associated to a specific instant to prove the ability of mentally re-experiencing a specific moment during the navigation.

Visuo-spatial recall test. In order to test the memory of the visuo-spatial combination of the "what," the "where," and the "when" components, participants were asked, immediately after the free recall, to locate scenes (with associated elements) on a real map supplied by the experimenter for 5 min. Each participant saw a map of their own itinerary.

Delayed free recall test. Twenty minutes after the Visuo-spatial recall test, the participants were asked to verbally report again the different elements of the scenes encountered during their navigation (what) and indicate for each of them the different (details, where, when) components (for 10 min).

Recognition test. After the delayed free recall test, participants underwent a brief visual recognition test. A series of 10 images were shown on a computer screen to test recognition for the item

FIGURE 2 | The four experimental conditions assessed during the virtual exploration in the VR–EM test.

of information ("what"). For each image, the participants were shown two snapshots of scenes. They had to decide which of the two displayed scenes was or not in the virtual town. Their response had to be based on the scene, and additionally on elements in the scene and on the spatial location of elements in the scene.

Scoring

Free recall test. Quantitative scoring was done for each of the 16 scenes viewed in the VE to evaluate event features recollection.

– The recall of *items* ("*what*") was evaluated out of a possible 57 points, namely 1 point per each of the 16 scenes (e.g., supermarket, post office, and a car accident) and 1 point per each of 41 associated salient elements (e.g., the monkey statue, the bus shelter, and the woman with a punk hairstyle). A percentage of correct responses was calculated by dividing the number of recalled items by the total number of possible items (57).
– "*Binding*" recall: For each recalled scene ("what"), we noted if the participants recalled associated components ("*perceptual details*," "*where*," and "*when*"). For instance, if they recalled the scene "I saw a car accident," we recorded whether perceptual details were associated with it (e.g., "one of the cars was yellow;" "there was a women with brown hair who witnessed the accident"), as well as recalls of where and when they saw it (e.g., "I turned left just after seeing the car accident," "It happened after I passed the supermarket"). A score of bn corresponded to the number of times the recall of a scene was associated with additional *n* relevant information; *n* varied from 1 to 3. For instance, a score of b2 corresponded to the number of times two relevant recalls were associated to the *what* recall (e.g., temporal and spatial recalls). For each bn score, we calculated a binding percentage by dividing the number of correct bindings by the total of scenes (what). We also calculated a total immediate and delayed binding score by adding all the *n* information divided by the number of scenes.
– Thanks to the Remember/Know paradigm, we obtained a score of intensity of subjective sense of remembering (R) in terms of percentage (score on the analogical scale divided by the maximum of five) and a score of justified sense of Remembering (justified R) by taking into account the percentage of

R responses justified by the recall of internal details such as thoughts and feelings associated to specific experiences during navigation.

Visuo-spatial test. The location of elements on a real map was scored based on the number of correct element locations on the map (out of 57). A percentage was calculated by dividing the number of items correctly located by the maximum number of elements (57).

Recognition task. A total percentage was calculated by dividing the number of correct responses by the total number of questions (10).

RESULTS

BRIEF COGNITIVE ASSESSMENT

First, a series of analyses of variance (ANOVAs) with Age and Condition as between-subject factors, followed by *post hoc* Tukey tests, was performed on the scores of the brief cognitive assessment to ensure that the participants were well matched across the four conditions. For the memory scores, we obtained an effect of age, but no effect of condition, or interaction. The older participants were also well matched across the four conditions concerning their cognitive flexibility and subjective memory complaints (see **Table 1**).

EXPERIMENTAL MEMORY VR ASSESSMENT (VR–EM TEST)

A series of two-way ANOVAs was conducted with Age and Condition as the between-subject factors for each measure of the VR–EM test (see **Table 2**). Moreover, to test the effect of delay of retention on free verbal recall scores directly, we carried out mixed ANOVAs with Age and Condition as the between-subject factors, and Delay as within-subject factor on the *what* and the *binding* scores. Finally, we ran a mixed ANOVA with Age and Condition as the between-subject factors, and Delay and Level of binding (b1, b2, and b3) as within-subject factors. The effect sizes were represented with partial eta squared (η^2). In agreement with Guéguen (2009), we considered effect sizes as small for $\eta^2 < 0.06$, medium for $0.06 \leq \eta^2 < 0.14$, and large for $\eta^2 \geq 0.14$. To determine the direction of the differences, we carried out *post hoc* Tukey tests. We also carried out correlations between VR binding scores and neuropsychological scores, then controlling for age.

FREE VERBAL RECALL SCORES

All the results are presented in **Table 2**. The effect of Condition in both age-groups concerning the duration of navigation was marginally significant ($p = 0.05$, $\eta^2 = 0.06$) but a *post hoc* pairwise Tukey test indicated no significant differences.

Items information

The $ANOVA_{RM}$ Group × Condition × Delay showed a significant main effect of Group [$F(1,119) = 20.36$, $p < 0.001$, $\eta^2 = 0.15$], of Condition [$F(1,119) = 4.83$, $p < 0.01$, $\eta^2 = 0.11$], and of Delay [$F(1,119) = 24.54$, $p < 0.001$, $\eta^2 = 0.17$], as well as a significant Delay × Group [$F(1,119) = 8.08$, $p < 0.01$, $\eta^2 = 0.07$] interaction. The young adults performed better than the older adults and *post hoc t*-tests indicated that the participants in the IC condition achieved a better performance than those in the Passive ($p < 0.05$) and the HNC ($p < 0.01$) conditions (25.12 vs. 21.50 and 19.65%). The participants in the LNC condition performed better than those in the HNC ($p < 0.05$) condition (22.65 vs. 19.65%). The overall performance of the younger group was greater after delayed than immediate recall (Delayed vs. Immediate: 26.66 vs. 23.09%, $p = 0.001$), whereas the performance did not differ between the two recalls in the older group (Delayed vs. Immediate: 19.96 vs. 19.23%, $p > 0.10$). Neither the Delay × Condition nor the Delay × Group × Condition interactions were significant [$F(1,119) < 1$, $p > 0.10$, $\eta^2 < 0.02$ for both interactions]. Thus, the effects of Condition on *what* performance did not vary according to the delay and the age.

Binding

The $ANOVA_{RM}$ Group × Condition × Delay showed a significant main effect of Group [$F(1,119) = 46.51$, $p < 0.001$, $\eta^2 = 0.29$], of Condition [$F(1,119) = 4.99$, $p < 0.01$, $\eta^2 = 0.11$], of Delay [$F(1,119) = 13.50$, $p < 0.001$, $\eta^2 = 0.10$], and a significant Delay × Group [$F(1,119) = 11.39$, $p < 0.01$, $\eta^2 = 0.09$] interaction. *Post hoc* tests indicated that participants who had navigated in the IC condition performed better than participants who had navigated in the Passive ($p < 0.05$) and HNC ($p < 0.01$) conditions (29.94 vs. 24.06 and 22.46%), and that participants who had navigated in the LNC condition performed better than those who had navigated in the Passive and the HNC (27.83 vs. 24.06%, $p = 0.06$, and vs. 22.46%, $p < 0.05$). The overall performance of the younger group was greater after delayed than immediate recall (Delayed vs. Immediate: 33.04 vs. 30.82%, $p < 0.05$), whereas the performance did not differ between the two recalls in the older group (Delayed vs. Immediate: 19.69 vs. 20.93%, $p > 0.10$). Neither the Delay × Condition, nor the Delay × Group × Condition interactions were significant [$F(1,119) < 1$, $p > 0.10$, $\eta^2 = 0.01$ or $\eta^2 = 0.03$]. Thus, the effects of Condition on binding performance did not vary according to the delay and the age.

The $ANOVA_{RM}$ Group × Condition × Delay × Level of binding (b1, b2, and b3) showed in addition a main effect of the Level of binding [$F(2,238) = 48.76$, $p < 0.001$, $\eta^2 = 0.30$], and a Level of binding × Group interaction [$F(2,238) = 16.42$, $p < 0.0001$, $\eta^2 = 0.12$]. *Post hoc* tests indicated that for the young group, the percentage of b2 was superior to the percentage of b1 and b3 (b1: 5.59%, b2: 21.09%, b3: 15.69%, $p < 0.0001$), and b3 was superior to b1 ($p < 0.0001$). For the older group, the percentage of b2 was superior to the percentage of b1 and b3 (b1: 9.56%, b2: 15.57%, b3: 6.73%, $p < 0.0001$), and b1 was superior to b3 ($p < 0.05$). Between-group comparisons indicated a performance difference in favor of the older group for b1 ($p < 0.05$), and in favor of the younger group for b2 and b3 ($p < 0.0001$).

Finally, the Level of binding × Condition [$F(6,238) = 3.39$, $p < 0.05$, $\eta^2 = 0.07$] interaction was significant (see **Figure 3**). The binding profile differed between participants who navigated in the Passive (b2 > b1, $p < 0.0001$; b2 > b3, $p < 0.01$, b1 = b3) and HNC (b2 > b1, $p < 0.05$; b2 > b3, $p < 0.01$, b1 = b3) conditions and those who navigated in the IC (b2 > b3 & b1, $p < 0.0001$; b3 > b1, $p < 0.05$) and LNC (b2 > b1, $p < 0.0001$, b3 > b1, $p < 0.05$, b2 = b3) conditions. In other words, while there was no effect of Condition for b1, there was an effect of Condition

Table 2 | Mean and SD of the VR–MEM test according to the age-group and the experimental condition and results of the ANOVAs.

	Score	Experimental conditions								ANOVAs		
		Passive (1)		Itinerary control (2)		Low navigation control (3)		High navigation control (4)		Age effect	Condition effect	Interaction
		YA	OA	YA	OA	YA	OA	YA	OA	F(1,120)	F(3,120)	F(3,120)
	Duration of the navigation (s)	327.75 (52.99)	366.50 (40.22)	350.50 (43.73)	379.68 (51.07)	350.37 (89.91)	314.00 (45.57)	366.50 (85.54)	380.94 (85.24)	1.00 $\eta^2 = 0.00$	2.61^{t} $\eta^2 = 0.06$	2.12 $\eta^2 = 0.05$
Verbal free recall	What (% Immediate)	21.38 (6.84)	18.31 (7.70)	25.88 (9.98)	22.25 (5.54)	25.71 (6.63)	19.18 (6.98)	19.41 (5.38)	16.99 (8.19)	11.52*** $\eta^2 = 0.09$	5.60^{**a} $\eta^2 = 0.13$	0.37 $\eta^2 = 0.00$
	What (% Delayed)	25.76 (7.07)	17.87 (6.67)	29.00 (10.93)	23.35 (6.74)	28.07 (8.44)	19.73 (6.81)	23.79 (7.27)	18.42 (7.52)	24.98*** $\eta^2 = 0.18$	3.29^{*b} $\eta^2 = 0.08$	0.32 $\eta^2 = 0.00$
	Binding (% Immediate)	29.17 (10.20)	19.01 (10.33)	34.11 (14.10)	25.65 (9.21)	34.38 (7.45)	20.96 (7.52)	25.65 (6.02)	18.10 (9.49)	31.02*** $\eta^2 = 0.21$	5.65^{***c} $\eta^2 = 0.13$	0.45 $\eta^2 = 0.01$
	Binding (% Delayed)	30.86 (11.56)	18.62 (6.61)	36.46 (13.13)	23.57 (9.43)	37.37 (12.13)	19.40 (8.29)	27.47 (7.99)	17.19 (9.29)	53.69*** $\eta^2 = 0.32$	3.54^{*d} $\eta^2 = 0.08$	1.23 $\eta^2 = 0.03$
	Remember (%)	58.75 (11.47)	56.25 (16.33)	65.00 (13.66)	66.25 (12.04)	58.75 (13.60)	60.00 (16.68)	61.25 (11.47)	58.13 (10.46)	0.04 $\eta^2 = 0.00$	2.06 $\eta^2 = 0.05$	0.18 $\eta^2 = 0.00$
	Justified R (%)	36.43 (23.54)	21.70 (23.55)	18.23 (21.81)	38.40 (23.95)	34.29 (25.75)	30.09 (26.08)	32.06 (23.35)	20.25 (25.79)	0.71 $\eta^2 = 0.00$	0.35 $\eta^2 = 0.00$	3.27^{*f} $\eta^2 = 0.08$
Visuo-spatial recall	Location (on a real map)	10.85 (4.13)	7.01 (4.45)	13.81 (6.49)	7.89 (5.20)	13.59 (5.05)	7.73 (3.93)	8.88 (4.13)	6.25 (3.74)	28.20*** $\eta^2 = 0.20$	4.86^{e} $\eta^2 = 0.11$	1.46 $\eta^2 = 0.04$
Recognition	Total score (%)	73.75 (10.24)	66.25 (12.04)	70.00 (15.95)	69.37 (9.97)	72.37 (11.17)	66.25 (18.21)	73.75 (16.68)	59.12 (19.73)	6.84** $\eta^2 = 0.06$	0.54 $\eta^2 = 0.01$	1.62 $\eta^2 = 0.04$

*ANOVA age × condition: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, $^{t}p \leq 0.06$.*
Post hoc Tukey pairwise comparisons on condition effect.
[a] 1 < 2, 2 > 4**, 3 > 4*.*
[b] 1 < 2[t], 2 > 4.*
[c] 1 < 2 & 3*, 2 > 4**, 3 > 4*.*
[d] 1 < 2[t], 2 > 4, 3 > 4[t].*
[e] 1 < 2 & 3[t], 2** & 3* > 4; and condition × age effect.*
[f] OA: 1 < 2, 2 > 4*, YA: 1 = 2 = 3 = 4.*

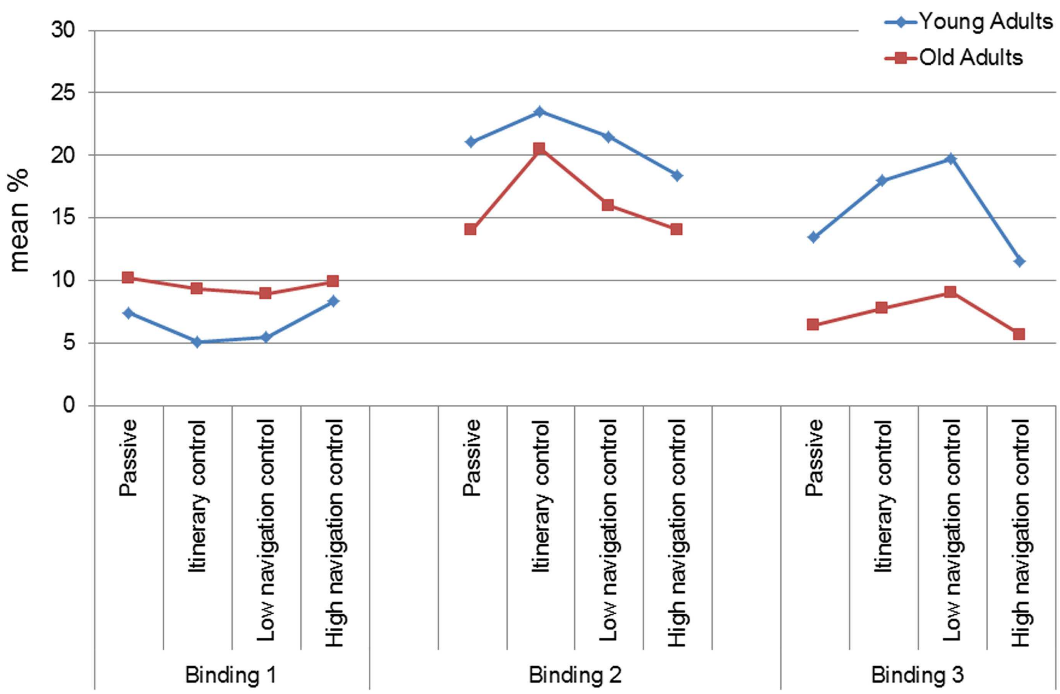

FIGURE 3 | Main effects of condition (mean and standard deviation) for the mean immediate and delayed binding score in the VR–EM test according to the level of binding and age-group.

for b2 and b3 (for b2: IC > Passive and LNC, $p < 0.05$, IC > HNC, $p < 0.05$; for b3: IC = LNC > HNC = Passive, $p < 0.05$).

Remember responses

The ANOVA (see **Table 2**) indicated that no simple effect of Age or Condition nor interaction was found for the Remember score, but an interaction was found for the justified Remember score. Older participants in the IC condition gave a higher percentage of justified R responses compared to Passive and HNC conditions ($p < 0.05$), while there was no difference between IC and LNC, and LNC and HNC. There was no difference between the conditions for the younger group.

VISUO-SPATIAL SCORE

The ANOVA on the score concerning the location of elements (see **Table 2**) indicated a decrease with aging and a significant effect of the condition regardless of the group. Those who were in the IC and the LNC conditions performed better than participants who were in the Passive ($p < 0.05$ and $p < 0.06$) and HNC condition ($p < 0.01$ and $p < 0.05$). There was no other difference.

RECOGNITION

A decrease of performance with aging was observed for the total recognition score (YA vs. OA: 72.47 vs. 65.00%). There was no effect of condition or interaction (see **Table 2**).

CORRELATION BETWEEN VR–EM TEST AND NEUROPSYCHOLOGICAL TESTS

As illustrated in **Table 3**, the mean VR binding score was significantly correlated with visual memory (except for the passive condition) and working visuo-spatial memory (including short-term binding). In addition, VR binding scores were correlated with executive function (shifting) for low and HNC conditions. When controlling for age, all significant correlations vanished except for the HNC. Indeed, the VR binding scores of participants who navigated in the HNC condition still remained correlated with visual memory, working memory, and executive function. The partial correlation between binding scores and executive function remained significant after application of the Bonferroni correction.

DISCUSSION

Using a naturalistic environment created with VR, the present study aimed to assess the distinctive role of decision or motor control on feature binding, and to illuminate the relationships between binding, form of encoding, and aging in order to suggest new procedures that could improve feature binding by focusing on the influence of action at encoding. We manipulated the amount of active navigation and decision of the itinerary while younger and older participants navigated in a virtual town trying to memorize all the events they experienced. We then assessed EM (e.g., what–where–when feature binding) via a series of immediate and delayed verbal and visuo-spatial tests. Our main findings showed that both LNC and the choice of the itinerary (IC) enhanced EM performance in young and older participants. By contrast, HNC and passive navigation did not help EM performance in the two age-groups. The role of action, either active navigation or decision, in EM is discussed as well as its influence in aging.

Table 3 | Correlations between VR binding mean scores and neuropsychological tests as a function of condition (*n* = 36 per condition).

	Age	Verbal memory	Visual memory	Working memory	Executive functions
Passive	**−0.47****	0.10	0.29	**0.43****	−0.31
Itinerary control	−0.41*	0.33*	**0.52**** (0.37*)	0.33*	−0.27
Low navigation control	**−0.72*****	0.31	**0.62*****	**0.67*****	**−0.43****
High navigation control	**−0.46****	0.32	**0.53***** (0.37*)	**0.55***** (0.42*)	**−0.58***** (−0.48**)**

*VR binding mean scores correspond to the mean of immediate and delayed binding scores; for neuropsychological measures (see **Table 1** and brief cognitive assessment).*

Correlations in brackets remain significant after controlling for age.

****p < 0.001; **p < 0.01; *p < 0.05.*

Correlations in bold remain significant after application of the Bonferroni correction of p = 0.002.

The benefit of active navigation on EM performance depended on the amount of active control (high vs. low control) regardless of the age. Although it is generally agreed that action at encoding enhances memory by enriching memory traces in laboratory settings (Engelkamp, 1998; Madan and Singhal, 2012; Zimmer and Cohen, 2001), and that increasing body-based interaction (i.e., translational and rotational body-based interaction) in participants who navigate through a VE generally improves spatial performances (Ruddle and Lessels, 2009; Ruddle et al., 2011), sensorimotor interaction in VEs, compared with no interaction, has not been always associated with better memory performance, especially for factual information (objects, elements, and scenes encountered, see also the Section "Introduction"). We postulated that when active navigation control is too demanding for participants' cognitive resources (Gaunet et al., 2001; Chrastil and Warren, 2012) it would not help EM performance. Consistent with this hypothesis, we clearly found that the HNC condition (i.e., ordinary drive-like manipulation of a steering-wheel and pedals) was generally the worst way (similar to the passive condition) to memorize episodic features from complex naturalistic scenes in our virtual setting. This damaging effect was observed whatever the VR measures (free verbal recall of What and Binding information, free recall of visuo-spatial information), except for the recognition of What information where no effect of condition was observed. In fact, HNC, like the passive condition, did not help young or older participants' high levels of binding (i.e., three pieces of information), contrarily to IC and LNC conditions. Our hypothesis was that HNC (controlling both the pedals and the steering-wheel in a complex VE) differed in the degree of interactive motor engagement but also in the degree of executive/attentional load compared to LNC. This was substantiated by correlational analyses revealing that memory performance during HNC was mainly related to executive function regardless of the age of the participants. Thus, these findings seem to confirm that HNC acted as a divided attention condition that required a higher level of attentional resources, regardless of the age of participants (Craik et al., 1996; Anderson et al., 1998; Naveh-Benjamin et al., 2005), which, in turn, impeded memory function.

By contrast, the effective role of low active motor control resulted in significantly enhanced EM. Importantly here, we confirm a benefit of active navigation control, compared to passive navigation, not only for visuo-spatial recall, as did previous studies (Brooks et al., 1999; Péruch and Wilson, 2004; Wallet et al., 2011; Plancher et al., 2012, 2013), but also for *item memory* (i.e., What scores: scenes/events with perceptible details) and *binding* scores (i.e., scenes/events situated in their specific spatiotemporal context). Interestingly, this positive effect was larger for the binding scores than for the What scores (e.g., no effect was noted for What delayed scores). LNC in particular helped young and older participants' high levels of binding (i.e., three pieces of information). The findings regarding What scores are in line with one study showing that item memory for objects placed in the rooms of a virtual apartment was enhanced by active (via a joystick) compared to passive navigation (Sauzéon et al., 2011), and contradict some other results showing no effect on item memory (Brooks et al., 1999; Plancher et al., 2013). They also confirmed previous results in aging (Plancher et al., 2012) where active navigation in VEs (as the driver of a car) yielded a better recall of the item memory and spatial information, as well as binding in comparison to passive navigation (as the passenger of the car). Therefore, the present study did not confirm the assumption that active navigation would be helpful for the encoding of spatial information (that is directly targeted by the action), but negative for the encoding of items (because indirectly related to the action proper) (Brooks et al., 1999; Plancher et al., 2013). This divergence may result from differences in the experimental designs (Wallet et al., 2011; Chrastil and Warren, 2012). For instance, instead of a joystick, active navigation used here a higher body-based interaction with the VE, asking participants to control the speed and the stops with pedals, not the turns. In this way, driving the virtual car was unlikely to prove difficult, especially when cornering (where most of the scenes and events were situated). Therefore, the LNC condition did not appear to require a higher level of attentiveness, unlike HNC, and interestingly this condition seemed to add an environmental support at encoding, even for the elderly [see Luo and Craik (2008) for a review], via motor action and driver assistance (Blankertz et al., 2010). Moreover, instructions asked for intentional encoding of elements and events with as much detail as possible, including spatiotemporal situation and perceptive details, not only for objects and spatial layout. Interestingly, the difference in the LNC effect according to the What and binding scores could explain the contradictory results regarding the effect of active navigation on subsequent memory, as binding memory measures are more sensitive to the enactment effect of active navigation. For instance, no effect of active navigation (compared to passive navigation) was found in several studies using spatial memory measures (Wilson, 1999; Gaunet et al., 2001; Sandamas and Foreman, 2003; Foreman et al., 2005; Taillade et al., 2013), or item memory measures (Brooks et al., 1999; Plancher et al., 2013), whereas such an effect was previously found using feature binding measures of associated what–where–when information (Plancher et al., 2012). All things considered, we can assume that after active motor control, when the task does not require too high a level of cognitive control (see Discussion above), memory of the scenes/events encountered in VE are enhanced because they are enriched by a motor trace at encoding that provides specific cues at retrieval (Engelkamp, 1998; Nilsson et al., 2000; Nyberg et al., 2001). As a result, it is suggested that in large-scale naturalistic VEs, possibly like in everyday memory, motor interaction can help integrated information with item-specific and associative information (Eichenbaum, 2000; Atienza et al., 2011).

The most interesting and novel finding of the present study is that decision of the itinerary (IC) without any physical activity was remarkably effective in boosting EM in both young and older participants. Although deciding has been related to executive/frontal functions (MacPherson et al., 2002; Denburg et al., 2007), this was the best condition for enhancing EM. This benefit was observed at immediate and delayed free verbal recall and visuo-spatial recall (IC was generally significantly better than Passive and HNC, and similar to LNC), leading to the best levels of binding. The crucial role of decision on memory encoding in virtual navigation is in line with previous assumptions (Wilson, 1999; Bakdash et al., 2008; Chrastil and Warren, 2012; Plancher et al., 2013). As far as we know, only two previous experimental studies have been published. In the VR study by Bakdash et al. (2008), the effect of decision-making was compared to motor control on subsequent spatial memory of young adults, but there was no passive condition. Performance was better when the VE was learned with decision-only (similar to our IC condition, the participant decided where to go by giving verbal directions to the experimenter) or decision plus motor control, compared to when only motor control was present (the participant only had joystick control, the experimenter instructed participants where to go). Using an experimental design very similar to the present study, Plancher et al. (2013) found that decision-only on the itinerary enhanced subsequent item and spatial memory, compared to passive navigation, while motor control-only benefited spatial memory. The present study therefore provides new evidence for the positive influence of decision-making on what–where–when feature binding.

How can we explain this benefit of decision-making on EM? This condition did not create body-based information of actions like HNC and LNC, only subject-directed activity. The finding here can nicely contribute to the debate on the mechanisms responsible for the enactment effect (using SPT or active navigation). The SPT literature attributes the enactment effect either to the multimodal nature of a motor action (Engelkamp, 1998) or to the involvement of subject-directed activity rather than motor activity *per se* (Kormi-Nouri, 1995). According to some authors (Wilson, 1999; Bakdash et al., 2008; Chrastil and Warren, 2012), the effect of active navigation on subsequent memory might be due to sensorimotor activity and the subject's directed activity (planning, decision-making, and attention). Neglecting to disentangle these two facets might explain the inconsistent results concerning the active–passive effect during virtual navigation. In the present study, the decisional condition allowed participants to have intentional control over the perceived environment during encoding by making right–left turn decisions where most of the scenes were situated. Thus, it appears that planning or deciding an action directly associated with a scene was particularly efficient in implementing binding processes representing the features of the action and scene, creating the representation of a personal event. As highlighted by Hommel (2004), integrating multimodal codes are important for binding, and applies not only to sensorimotor processing but also to action planning. In the same vein, Voss et al. (2011) suggested that "volitional control" may improve the performance in memory thanks to the interplay between distinct neural systems related to planning, attention, and object processing. They argued that such control improves EM performance because the hippocampus is not only concerned by relational feature binding (Eichenbaum, 2000; Ergorul and Eichenbaum, 2004), but also by planning (Bird and Burgess, 2008; Viard et al., 2011). Moreover, binding processes involved in the IC condition could be more or less automatic (Van Asselen et al., 2006) mainly related to hippocampal processes (performance after IC correlated with visual memory performance) providing effective cues at retrieval rather than related to executive/frontal control processes (there was no correlation with executive function). We postulate that deciding the itinerary and memorizing the scenes benefits from multimodal coding: e.g., specific information based on deciding the itinerary, imagining the action (cornering), and viewing the imagined/decided environment (comparing expectations with actual scenes). Imagining a subject-directed activity or imagining personal future events (Buckner and Carroll, 2007; Schacter et al., 2007; Maguire and Hassabis, 2011; Viard et al., 2012) depends to a very large extent on the same neural network as real personal actions or events. Along the same lines, Bakdash et al. (2008) consider that the positive effect of IC may be related to the use of both egocentric and allocentric representations (i.e., local and global spatial information) of the environment, whereas motor control may be achieved using just an egocentric representation. Egocentric frames of reference specify route knowledge of spatial layout from the perspective of a ground-level observer (e.g., eye and body coordinates) navigating the environment and storing sequences of combinations of scenes. Allocentric frames of reference specify survey knowledge characterized by an external perspective, independently of the viewer's position, allowing direct access to the global spatial layout. Further studies need to determine the most crucial strategies that determine the enactment effect via IC in virtual navigation (Dahmani and Bohbot, 2014).

Regarding the benefit of enactment in aging, even if we reported a benefit of IC and LNC on memory in both young and older adults, it must be acknowledged that these encoding conditions did not fully compensate for age-related effects on EM (i.e., no interaction between condition and age was generally observed). This pattern has been found by manipulating other factors known to enhance memorization such as self-reference processing (Gutchess et al., 2007; Lalanne et al., 2013) or self-performed tasks (Feyereisen, 2009) during encoding: enhanced performances are usually reported in aging, but older people still perform more poorly than young adults. Regardless of the condition, a decrease in performance with aging was found for event feature bindings and we showed that the age-related decline was larger for the *binding* scores than for the *what* scores, i.e., larger for associative memory than for item memory (Parkin and Walter, 1992; Kessels et al., 2007; Mitchell and Johnson, 2009). More precisely, we found that older adults had greater difficulty in binding several pieces of information with event content compared to young adults (i.e., binding with just one piece of information). The present study confirms this point with a naturalistic paradigm, highlighting that the binding difficulties in the elderly came from encoding. Indeed, free recall performance remained stable after a retention time of 20 min, while the performance of young adults improved, and age decline was persistent in recognition. These age-related effects on feature binding were generally mediated by verbal (for IC) and visual memory (for IC, LNC, and HNC), working memory including short-term binding (for Passive, IC, LNC, and HNC), and executive function (for LNC and HNC). This is in line with previous findings in aging demonstrating that age decline in VR navigation is mediated by composite processes including episodic and working memory (Gyselinck et al., 2013), and executive function (Taillade et al., 2013), confirming age-related effects on both the *associative* and *strategic* components of EM (Moscovitch, 1992; Shing et al., 2008).

Interestingly, in older participants the IC condition was able to boost feature binding and the capacity to mentally re-experience the original navigation, providing personal details of a specific moment. Both capacities are generally altered in aging (Parkin and Walter, 1992; Spencer and Raz, 1995; Piolino et al., 2006; Mitchell and Johnson, 2009). A subject-directed activity in the IC condition thus seems able to reduce age-related EM deficits (compared to other conditions) by enhancing both the subjective (i.e., sense of remembering or autonoetic consciousness, Tulving, 2002) and objective aspects (i.e., contextual information) of specific events memory. Moreover, although participants in each condition experienced similar first-person visual information (i.e., egocentric VR exposure in the encoding phase), which is consider to alter spatial memory in aging (Morganti and Riva, 2014), it may be suggested that the IC condition induced the use of specific reference frames such as allocentric representations (Bakdash et al., 2008), which have no impact on spatial memory in the elderly. Future research is needed to investigate this important issue (Ruggiero et al., 2009). This suggests that the IC condition may result in enhanced EM performance in older adults by supporting multiple memory aspects including allocentric representations (Morganti and Riva, 2014), verbal processes (Brickman and Stern, 2009), hippocampal-related processes (Voss et al., 2011), and future-oriented behaviors (Buckner and Carroll, 2007; Schacter et al., 2007).

Finally, despite its promising results, the present pilot study has a few limitations that further research will be able to overcome. First, the sample size of groups was rather small (16 participants for each Condition × Age). Nevertheless, size effects were generally large for age and medium for condition. Second, we used intentional encoding, while real-life is generally concerned by incidental encoding. In a previous study, we showed that the age-related difference was similar for feature binding with both types of encoding (Plancher et al., 2010), but it would be interesting to further investigate the effect of navigation or IC using incidental encoding. Moreover, since elderly memory performance is inherent in egocentric and/or allocentric strategies on navigational tasks (Morganti and Riva, 2014), our findings might be partly dependent on the use of an egocentric VR exposure. This domain of research could be interestingly extended to the comparison between healthy aging and Alzheimer's disease since the former is more specially concerned by egocentric encoding (Iachini et al., 2009b; Morganti and Riva, 2014) while the latter is more concerned by allocentric encoding (e.g., map and GPS), or transfer from allocentric to egocentric representations (Morganti et al., 2013; Morganti and Riva, 2014; Serino et al., 2014). We can expect the IC condition to be less effective than LNC in patients with Alzheimer's disease, unlike in healthy aging. A further important issue would be to substantiate the findings using different reference frames (Committeri et al., 2004; Avraamides and Kelly, 2008; Ruggiero et al., 2009). It will be particularly interesting to test the impact of decision-making or motor control by contrasting allocentric and egocentric strategies on feature binding. Finally, future research should also include a condition in which participants are both active in navigation and decision on the itinerary. We did not plan this condition here because it is the one that was generally addressed in previous VR studies on spatial memory and that gave conflicting results. Our objective in the present study was therefore to distinguish the two components to clarify the pattern of results on effect of action in VE regarding EM performances, especially as regards feature binding. However, while we have shown that both LNC and IC can boost EM, further research should investigate the effect of combining the two as done by Bakdash et al. (2008) on spatial performances. Although these authors did not find any differences between decision-only and decision *plus* motor control conditions, it can be assumed that this combined condition (LNC *plus* IC) could help feature binding more than the two conditions separately, and could in this case reduce the difference between young and old.

In conclusion, the novelty of this study was to highlight the benefit of both IC and LNC in EM performance in young and older adults, emphasizing the advantageous influence on long-term feature binding. While this research needs to be continued to strengthen its conclusions, the initial findings suggest that navigational and decisional activity during real-life events should be useful in aging to boost EM. It could encourage older adults to use their own actions, both via active navigation and decisional control, to boost the encoding of complex events in their daily life. Moreover, it could be useful for EM training programs in aging and patients with authentic EM deficits due to encoding impairment, such as Alzheimer's disease. Our study offers new insights into the relationship between EM, different action related processes, and aging, and opens up new avenues of research in this area and training programs. Indeed, looking at the conditions under which older adults' EM can be enhanced, using conditions somewhat similar to real-life settings that allow for increased interaction with the environment is an important issue for future research.

ACKNOWLEDGMENTS

We thank the CNRS and the University Paris Descartes for their grant allocated to the constructions of the virtual world, the DGCIS grant for the post-doctoral bursary allocated to Najate Jebara within the framework of the SCORE (Serious games for Cybertherapy in populated Realistic city) project. We thank Gaën Plancher and Julien Barra for their contribution to the construction of the protocol. Finally, we thank all the participants of this study for their time, Marco Sperduti and Elizabeth Rowley-Jolivet for the English corrections.

REFERENCES

Albert, M. (1994). "Age-related changes in cognitive function," in *Clinical Neurology of Aging*, eds M. Albert and J. Knoefel (New York, NY: Oxford University Press), 314–326.

Anderson, N. D., Craik, F. I. M., and Naveh-Benjamin, M. (1998). The attentional demands of encoding and retrieval in younger and older adults: 1. Evidence from divided attention costs. *Psychol. Aging* 13, 405–423. doi:10.1037/0882-7974.13.3.405

Arvind-Pala, P., N'Kaoua, B., Mazaux, J. M., Simion, A., Lozes, S., Sorita, E., et al. (2014). Everyday-like memory and its cognitive correlates in healthy older adults and in young patients with traumatic brain injury: a pilot study based on virtual reality. *Disabil. Rehabil.* 9, 463–73. doi:10.3109/17483107.2014.941952

Atienza, M., Atalaia-Silva, K. C., Gonzalez-Escamilla, G., Gil-Neciga, E., Suarez-Gonzalez, A., and Cantero, J. L. (2011). Associative memory deficits in mild cognitive impairment: the role of hippocampal formation. *Neuroimage* 57, 1331–1342. doi:10.1016/j.neuroimage.2011.05.047

Avraamides, M., and Kelly, J. (2008). Multiple systems of spatial memory and action. *Cogn. Process.* 9, 93–106. doi:10.1007/s10339-007-0188-5

Bakdash, J. Z., Linkenauger, S. A., and Profitt, D. (2008). Comparing decision-making and control for learning a virtual environment: backseat drivers learn where they are going. *Proc. Hum. Fact. Ergon. Soc. Annu. Meet.* 52, 2117–2121. doi:10.1177/154193120805202707

Barra, J., Laou, L., Poline, J. B., Lebihan, D., and Berthoz, A. (2012). Does an oblique/slanted perspective during virtual navigation engage both egocentric and allocentric brain strategies? *PLoS ONE* 7:e49537. doi:10.1371/journal.pone.0049537

Berthoz, A. (2003). *La Décision*, ed. O. Jacob (Paris).

Bird, C. M., and Burgess, N. (2008). The hippocampus and memory: insights from spatial processing. *Nat. Rev. Neurosci.* 9, 182–194. doi:10.1038/nrn2335

Blankertz, B., Tangermann, M., Vidaurre, C., Fazli, S., Sannelli, C., Haufe, S., et al. (2010). The Berlin brain–computer interface: non-medical uses of BCI technology. *Front. Neurosci.* (2010) 4:198. doi:10.3389/fnins.2010.00198

Bohbot, V. D., McKenzie, S., Konishi, K., Fouquet, C., Kurdi, V., Schachar, R., et al. (2012). Virtual navigation strategies from childhood to senescence: evidence for changes across the life span. *Front. Aging Neurosci.* 4:28. doi:10.3389/fnagi.2012.00028

Bohil, C. J., Alicea, B., and Biocca, F. A. (2011). Virtual reality in neuroscience research and therapy. *Nat. Rev. Neurosci.* 12, 752–762. doi:10.1038/nrn3122

Brickman, A. M., and Stern, Y. (2009). "Aging and memory in humans," in *Encyclopedia of Neuroscience*, Vol. 1. ed. L. R. Squire (Oxford: Academic Press), 175–180.

Brooks, B. M., Attree, E. A., Rose, F. D., Clifford, B. R., and Leadbetter, A. G. (1999). The specificity of memory enhancement during interaction with a virtual environment. *Memory* 7, 65–78. doi:10.1080/741943713

Buckner, R. L., and Carroll, D. C. (2007). Self-projection and the brain. *Trends Cogn. Sci.* 11, 49–57. doi:10.1016/j.tics.2006.11.004

Burgess, N., Maguire, E. A., and O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron* 35, 625–641. doi:10.1016/S0896-6273(02)00830-9

Burgess, N., Maguire, E. A., Spiers, H. J., and O'Keefe, J. (2001). A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. *Neuroimage* 14, 439–453. doi:10.1006/nimg.2001.0806

Carassa, A., Geminiani, G., Morganti, F., and Varotto, D. (2002). Active and passive spatial learning in a complex virtual environment: the effect of efficient exploration. *Cogn. Process.* 3-4, 65–81.

Chalfonte, B. L., and Johnson, M. K. (1996). Feature memory and binding in young and older adults. *Mem. Cognit.* 24, 403–416. doi:10.3758/BF03200930

Chrastil, E. R., and Warren, W. H. (2012). Active and passive contributions to spatial learning. *Psychon. Bull. Rev.* 19, 1–23. doi:10.3758/s13423-011-0182-x

Committeri, G., Galati, G., Paradis, A. L., Pizzamiglio, L., Berthoz, A., and Le Bihan, D. (2004). Reference frames for spatial cognition: different brain areas are involved in viewer-, object- and landmark-centered judgments about object location. *J. Cogn. Neurosci.* 16, 1517–1535. doi:10.1162/0898929042568550

Craik, F. I. M. (1986). "A functional account of age differences in memory," in *Human Memory and Cognitive Abilities, Mechanisms and Performance*, eds F. Klix and H. Hagendorf (New York, NY: Elsevier), 409–422.

Craik, F. I. M., Govoni, R., Naveh-Benjamin, M., and Anderson, N. D. (1996). The effects of divided attention on encoding and retrieval processes in human memory. *J. Exp. Psychol.* 125, 159–180. doi:10.1037/0096-3445.125.2.159

Dahmani, L., and Bohbot, V. D. (2014). Dissociable contributions of the prefrontal cortex to hippocampus- and caudate nucleus-dependent virtual navigation strategies. *Neurobiol. Learn. Mem.* doi:10.1016/j.nlm.2014.07.002

Deltour, J. J. (1993). *[Mill Hill Vocabulary Scale of J.C. Raven. French Adaptation and Comparative Norms of the Mill Hill and of Standard Progressive Matrices (PM38)]. Manuel Editions l'Application Des Techniques Modernes.* Braine-le-Château, Belgium: Editions L'Application des Techniques Modernes SPRL.

Denburg, N. L., Cole, C. A., Hernandez, M., Yamada, T. H., Tranel, D., and Bechara, A. (2007). The orbitofrontal cortex, real-world decision making, and normal aging. *Ann. N. Y. Acad. Sci.* 1121, 480–498. doi:10.1196/annals.1401.031

Earles, J. L., and Kersten, A. W. (2002). Directed forgetting of actions by younger and older adults. *Psychon. Bull. Rev.* 9, 383–388. doi:10.3758/BF03196297

Earles, J. L., Kersten, A. W., Mas, B. B., and Miccio, D. M. (2004). Aging and memory for self-performed tasks: effects of task difficulty and time pressure. *J. Gerontol.B Psychol. Sci. Soc. Sci.* 59B, 285–293. doi:10.1093/geronb/59.6.P285

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nat. Rev. Neurosci.* 1, 41–50. doi:10.1038/35036213

Engelkamp, J. (1998). *Memory for Actions.* Hove: Psychology Press.

Engelkamp, J., Zimmer, H. D., Mohr, G., and Sellen, O. (1994). Memory of self-performed tasks: self-performing during recognition. *Mem. Cognit.* 22, 34–39. doi:10.3758/BF03202759

Ergorul, C., and Eichenbaum, H. (2004). The hippocampus and memory for "what," "where," and "when". *Learn. Mem.* 11, 397–405. doi:10.1101/lm.73304

Fabiani, M., and Friedman, D. (1997). Dissociations between memory for temporal order and recognition memory in aging. *Neuropsychologia* 35, 129–141. doi:10.1016/S0028-3932(96)00073-5

Feyereisen, P. (2009). Enactment effects and integration processes in younger and older adults' memory for actions. *Memory* 17, 374–385. doi:10.1080/09658210902731851

Folstein, M. F., Folstein, S. E., and Mc Hugh, P. R. (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi:10.1016/0022-3956(75)90026-6

Foreman, N., Stanton-Fraser, D., Wilson, P. N., Duffy, H., and Parnell, R. (2005). Transfer of spatial knowledge to a two-level shopping mall in older people, following virtual exploration. *Environ. Behav.* 37, 275–292. doi:10.1177/0013916504269649

Fuchs, P., Moreau, G., Berthoz, A., and Vercher, J. L. (2006). *Le traité de la réalité virtuelle – Volume 1: L'homme et l'environnement virtuel.* Paris: Presses De l'Ecole Des Mines De Paris.

Galati, G., Pelle, G., Berthoz, A., and Committeri, G. (2010). Multiple reference frames used by the human brain for spatial perception and memory. *Exp. Brain Res.* 206, 109–120. doi:10.1007/s00221-010-2168-8

Gardiner, J. M. (2001). Episodic memory and autonoetic consciousness: a first-person approach. *Philos. Trans. R. Soc.* 356, 1351. doi:10.1098/rstb.2001.0955

Gaunet, F., Vidal, V., Kemeny, A., and Berthoz, A. (2001). Active, passive and snapshot exploration in a virtual environment: influence on scene memory, reorientation and path memory. *Brain Res. Cogn. Brain Res.* 11, 409–420. doi:10.1016/S0926-6410(01)00013-1

Glisky, E. L. (2001). "Source memory, aging, and the frontal lobes," in *Perspectives on Human Memory and Cognitive Aging: Essays in Honor of Fergus Craik*, eds M. Naveh-Benjamin, M. Moscovitch, and H. L. Roediger III (New York, NY: Taylor & Francis), 265–276.

Glisky, E. L., and Kong, L. L. (2008). Do young and older adults rely on different processes in source memory tasks? A neuropsychological study. *J. Exp. Psychol. Learn. Mem. Cogn.* 34, 809–822. doi:10.1037/0278-7393.34.4.809

Gras, D., Gyselinck, V., Perrussel, M., Orriols, E., and Piolino, P. (2013). The role of working memory components and visuospatial abilities in route learning within a virtual environment. *J. Cogn. Psychol.* 25, 38–50. doi:10.1080/20445911.2012.739154

Guéguen, N. (2009). L'importance d'un effet: méthodologie simple de détermination et d'évaluation de l' effect size. *Eur. J. Sci. Res.* 38, 20–25. doi:10.1684/san.2011.0240

Gutchess, A. H., Kensinger, E. A., and Schacter, D. L. (2007). Aging, self-referencing, and medial prefrontal cortex. *Soc. Neurosci.* 2, 117–133. doi:10.1080/17470910701399029

Gyselinck, V., Meneghetti, C., Bormetti, M., Orriols, E., Piolino, P., and De Beni, R. (2013). Considering spatial ability in virtual route learning in early aging. *Cogn. Process.* 14, 309–316. doi:10.1007/s10339-013-0557-1

Head, D., and Isom, M. (2010). Age effects on wayfinding and route learning skills. *Behav. Brain Res.* 209, 49–58. doi:10.1016/j.bbr.2010.01.012

Hommel, B. (2004). Event files: feature binding in and across perception and action. *Trends Cogn. Sci.* 8, 494–500. doi:10.1016/j.tics.2004.08.007

Iachini, T., Ruggiero, G., and Ruotolo, F. (2009b). The effect of age on egocentric and allocentric spatial frames of reference. *Cogn. Process.* 10, 222–224. doi:10.1007/s10339-009-0276-9

Iaria, G., Palermo, L., Committeri, G., and Barton, J. S. (2009). Age differences in the formation and use of cognitive maps. *Behav. Brain Res.* 196, 187–191. doi:10.1016/j.bbr.2008.08.040

Iglói, K., Doeller, C. F., Berthoz, A., Rondi-Reig, L., and Burgess, N. (2010). Lateralized human hippocampal activity predicts navigation based on sequence or place memory. *Proc. Natl. Acad. Sci. U. S. A.* 107, 14466–14471. doi:10.1073/pnas.1004243107

Johnson, M. K., Hashtroudi, S., and Lindsay, D. S. (1993). Source monitoring. *Psychol. Bull.* 114, 3–28. doi:10.1037/0033-2909.114.1.3

Kessels, R. P. C., Hobbel, D., and Postma, A. (2007). Aging, context memory and binding: a comparison of "what, where and when" in young and older adults. *Int. J. Neurosci.* 117, 795–810. doi:10.1080/00207450600910218

Klencklen, G., Després, O., and Dufour, A. (2012). What do we know about aging and spatial cognition? Reviews and perspectives. *Ageing Res. Rev.* 11, 123–135. doi:10.1016/j.arr.2011.10.001

Kormi-Nouri, R. (1995). The nature of memory for action events: an episodic integration view. *Eur. J. Cogn. Psychol.* 7, 337–363. doi:10.1080/09541449508403103

Lalanne, J., Rozenberg, J., Grolleau, P., and Piolino, P. (2013). The self-reference effect on episodic memory recollection in young and older adults and Alzheimer's disease. *Curr. Alzheimer Res.* 10, 1107–1117. doi:10.2174/15672050113106660175

Lambrey, S., Amorim, M. A., Samson, S., Noulhiane, M., Hasboun, D., Dupont, S., et al. (2008). Distinct visual perspective-taking strategies involve the left and right medial temporal lobe structures differently. *Brain* 31, 523–534. doi:10.1093/brain/awm317

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., and Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychol. Aging* 17, 677–689. doi:10.1037/0882-7974.17.4.677

Lezak, M. D., Howieson, D. B., and Loring, D. W. (2004). *Neuropsychological Assessment*, 4th Edn. Oxford: Oxford University Press.

Lövden, M., Schellenbach, M., Grossman-Hutter, B., Krüger, A., and Lindenberger, U. (2005). Environmental topography and postural control demands shape aging associated decrements in spatial navigation performance. *Psychol. Aging* 20, 683–694. doi:10.1037/0882-7974.20.4.683

Luo, L., and Craik, F. I. (2008). Aging and memory: a cognitive approach. *Can. J. Psychiatry* 53, 346–353.

MacPherson, S. E., Phillips, L. H., and Della Sala, S. (2002). Age, executive function, and social decision making: a dorsolateral prefrontal theory of cognitive aging. *Psychol. Aging* 17, 598–609. doi:10.1037/0882-7974.17.4.598

Madan, C. R., and Singhal, A. (2012). Using actions to enhance memory: effects of enactment, gestures, and exercise on human memory. *Front. Psychol.* 3:507. doi:10.3389/fpsyg.2012.00507

Maguire, E. A., Frackowiak, R. S. J., and Frith, C. D. (1997). Recalling route around London: activation of the right hippocampus in taxi drivers. *J. Neurosci.* 17, 7103–7110.

Maguire, E. A., and Hassabis, D. (2011). Role of the hippocampus in imagination and future thinking. *Proc. Natl. Acad. Sci. U. S. A.* 108, E39. doi:10.1073/pnas.1018876108

Martinelli, P., Anssens, A., Sperduti, M., and Piolino, P. (2013). The influence of normal aging and Alzheimer's disease in autobiographical memory highly related to the self. *Neuropsychology* 27, 69–78. doi:10.1037/a0030453

McNair, D., and Kahn, R. (1983). "Self-assessment of cognitive deficits," in *Assessment in Geriatric Psychopharmacology*, eds T. Crook, S. Ferris, and R. Bartus (New Canaan, CT: Powley), 137–143.

Mitchell, K. J., and Johnson, M. K. (2009). Source monitoring 15 years later: what have we learned from fMRI about the neural mechanisms of source memory? *Psychol. Bull.* 135, 638–677. doi:10.1037/a0015849

Mitchell, K. J., Johnson, M. K., Raye, C. L., Mather, M., and D'Esposito, M. (2000). Aging and reflective processes of working memory: binding and test load deficits. *Psychol. Aging* 15, 527–541. doi:10.1037/0882-7974.15.3.527

Moffat, S. D. (2009). Aging and spatial navigation: what do we know and where do we go? *Neuropsychol. Rev.* 19, 478–489. doi:10.1007/s11065-009-9120-3

Morganti, F., and Riva, G. (2014). Virtual reality as allocentric/egocentric technology for the assessment of cognitive decline in the elderly. *Stud. Health Technol. Inform.* 196, 278–284.

Morganti, F., Stefanini, S., and Riva, G. (2013). From allo- to egocentric spatial ability in early Alzheimer's disease: a study with virtual reality spatial tasks. *Cogn. Neurosci.* 4, 171–180. doi:10.1080/17588928.2013.854762

Moscovitch, M. (1992). Memory and working-with-memory: a component process model based on modules and central systems. *J. Cogn. Neurosci.* 4, 257–267. doi:10.1162/jocn.1992.4.3.257

Mueller, C., Luehrs, M., Baecke, S., Adolf, D., Luetzkendorf, R., Luchtmann, M., et al. (2012). Building virtual reality fMRI paradigms: a framework for presenting immersive virtual environments. *J. Neurosci. Methods* 209, 290–298. doi:10.1016/j.jneumeth.2012.06.025

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: tests of an associative deficit hypothesis. *J. Exp. Psychol. Learn. Mem. Cogn.* 26, 1170–1187. doi:10.1037/0278-7393.26.5.1170

Naveh-Benjamin, M., Craik, F. I., Guez, J., and Kreuger, S. (2005). Divided attention in younger and older adults: effects of strategy and relatedness on memory performance and secondary task costs. *J. Exp. Psychol. Learn. Mem. Cogn.* 31, 520–537.

Naveh-Benjamin, M., Craik, F. I. M., and Ben-Shaul, L. (2002). Age-related differences in cued recall: effects of support at encoding and retrieval. *Aging Neuropsychol. Cogn.* 9, 276–287. doi:10.1076/anec.9.4.276.8773

Naveh-Benjamin, M., Guez, J., and Shulman, S. (2004). Older adult's associative deficit in episodic memory: assessing the role of decline in attentional resources. *Psychon. Bull. Rev.* 11, 1067–1073. doi:10.3758/BF03196738

Nilsson, L. G., Nyberg, L., Klingberg, T., Aberg, C., Persson, J., and Roland, P. E. (2000). Activity in motor areas while remembering action events. *Neuroreport* 11, 2199–2201. doi:10.1097/00001756-200007140-00027

Nyberg, L., Petersson, K.-M., Nilsson, L.-G., Sandblom, J., Åberg, C., and Ingvar, M. (2001). Reactivation of motor brain areas during explicit memory for actions. *Neuroimage* 14, 521–528. doi:10.1006/nimg.2001.0801

Parkin, A. J., and Walter, B. M. (1992). Recollective experience, normal aging, and frontal dysfunction. *Psychol. Aging* 7, 290–298. doi:10.1037/0882-7974.7.2.290

Parsons, T. D., and Rizzo, A. A. (2008). Initial validation of a virtual environment for assessment of memory functioning: virtual reality cognitive performance assessment test. *Cyberpsychol. Behav.* 11, 17–25. doi:10.1089/cpb.2007.9934

Péruch, P., and Wilson, P. N. (2004). Active versus passive learning and testing in a complex outside built environment. *Cogn. Process.* 5, 218–227. doi:10.1007/s10339-004-0027-x

Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F., and Piolino, P. (2012). How do the different components of episodic memory develop? Role of executive functions and feature-binding abilities. *Child Dev.* 83, 1037–1050. doi:10.1111/j.1467-8624.2012.01736.x

Piolino, P., Coste, C., Martinelli, P., Macé, A., Quinette, P., Guillery-Girard, B., et al. (2010). Reduced specificity of autobiographical memory and aging: do the executive and feature binding functions of working memory have a role? *Neuropsychologia* 48, 429–440. doi:10.1016/j.neuropsychologia.2009.09.035

Piolino, P., Desgranges, B., Benali, K., and Eustache, F. (2002). Episodic and semantic remote autobiographical memory in ageing. *Memory* 10, 239–257. doi:10.1080/09658210143000353

Piolino, P., Desgranges, B., Clarys, D., Guillery-Girard, B., Isingrini, M., and Eustache, F. (2006). Autobiographical memory and sense of remembering in aging. *Psychol. Aging* 21, 510–525. doi:10.1037/0882-7974.21.3.510

Plancher, G., Barra, J., Orriols, E., and Piolino, P. (2013). The influence of action on episodic memory: a virtual reality study. *Q. J. Exp. Psychol.* 66, 895–909. doi:10.1080/17470218.2012.722657

Plancher, G., Gyselinck, V., Nicolas, S., and Piolino, P. (2010). Age effect on components of episodic memory and feature binding: a virtual reality study. *Neuropsychology* 24, 379–390. doi:10.1037/a0018680

Plancher, G., Nicolas, S., and Piolino, P. (2008). Apport de la réalité virtuelle en neuropsychologie de la mémoire: étude dans le vieillissement. *Psychol. NeuroPsychiatr. Vieil.* 6, 7–22. doi:10.1684/pnv.2008.0119

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., and Piolino, P. (2012). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active/passive encoding. *Neuropsychologia* 50, 592–602. doi:10.1016/j.neuropsychologia.2011.12.013

Rauchs, G., Orban, P., Balteau, E., Schimdt, C., Degueldre, C., Luxen, A., et al. (2008). Partially segregated neural networks for spatial and contextual memory in virtual navigation. *Hippocampus* 18, 503–518. doi:10.1002/hipo.20411

Ruddle, R. A., and Lessels, S. (2009). The benefits of using a walking interface to navigate virtual environments. *ACM Trans. Comput. Hum. Interact.* 16, 5. doi:10.1145/1502800.1502805

Ruddle, R. A., Volkova, E., Mohler, B., and Bulthoff, H. H. (2011). The effect of landmark and body-based sensory information on route knowledge. *Mem. Cognit.* 39, 686–699. doi:10.3758/s13421-010-0054-z

Ruggiero, G., Iachini, T., Ruotolo, F., et al. (2009). "Spatial memory: the role of egocentric and allocentric frames of reference," in *Spatial Memory: Visuospatial Processes*, ed. J. B. Thomas (Nova Science Publishers, Inc), 1–25.

Sandamas, G., and Foreman, N. (2003). Active and passive spatial learning from a desktop virtual environment in male and female participants: a comparison with guessing controls. *J. Health Soc. Environ. Issues* 4, 15–22. doi:10.1177/2158244014525424

Sauzéon, H., Arvind Pala, P., Larrue, F., Wallet, G., Déjos, M., Zheng, X., et al. (2011). The use of virtual reality for episodic memory assessment: effects of active navigation. *Exp. Psychol.* 59, 99–108. doi:10.1027/1618-3169/a000131

Schacter, D. L., Addis, D. R., and Buckner, R. L. (2007). Remembering the past to imagine the future: the prospective brain. *Nat. Rev. Neurosci.* 8, 657–661. doi:10.1038/nrn2213

Schultheis, M. T., Himelstein, J., and Rizzo, A. R. (2002). Virtual reality and neuropsychology: upgrading the current tools. *J. Head Trauma Rehabil.* 17, 379–394. doi:10.1097/00001199-200210000-00002

Serino, S., Cipresso, P., Morganti, F., and Riva, G. (2014). The role of egocentric and allocentric abilities in Alzheimer's disease: a systematic review. *Ageing Res. Rev.* 16, 32–44. doi:10.1016/j.arr.2014.04.004

Shing, Y. L., Werkle-Bergner, M., Li, S.-C., and Lindenberger, U. (2008). Associative and strategic components of episodic memory: a lifespan dissociation. *J. Exp. Psychol. Gen.* 137, 495–513. doi:10.1037/0096-3445.137.3.495

Simons, J. S., and Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nat. Rev. Neurosci.* 4, 637–648. doi:10.1038/nrn1178

Spencer, W. D., and Raz, N. (1995). Differential effects of aging on memory for content and context: a meta-analysis. *Psychol. Aging* 10, 527–539. doi:10.1037/0882-7974.10.4.527

Taillade, M., Sauzéon, H., Arvind Pala, P., Déjos, M., Larrue, F., Gross, C., et al. (2013). Age-related wayfinding differences in real large-scale environments: detrimental motor control effects during spatial learning are mediated by executive decline? *PLoS ONE* 8:e67193. doi:10.1371/journal.pone.0067193

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi:10.1037/h0080017

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Van Asselen, M., Van der Lubbe, R. H., and Postma, A. (2006). Are space and time automatically integrated in episodic memory? *Memory* 14, 232–240. doi:10.1080/09658210500172839

Viard, A., Desgranges, B., Eustache, F., and Piolino, P. (2012). Factors affecting medial temporal lobe engagement for past and future episodic events: an ALE meta-analysis of neuroimaging studies. *Brain Cogn.* 80, 111–125. doi:10.1016/j.bandc.2012.05.004

Viard, A., Doeller, C. F., Hartley, T., Bird, C. M., and Burgess, N. (2011). Anterior hippocampus and goal-directed spatial decision making. *J. Neurosci.* 31, 4613–4621. doi:10.1523/JNEUROSCI.4640-10.2011

Von Zerssen, D., Strain, F., and Schwarz, D. (1974). "Evaluation of depressive states, especially in longitudinal studies," in *Psychological Measurements in Psychopharmacology*, ed. B. Pichot (Basel: Karger), 189–202.

Voss, J. L., Gonsalves, B. D., Federmeier, K. D., Tranel, D., and Cohen, N. J. (2011). Hippocampal brain-network coordination during volitional exploratory behaviour enhances learning. *Nat. Neurosci.* 14, 115–122. doi:10.1038/nn.2693

Wallet, G., Sauzéon, H., Pala, P. A., Larrue, F., Zheng, X., and N'Kaoua, B. (2011). Virtual/real transfer of spatial knowledge: benefit from visual fidelity provided in a virtual environment and impact of active navigation. *Cyberpsychol. Behav. Soc. Netw.* 14, 417–423. doi:10.1089/cyber.2009.0187

Wechsler, D. (2000). *WAIS-III: Echelle d'Intelligence De Wechsler Pour Adultes*, 3ème édition Edn. Paris: Les Editions Du Centre De Psychologie Appliquée.

Widmann, C. N., Beinhoff, U., and Riepe M. W. (2012). Everyday memory deficits in very mild Alzheimer's disease. *Neurobiol. Aging* 33, 297–303. doi:10.1016/j.neurobiolaging.2010.03.012

Wilson, P. N. (1999). Active exploration of a virtual environment does not promote orientation or memory for objects. *Environ. Behav.* 31, 752–763. doi:10.1177/00139169921972335

Wilson, P. N., and Péruch, P. (2002). The influence of interactivity and attention on spatial learning in a desktop virtual environment. *Curr. Psychol. Cogn.* 21, 601–633.

Wolbers, T., and Hegarty, M. (2010). What determines our navigational abilities? *Trends Cogn. Sci.* 14, 138–146. doi:10.1016/j.tics.2010.01.001

Zawadzki, J. A., Girard, T. A., Foussias, G., Rodrigues, A., Siddiqui, I., Lerch, J. P., et al. (2013). Simulating real world functioning in schizophrenia using a naturalistic city environment and single-trial, goal-directed navigation. *Front. Behav. Neurosci.* 7:180. doi:10.3389/fnbeh.2013.00180

Zimmer, H. D., and Cohen, R. L. (2001). "Remembering actions: a specific type of memory?," in *Memory for Action: A Distinct form of Episodic Memory*?, eds H. D. Zimmer, R. L. Cohen, M. Guynn, J. Engelkamp, R. Kormi-Nouri, and M. N. Foley (New York, NY: Oxford University Press), 3–24.

Zimmer, H. D., Mecklinger, A., Lindenberger, U., Zimmer, H. D., Mecklinger, A., and Lindenberger, U. (2006). *Handbook of Binding and Memory: Perspectives from Cognitive Neuroscience.* Oxford, NY: Oxford University Press.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 06 September 2014; accepted: 30 November 2014; published online: 17 December 2014.

Citation: Jebara N, Orriols E, Zaoui M, Berthoz A and Piolino P (2014) Effects of enactment in episodic memory: a pilot virtual reality study with young and elderly adults. Front. Aging Neurosci. ***6****:338. doi: 10.3389/fnagi.2014.00338*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 07 July 2015
doi: 10.3389/fnagi.2015.00128

An interactive web tool for facilitating shared decision-making in dementia-care networks: a field study

Marijke Span[1], Carolien Smits[1], Jan Jukema[1], Leontine Groen-van de Ven[1], Ruud Janssen[2], Myrra Vernooij-Dassen[3,4], Jan Eefsting[5] and Marike Hettinga[2]*

[1] *Research Group Innovation of Care of Older Adults, Windesheim University of Applied Sciences, Zwolle, Netherlands,* [2] *Research Group IT Innovation in Health Care, Windesheim University of Applied Sciences, Zwolle, Netherlands,* [3] *Department of Primary Care, IQ HealthCare, Radboud University, Nijmegen, Netherlands,* [4] *Radboud Alzheimer Centre, Nijmegen, Netherlands,* [5] *Department of Nursing Home Medicine, VU University Medical Centre, EMGO Institute for Health and Care Research, Amsterdam, Netherlands*

Edited by:
Iracema Leroi, Manchester Academic Health Sciences Centre, UK

Reviewed by:
Vijaykumar Harbishettar, South Essex Partnership University NHS Foundation Trust, UK
Abebaw Mengistu Yohannes, Manchester Metropolitan University, UK

****Correspondence:***
Marijke Span, Research Group Innovation of Care for Older Adults, Windesheim University of Applied Sciences, Campus 2-6, P.O. Box 10090, Zwolle 8000 GB, Netherlands
m.span@windesheim.nl

Received: *11 January 2015*
Accepted: *22 June 2015*
Published: *07 July 2015*

Citation:
Span M, Smits C, Jukema J, Groen-van de Ven L, Janssen R, Vernooij-Dassen M, Eefsting J and Hettinga M (2015) An interactive web tool for facilitating shared decision-making in dementia-care networks: a field study. Front. Aging Neurosci. 7:128. doi: 10.3389/fnagi.2015.00128

Background: An interactive web tool has been developed for facilitating shared decision-making in dementia-care networks. The *DecideGuide* provides a *chat* function for easier communication between network members, a *deciding together* function for step-by-step decision-making, and an *individual opinion* function for eight dementia-related life domains. The aim of this study was to gain insight in the user friendliness of the *DecideGuide*, user acceptance and satisfaction, and participants' opinion of the *DecideGuide* for making decisions.

Materials and methods: A 5-month field study included four dementia-care networks (19 participants in total). The data derived from structured interviews, observations, and information that participants logged in the *DecideGuide*. Structured interviews took place at the start, middle, and end of the field study with people with dementia, informal caregivers, and case managers. Four observations of case managers' home visits focused on members' responses and use of the tool.

Results: (1) The user friendliness of the *chat* and *individual opinion* functions was adequate for case managers and most informal caregivers. Older participants, with or without dementia, had some difficulties using a tablet and the *DecideGuide*. The *deciding together* function does not yet provide adequate instructions for all. The user interface needs simplification. (2) User acceptance and satisfaction: everybody liked the *chat*'s easy communication, handling difficult issues for discussion, and the option of individual opinions. (3) The *DecideGuide* helped participants structure their thoughts. They felt more involved and shared more information about daily issues than they had done previously.

Conclusion: Participants found the *DecideGuide* valuable in decision-making. The *chat* function seems powerful in helping members engage with one another constructively. Such engagement is a prerequisite for making shared decisions. Regardless of participants' use of the tool, they saw the *DecideGuide's* added value.

Keywords: dementia, shared decision-making, web tool, field study, care network, case managers

Introduction

Decision-making in dementia-care networks is complex (Epstein and Gramling, 2013). The person with dementia, his/her informal caregivers, and professionals (who form a care network) have to make many difficult care- and well-being-related decisions over a prolonged period of time (Livingston et al., 2010; Smebye et al., 2012; Wolfs et al., 2012). The care network members have different capacities and sometimes competing interests, but have to interact with each other in the decision-making. Moreover, dementia is characterized by a progressive cognitive decline (Prince et al., 2011). Nevertheless, people with dementia have the fundamental and ethical right to be involved in decisions about their own situation (Reamy et al., 2011). Unfortunately, participation of people with dementia in decision-making about their own situation is not self-evident; informal caregivers and professionals tend to decide *for* them rather than *with* them (Dupuis et al., 2011; von Kutzleben et al., 2012).

Shared decision-making, which has its roots in the medical encounter, is an approach that involves patients in decision-making in collaboration with their professional caregivers (Elwyn et al., 1999, 2010). In the context of dementia, shared decision-making gives patients a voice by expressing their needs and preferences. Further, shared decision-making leads to increased feelings of well-being and autonomy in both the people with dementia and their informal caregivers (Menne et al., 2008; Dupuis et al., 2011). Although there is growing attention and need for involving patients in shared decision-making, it is not routine in daily practice for professionals, either in clinical practice or in dementia-care practice. This may be due to the fact that decision-making is seen as an individual and cognitive task rather than a relational task (Elwyn et al., 2014). Elwyn et al. (2014) advocate a focus on interpersonal aspects because they importantly affect how decisions are formed. Although shared decision-making is the preferred approach for making decisions in the care networks of people with dementia, professionals, such as case managers (see **Box 1**), have difficulty promoting shared decision-making in dementia practice (Dutch Alzheimers's Association and Vilans, 2013). Therefore, tools that can assist professionals in this matter are welcome (Stacey et al., 2014).

BOX 1 | Case management.

Case management in dementia care is a fairly recent phenomenon. As in most countries in Europe, Canada, and the United States, community-dwelling patients in the Netherlands diagnosed with dementia and their caregivers are entitled to receive assistance in the form of case management (Koch et al., 2012). Different forms of case management in dementia care exist (Alzheimer Europe, 2008). In the Dutch context, the purpose of case management is to support informal caregivers and people with dementia with practical help during the complex care trajectory, and to help people with dementia live independently as long as possible (Peeters et al., 2012). One of the tasks of case managers is to navigate smoothly through the jungle of care and well-being. In daily practice, this implies that case managers have to balance the possibly competing interests and values of the person with dementia, the spouse, and other informal caregivers (who may be the adult children of the person). Informal caregivers nearby or at a distance often see the situation of the person with dementia differently.

Supportive tools that enable shared decision-making in the clinical encounter can be paper based or web based (Stacey et al., 2014). The benefits of web-based tools include their flexibility about the individual's preferred time and place for using it, its relatively anonymous use, the easy involvement of people at a distance, and its ability to record all activities and information. Dementia-care networks could benefit from such a web-based tool. Unfortunately, such tools for dementia-care practice are lacking.

Our intended improvement is an interactive web tool, the *DecideGuide*, which addresses the complexity of decision-making in dementia-care networks. The *DecideGuide* aids case managers facilitate shared decision-making in dementia-care networks. The *DecideGuide* was developed and improved in an iterative participatory design process that involved groups of all end users: people with dementia, their informal caregivers, and their case managers. End-user participation in all phases of development increases the likelihood of user-friendly and usable IT applications (Span et al., 2013). The user requirements we identified (Span et al., 2014a) determined the design of our tool; they were derived from end-user feedback (Span et al., 2014). The next step is to test the *DecideGuide* in the daily routine of dementia-care networks. We are interested in the experiences of all end users, including people with dementia. In order to implement a user-friendly and useful tool, a decisive assessment of the tool is necessary. Therefore, the aim of this study was to gain insight into the daily use of the *DecideGuide* by people with dementia, informal caregivers, and case managers. The research questions are

1. What do people with dementia, informal caregivers, and case managers think of the user friendliness of the *DecideGuide*?
2. Are users of the *DecideGuide* satisfied with it, and how easily do they accept it?
3. What value do people with dementia, informal caregivers, and case managers put on the *DecideGuide* for decision-making?

Materials and Methods

Design Overview

During the 5-month field study, 4 community-dwelling people with dementia, their 12 informal caregivers, and 3 case managers used the *DecideGuide*. The study was conducted between June and October 2014 and included structured interviews (at the beginning, middle, and end), observations, and information that the participants recorded in the *DecideGuide*.

The *DecideGuide*

The *DecideGuide* is an interactive web tool that helps people with dementia, informal caregivers, and case managers make shared decisions. There are three design principles in the *DecideGuide*: transparency, open communication and information, and giving voice to people with dementia. The *DecideGuide* promotes three perspectives: those of the people with dementia, their informal caregivers, and their case managers. All three parties can use the *DecideGuide*, which has three functions (**Figure 1**). The first function, *chat*, enables users to communicate with each other, also from a distance. The second function, *deciding together*, assists decision-making step by step. The third function, *individual opinion*, enables

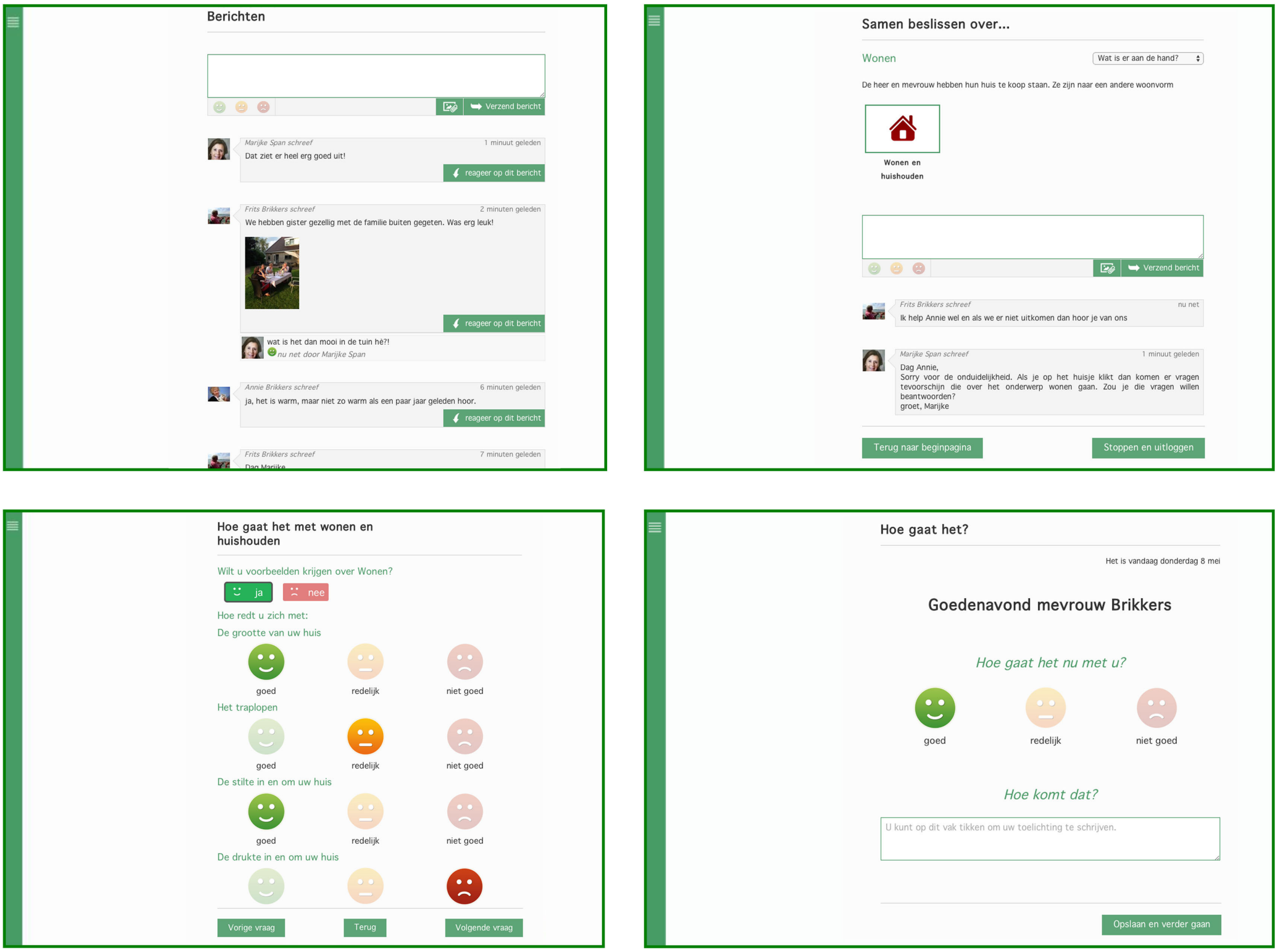

FIGURE 1 | Final layout of the three functions of the *DecideGuide* (screen view for the person with dementia). Clockwise from top left: *chat*, *deciding together*, *individual opinion* "How are you right now?", and *individual opinion* in questionnaire with examples (Span et al., 2014b).

users to give their individual opinions about dementia-related topics and individual circumstances. This function help give voice to the person with dementia. The *DecideGuide* is a safe and shielded web tool, and it is available for tablets, laptops, and computers. The case manager, the person with dementia, and the informal caregivers discuss whether they will use the *DecideGuide*. All participants in a care network have an individual login and use the tool on their own as they wish or after an alert from the case manager (Span et al., 2014b).

The *DecideGuide* was developed in an iterative process in collaboration with the end users, namely, people with dementia, informal caregivers, and case managers (Span et al., 2014a,b). Although a process map is developed specifically for web-based decision support interventions (Elwyn et al., 2011), we followed the five phases of the Center for eHealth Research and Disease Management (CeHRes) roadmap because of its holistic approach and focus on the sustainability of eHealth technologies (Van Gemert-Pijnen et al., 2011). The *DecideGuide* was developed and refined in four iterations, on the basis of feedback from the end users. Previous publications provide further information (Span et al., 2014a,b).

Two manuals for using the *DecideGuide* were produced during the field study. The manual for case managers explains the buttons and provides an overview of shared decision-making principles and steps. It also shows how these principles and steps are incorporated into the *DecideGuide*. The manual for people with dementia and their informal caregivers provides a short overview of shared decision-making principles and explains the buttons with screenshots of the *DecideGuide*.

Potential Participants and Recruitment

The principal researcher recruited case managers who had participated earlier in the development of the *DecideGuide*. In order to achieve information-rich cases, these case managers were selected purposively from a case managers' network and represented three different organizations providing dementia care (Coyne, 1997). The inclusion criteria were a positive attitude toward shared decision-making and the *DecideGuide* and variation in the type of organizations that the case managers worked for. The case managers, who had given written informed consent for their participation, were asked to select people with dementia and informal caregivers from their caseload who would likely be willing to participate in the field study. We aimed at diversity of characteristics of the people with dementia (with regard to gender, age, marital status, and socio-economic status) and types of informal caregivers (spouses, children, other family members, and other informal caregivers). Computer literacy was not required.

The inclusion criteria were

1. Mild to moderate dementia and the ability to participate in a conversation.
2. Availability of a care network consisting of a person with dementia and a minimum of two informal caregivers.
3. Willingness to use an interactive web tool like the *DecideGuide* for 4–5 months.
4. Willingness to provide oral or written feedback.

The case managers explained the study to potential participants and asked for their consent to give their contact details to the researchers. Then, the principal researcher (Marijke Span) contacted the people with dementia and the informal caregivers (whom the case manager had approached and selected by phone) and explained the aims and methods of the field study. The potential participants were asked for their oral consent. Then, a confirmation of their participation and written information about the pilot study was emailed to them or sent by regular mail. A week later, the principal researcher phoned them, checked whether they still consented, and if so, made an appointment to get acquainted at their homes. The people with dementia were asked who were important to them, and the informal caregivers they named were also approached for participation in the field study. The same procedure was followed for these participants as for the people with dementia.

Procedure

Participants used the *DecideGuide* on an iPad for 5 months. The participants who did not have an iPad could borrow one from the research team. The iPad was equipped with a mobile Internet subscription because the *DecideGuide* is accessible via an Internet website. Four consecutive steps were taken.

First, the principal researcher (Marijke Span) explained to the participating case managers how to use the *DecideGuide* on the iPad. All the buttons were explained orally, and a manual was provided. The case managers also received manuals for the people with dementia and informal caregivers. This all took place in a 2-h session about the field study and the *DecideGuide*.

Second, the principal researcher visited the people with dementia and their informal caregivers who had initially consented to getting acquainted at home, where they received the explanation of the study, the iPad, and the *DecideGuide* on the iPad. The participants gave their written informed consent. The personal login gave them access to start using the *DecideGuide* immediately. All participants received a simple and detailed written manual that, after a brief explanation of shared decision-making principles, focuses mainly on the explanation of the buttons. These visits lasted 1–2 h.

Third, the principal researcher made new appointments with all the participants for the first interview cycle. During the visit, the participants could also discuss anything that was unclear, as well as any errors or mistakes in using the *DecideGuide* that had come up after the explanation of the *DecideGuide* at home or at work.

Fourth, at the end of each interview in the intervention period, the participants were given ample opportunity for small talk, and the researcher expressed and emphasized the importance of their participation and information. As most participants were interested in the results of the field study, preliminary results were shared with them after the interview.

The principal researcher was on stand-by during office hours in the intervention period. The participants could contact the principal researcher by phone or email if questions or problems arose.

Data Collection

The data collected (**Table 1**) included (1) structured interviews with 19 people, namely, 4 people with dementia, 12 informal caregivers, and 3 case managers; (2) observations of case managers' home visits with the 4 people with dementia; (3) information recorded in the *DecideGuide*; and (4) the principal researcher's memos and field notes.

Interviews

The structured interviews lasted from 45 to 75 min. They were carried out at the beginning (t_0), middle (t_1 = 2.5 months), and end (t_2 = 5 months), and all were audiotaped. Most t_0 interviews were conducted a few days after the oral instruction for using the *DecideGuide*. Some t_0 interviews with informal caregivers took place during the same appointment because of time and distance constraints.

The interview topics at t_0 were the participants' IT skills (e.g., "What is your experience with computers?", "Which device and programs do you use?"), general characteristics, experience with decision-making in the care networks (e.g., "What changed lately in your situation?", "What was the last decision you made?", "Who were involved?", "What is important for you in making the decision?"), and their role and support in decision-making (e.g., "What was your role in making the decision?", "Which role would you like to have in decision-making about your own situation?"). The t_0 interview addressed research question 3.

The interview topics at t_1 addressed participants' experience and satisfaction with using the *DecideGuide*: how often they used the

TABLE 1 | Overview of the data collected for answering the research questions.

	Research question 1	Research question 2	Research question 3
Interview at t_0			X
Interview at t_1 (after 2.5 months)	X	X	X
Interview at t_2 (after 5 months)	X	X	X
Observations	X	X	X
Information in tool			X
Field notes and memos	X	X	X

tool, the parts they used, the time they spent per session, and the usefulness and user friendliness of the various functions of the tool (e.g., "What do you think of the ease of use of the *DecideGuide*?", "What should be improved of the *DecideGuide*?", "How often did you use the *DecideGuide*?", "Which functionalities did you use?", "What do you think of the functionalities you used?",). This interview addressed all three research questions.

At t_2, the interview topics were the participants' experience with decision-making in the care networks, including their role and support (e.g., "Was the *DecideGuide* helpful in making the decision?", "Which parts of the *DecideGuide* were helpful in decision-making?"). The topic first discussed at t_1, their experience of using the *DecideGuide*, was discussed anew. The interviews at t_2 also addressed all three research questions.

The IT skills were measured with a self-developed instrument. The topics were the devices participants used, the programs they used with the devices, and a self-estimation of their IT skills. Decision-making was measured with a self-developed interview guideline that was based on existing measures about decision-making: decision self-efficacy, decision regret scale, and decision conflict scale (O'Connor, 0000; Scholl et al., 2011). The user friendliness was measured with an instrument based on the CeHRes assessment of design quality (Nijland, 2011). User acceptance and satisfaction with the *DecideGuide* were measured on a 5-point Likert scale (*strongly agree* to *strongly disagree*).

Observations

The principal researcher observed four case-manager visits with people with dementia at home. The attendees of these visits were people with dementia, their spouses, case managers, and in one case, two children as well. The visits lasted 60–90 min. The observations focused on verbal and non-verbal communication, the atmosphere, and the role and meaning of the *DecideGuide*. Field notes were taken and elaborated immediately afterwards. The observations addressed the three research questions.

Information Logged in the DecideGuide

All participant activities were logged in the *DecideGuide*. The activities were the group chat (frequency of use, how network members interacted with and responded to each other, and the topics they discussed) and also participants' individual views about dementia-related life domains in the questionnaires. The information logged addressed research questions 2 and 3.

Field Notes and Memos

During the pilot study, the principal researcher took field notes at the home visits and, for case managers, at work. She produced salient memos about what happened and about participants' problems and questions while using the *DecideGuide*. These field notes and memos were used to interpret the other data.

Analysis

To answer the three research questions, we used qualitative content analysis to analyze the interviews, observations, information logged in the *DecideGuide*, and the field notes and memos (Hsieh and Shannon, 2005; Bryman, 2008). The principal researcher (Marijke Span) started the analysis, and another researcher (Ruud Janssen) assisted. The analysis consisted of reading and rereading the data, coding relevant paragraphs addressing the research questions (Marijke Span and Ruud Janssen coded independently), searching for themes, and reviewing and interpreting themes by means of constant comparison (Corbin and Strauss, 1990). Marijke Span and Ruud Janssen discussed the interpretation of the themes until consensus was reached.

Ethical Considerations

All participants gave their written informed consent. Special attention was paid to the informed consent of the people with dementia, the most vulnerable group in this study. Our investment in their ongoing consent included reserving time for social talk to get to know them, checking that their consent was still valid during the pilot study, and giving positive affirmation by emphasizing the importance of their contribution (Murphy et al., 2014). The researchers were careful to notice any signs, non-verbal or otherwise, of discomfort or restlessness of the people with dementia. In such a case, the participant was given ample opportunity to quit without having to give a reason. The institutional review board of the regional medical ethics committee of the Isala Clinics (number 10.111113) gave written approval for the study.

Results

Characteristics of Networks and Participants

Three of the six case managers we reached agreed to participate. In the opinion of the case managers, the reason for non-participation was the lack of dementia-care networks who could or would participate and use the interactive web tool. The three case managers selected six care networks, of which four care networks completed their participation in the 5-month field study. The care networks included 4 people with dementia, 12 informal caregivers, and 3 case managers (**Table 2**). One case manager participated with two networks in her caseload.

From the two dropouts, a daughter of a person with moderate dementia who had been willing to participate canceled their consent and participation. She believed that her mother was unable to participate, that it would be too difficult for her because she had no experience using a computer, and that participation would confuse her. In another selected network, the spouse of the person with dementia canceled their participation 2 weeks after starting the field study. The condition of the person with dementia deteriorated to such an extent that relocation was necessary, and the spouse's burden increased to such an extent that they refrained from participating. Moreover, their daughters were not as enthusiastic about their participating as the spouse had expected.

Of the remaining networks, network 1 consisted of four people: a person with dementia living independently with a spouse, a younger sister living nearby, and a case manager. Network 2 consisted of five people: a person with dementia (who was already using an iPad) living independently with a spouse, two sons (one nearby and the other at distance), and a case manager. Network 3 consisted of six people: a person with dementia living independently with a spouse and a son, a

TABLE 2 | Characteristics of the participants in the field study.

Characteristics	Participants (n = 19)		
	People with dementia (n = 4)	**Informal caregivers (n = 12)**	**Case managers (n = 3)**
Gender	3 Male 1 Female	5 Male 7 Female	0 Male 3 Female
Age in years	72–82 (M = 77.5)	19–86 (M = 54.3) Specification Spouse: 60–86 (M = 76.0) Adult child: 19–62 (M = 43.5)	40–62 (M = 48.0)
Educational level[a]	1 Low 1 Medium 2 High	1 Low 4 Medium 6 High	0 Low 1 Medium 2 High
Type of dementia	2 Alzheimer's disease 1 Vascular dementia 1 Lewy body		
Reisberg scale	2–4		
Marital status	4 Married	10 Married 2 Single 0 Widowed	
Relation to person with dementia		4 Spouse 7 Daughter/son 1 Brother/sister	
Experience as a case manager in years			3.3–4
Electronic equipment (computer, laptop, tablet, smartphone)	2 Computer 2 Laptop 1 Tablet 0 Smartphone	6 Computer 9 Laptop 8 Tablet 8 Smartphone	3 Computer 1 Laptop 3 Tablet 3 Smartphone
Software and networks used (Word, Excel, Power Point, Email, Internet, Social media)	2 Word/Excel/ Power Point 3 Email 1 Internet 0 Social media 0 Gaming	10 Word/Excel/ Power Point 10 Email 11 Internet 7 Social media 4 Gaming	3 Word/Excel/ Power Point 3 Email 3 Internet 2 Social media 2 Gaming
Assessment of one's own IT abilities (excellent, good, moderate, or poor)	0 Excellent 1 Good 1 Moderate 2 Poor	4 Excellent 2 Good 4 Moderate 2 Poor	0 Excellent 2 Good 1 Moderate 0 Poor

[a]*Low, primary or secondary school graduate; medium, high school graduate; high, college graduate.*

son and daughter at a distance, and a case manager. Network 4 consisted of five people: a person with dementia living independently with a spouse, two daughters (one nearby and the other at a distance), and a case manager. **Table 2** shows the characteristics of all participants.

Two people with dementia were very motivated to participate, and they appreciated the researcher's regular visits. In their opinion, dementia research is very useful; it is important to generate more knowledge about dementia. Both their spouses were more reluctant, and they participated only because their spouses were so motivated. The other two people with dementia were less outspoken about why they participated, although they mentioned communication as an item to be improved. In these networks, the people with dementia needed more time to express themselves because they had speech problems. Their spouses did the speaking most of the time.

Research Question 1: User Friendliness of the *DecideGuide*

The findings resulting from the analysis of the user friendliness of the *DecideGuide* addressed four themes: the ease of use of the *DecideGuide* functions, technical failures, "nice to haves," and the age and capability of the users.

Ease of Use of the *DecideGuide* Functions

The ease of use of the *DecideGuide* expresses how easy it is for users to comprehend the system's functions. There were both differences and similarities in the participants' experience of the ease of use of the three main functions of the *DecideGuide*.

The *chat* function was easy to use for almost all informal caregivers and case managers. Participants older than 70 years, including the people with dementia and some older informal caregivers who used the *DecideGuide* on the iPad independently, had some difficulties in using the functionalities of the iPad (e.g., the keyboard) and the *DecideGuide* log in. Logging in and sending a message took them a long time. Moreover, most participants said that the text and buttons needed to be enlarged and made more distinctive for the users older than 70. The use of the decision-making phases in the *deciding togethe*r function proved to be too difficult for all participants. The case managers said that there was a need to get more grasp of the usage, e.g., an extra explanation or help function in the tool for using a function and its steps adequately in the network. In contrast to case managers and most of the informal caregivers, older participants said that the questionnaires in the *individual opinion* function were difficult to find. Besides, as the completed questionnaires were sent automatically and silently to the case managers, the network members could not check whether they had been sent. This confused them a bit because they were not sure that the case managers had received their answers. The questionnaire icons were unclear and too abstract for some of the informal caregivers. Moreover, informal caregivers and case managers wanted a chance to edit their messages for typo's or mistakes or to delete them.

> A little difficult, in spite of my past experience with computers. I do have trouble with my memory. Logging in is too much effort for me, too much energy. But of course it has to be safe. (R1, person with dementia (pwd))

> In general, practical and easy. Self-explanatory. Deciding together is the most difficult part. Easy way of making contact. Everybody can do it at the times that suit them. (R7, case manager (cm))

Technical Failures

Technical failures influence the user-friendliness experience of a tool. The technical failures that occurred during the field study concerned lost messages and a temporary non-access to the *DecideGuide*. Some case managers had problems with the IT department and the Internet access of their own organizations, e.g., the iPad could not connect to the Internet network of the organization, and the case managers were not allowed to download Google Chrome onto their computers.

"Nice to Haves"

Functions that have not yet been included in the tool, but which participants would like, and which influence the sense of user friendliness are "nice to haves." One "nice to have" that case managers and informal caregivers suggested was a notification at the *DecideGuide* icon or sending an email message to all network members when a new activity in the tool has occurred. This would stimulate the interaction in the network. Other "nice to haves" were an agenda function, photo gallery, and (memory) games. The informal caregivers said that people with dementia might take advantage of speech recognition to make using the *DecideGuide* easier for them. Informal caregivers, case managers, and people with dementia said that, besides the chat, they would like to be able to send a message to just one person in the network. Two "nice to haves" for case managers' practice would be a function to connect professionals' record systems to avoid double registration activities and connections of several technical solutions (e.g., homecare technology) to one tablet.

> Add notification of new activity. By email or on the app itself, like Facebook does. It would encourage people to react to each other. (R19, informal caregiver (ic))

> More things could be added to the tool, for example, connections to client registration systems and domotica. (R7, cm)

Age and Capability of Users

Participants 70 years of age or younger were very well able to use the *DecideGuide*. The ones who were already used to social media, chatting, and tablet use had an advantage. The use of the *DecideGuide* proved difficult for almost all adults more than 70 years old, including people with dementia. They were motivated to use the tool and to learn to use it on an iPad. They tried very hard, but it did not become a daily routine for them during the field study. Some of them said that they started trying out the tool too late; they would have benefited more if they had done it at a younger age. Most informal caregivers and case managers emphasized their concerns about the usefulness of the tool for the current generation of older adults with little or no IT experience. They all thought that the tool would be much easier for the future generation of older adults. They expected that improved ease of use of the *DecideGuide* for older adults would influence their acceptance and satisfaction.

One case manager stated that the tool was too difficult to use from the perspective of the person with dementia because the estimated level of functioning of people with dementia was too high in this study. The people with dementia said that it took a lot of their energy, that they needed to get used to it, and that it took time.

> I do have trouble with my memory. If I were younger, it would have been a very handy thing for me. (R1, pwd)

> Older people have to work very hard to get used to a tablet, even if things go well in the pilot study. Older people have to keep on using the iPad and the tool, otherwise they lose the skill. (R7, cm)

> The most important hindrance is that it is more difficult for people older than 80 years than I had thought. (R9, ic)

Research Question 2: User Acceptance of and Satisfaction with the *DecideGuide*

Most participants older than 70 years needed time to learn to get access to the tool and send a message. This improved with practice. They tried to use the *DecideGuide* repeatedly, and tried more often in the first months (daily or two – three times a week) than in the last 2 months. This was due to technical failures and the lack of activity in the network. The participants said that when they sent messages and nobody responded, their motivation to use the tool decreased. Analysis of the data about user acceptance and satisfaction resulted in three themes: the use of the *DecideGuide* in daily life, the added value of the *DecideGuide*, and concerns about using it.

Use of the *DecideGuide* in Daily Life

Most of the participants used the *DecideGuide* once or twice a week. They were eager and curious. Some of the younger informal caregivers checked the *DecideGuide* every day to see whether the person with dementia had posted a message. When no activity was visible, they left the tool. They waited for a message from another network member to respond to. When network members themselves did post a message, they were sometimes a little disappointed when no one responded. They said that this decreased their motivation to actually use the tool. The participants named several factors that influenced the use of the tool: their age, their need for such a tool, their daily routine (or the lack thereof for using such a tool), whether or not there was time to make decisions, the occurrence of problems, the size of the network, and how network members communicated without the *DecideGuide*. They stated that network members who already frequently contacted each other used the tool less often.

> I think not, it's not in my system. (R6, ic)

> I don't use it enough. Don't really need it. But would need it if the dementia gets worse. (R11, ic)

> There is too little activity, and then you don't use it as much. (R5, pwd)

> Nice to see how people do their best to work with the tool, and to master the art of using the iPad and the tool. (R7, cm)

Among the 19 participants, 3 informal caregivers from different networks did not participate actively. One older informal caregiver lacked any interest in IT, one young informal caregiver felt that he did not need the tool because he was still living with his parents, and another informal caregiver, although initially very enthusiastic, did not really participate. No reason for her inactivity could be determined because this participant did not react to any email or phone calls. The network members recognized this behavior in their family life.

Added Value of the *DecideGuide*

All participants valued the tool positively, despite the low frequency of their use. They liked the easy way of communicating within the network, and they said that it was a handy tool for that. Nevertheless, some informal caregivers stated that they did not yet need such a tool, despite the benefits. They felt that this might change if the condition of the person with dementia became worse and more problems occurred. People with dementia found the *chat* function useful and handy, particularly for staying in touch with people at a distance. The added value of the *DecideGuide* is its easy access, according to informal caregivers and case managers. It has a low threshold for sharing and deliberating the home situation even for participants at a distance and the person with dementia in the network. Informal caregivers and case managers appreciated the overview of the network that the *DecideGuide* provides, including the people who are important to the person with dementia. Moreover, they appreciated the *DecideGuide* for its stimulation of thinking about the situation in a structured way. It gave participants an overview.

> In general, valuable and useful! Especially for me and those around me. A little group conversation is useful. Easy to use for solving problems. It was good to be able to speak freely. A lot of contact with the case manager too. The tool has to be used regularly, otherwise it fades away. The tool suits me well so far. It will become more difficult in the future because of my memory. (R5, pwd)

> The tool is interesting as a lovely aid to have conversations with each other. Otherwise it is not so easy to talk about things. It has a low threshold for starting a conversation. (R8, ic)

> The tool can be valuable if you can get things off your chest. Using the tool was good. I had less need of it. I'm not in that phase yet. It would have been a lot more helpful to me when the person with dementia had a stroke (a year or a year and a half ago). Now I don't have any burning questions that I need help with. (R15, ic)

> It's a real plus that the person with dementia takes part. It is a pleasant way of consulting each other. It's easy to use and you can use it in your own sweet time. It is more accessible than email. (R7, cm)

> Valuable tool, I see that now more than in the beginning, especially now that I am not using it (due to personal circumstances). I miss it. A pity that he doesn't continue. Informal caregivers can let off steam with it. (R13, cm)

The *deciding together* function was particularly appreciated for its questionnaires. The decision-making steps were less appreciated because the value of this function was not self-evident. Hence, the participants hardly used the steps, though they could envision the importance, particularly after the questionnaires were sent to the case managers. However, what happened after that was unclear to the participants.

> It would be nice to use deciding together more often, especially after the questionnaires have been answered. It organizes one's thoughts, but there is no step after that, about how to continue. (R19, ic)

The questionnaires about the eight dementia-related life domains helped informal caregivers with a structured analysis of problems, and they appreciated the individual aspect of the questionnaires. Moreover, they were very interested in the opinions of the other network members. People with dementia liked having their answers in the questionnaires visible; it was handy because of their memory difficulties. Case managers appreciated the questionnaires because they showed all the opinions in the networks. It helped them prepare the home meetings.

> The tool structures your thoughts and lets you look and think more broadly. It's a good thing that you answer the questionnaires individually. Though I would like to know what the others and the person with dementia say. But privacy is a very valuable thing. (R4, ic)

> It adds something. A good supply for the process. Handy to have all the opinions beforehand. Then you can get deeper into a conversation. (R7, cm)

> But if you are forgetful, it is great. (R1, pwd)

Concerns About Using the *DecideGuide*

The participants had two concerns about using the *DecideGuide*. First, some of them thought that the questionnaires in the tool were too confronting. Sometimes, this made them hesitate to use the tool. One informal caregiver related this hesitation to her way of coping with the situation, namely, she avoided discussing difficult topics. Second, older participants were not familiar with "talking" in a "chat" function. It was sometimes difficult for them to know what to write, and they shared less information. They thought that their daily vexations were not interesting for the other network members.

> Sometimes the questions are too difficult. I'm not such a talker. I keep some things to myself. Sometimes I don't know what I think of things. I just try to be myself. (R14, pwd)

> I'd rather do fun things than answer 'difficult questions'. It's confronting. (R11, ic)

Research Question 3: Participants' Appraisal of the *DecideGuide* for Making Decisions

Four themes emerged from the participants' appraisal of the *DecideGuide* for decision-making: the *DecideGuide* as a supportive tool, short lines in communication, awareness of the steps in decision-making, and improvements for a supportive tool.

The *DecideGuide* as a Supportive Tool

The informal caregivers and case managers reported that the *DecideGuide* helped reach a shared decision, although not all of them used the *DecideGuide* for all steps of shared decision-making, and no decisions were made with the tool. Some issues were not discussed in the *DecideGuide* because the network members needed to see each other more often, particularly when sensitive issues or the situation required a quick decision. They then made the decision without the *DecideGuide*. Nevertheless, they said that the *DecideGuide* had led to extra face-to-face contacts and conversations.

> The tool did not help directly, but it did indirectly because we were concerned with all the elements. We just didn't do it via the tool. Family conversations and the telephone were quicker and better. (R9, ic)
>
> The tool does help in the various decision phases and in moving toward a decision. The decision itself occurs mainly in oral conversation. (R17, ic)
>
> The tool certainly helps with the various parts. Only not all of them. (R19, ic)
>
> The tool did ensure that we got talking to each other – because of the questions. The decision-making took place outside the tool. It speeded up. (R11, ic)
>
> The tool was sometimes used to make decisions and sometimes not. It also happened partially in a conversation. (R7, cm)

Short Lines in Communication

All the respondents appreciated the short, direct communication lines with the network members and the case manager. Their opinion was that the *DecideGuide* improved the communication within the networks and with the case manager and better involved informal caregivers at a distance. Moreover, the network members became more aware of the daily issues of the people with dementia and their spouses.

> It is pleasant to have a direct communication line. It is also handy that other family members can join in. (R13, cm)
>
> It does improve communication and includes parties at a distance. (R8, ic)

Awareness of the Steps in Decision-Making

Using the *DecideGuide* improved informal caregivers' awareness of the steps of decision-making, from clarifying the problem – by exploring options, important values, possible solutions, and discussing the pros and cons – to making a shared decision. It helped them sift things out and to identify the exact issues, it supported them in organizing their thoughts, and it offered them a structured way of making a decision.

> You work in a structured way to get to a decision. (R9, ic)
>
> You think more precisely about what's going on in reference to the questionnaire. The person with dementia has to think about what she wants in order to type it in. Become more aware. Problems are observed by the case manager. (R4, ic)
>
> The DecideGuide did help me think about the questions that were asked. Sometimes that was good. Sometimes not so good (can't think of an example at the moment). You become more aware of yourself. (R14, pwd)
>
> The tool gave me suggestions. The preparatory work went through the tool and the joint decision took place in a conversation at the table. (R11, ic)

In the case managers' opinion, they were overall more aware of the decision-making steps and this awareness helped them, although they did not always record the results of the steps in the *DecideGuide*. Sometimes, network members preferred to talk to others by telephone or face to face.

> In general, the tool works supportively. It helps in the process (the landscape you have to walk through) towards a decision. You do have to be able to reason further yourself. It is remarkable and peculiar that I miss the tool, now that I have not used it for a while. (R13, cm)
>
> The deciding together function with questionnaires is great. Only I have not used the steps and phases well. I do the steps, but not consciously; I don't write them down. (R7, cm)

The questionnaires with examples about dementia-related problems helped informal caregivers map out the options. The case managers were pleasantly surprised at the different opinions that arose from the completed questionnaires and at the conclusions. The answers led to valuable information. People with dementia noted some restrictions. They did not want to expose all their thoughts in the tool. Sometimes they preferred the telephone and sometimes they kept things to themselves.

> Questionnaires provide a lot of information. They open the conversations. As a case manager, you can use them to prepare a talk well. It worked well. You can always get it again because it's in the system. Because of the questionnaires other things and ideas came forward. (R3, cm)
>
> But not your innermost thoughts. Then I phone. (R1, pwd)
>
> But I don't want to talk about everything. Some things you keep to yourself. (R15, pwd)

Improvements for a Supportive Tool

The main point of improvement was in the steps of the *deciding together* function. The network members hardly used this function. Only the questionnaires were used. Network members completed them and sent them off. It was unclear to some network members what happened after the questionnaires were completed and returned to the case manager.

> Handy. Organizes the thoughts (questionnaires). But how to continue? That's left up in the air. What we do after that is not entirely clear. (R19, ic)

Discussion

Summary of Results

In this study, the *DecideGuide*, an interactive web tool to facilitate shared decision-making in care networks of people with dementia, was used and tested in the daily lives of people with dementia, their informal caregivers, and their case managers. We found that

1. The participants thought that the *DecideGuide* was a usable tool in dementia-care practice. The user friendliness of the tool for case managers and younger informal caregivers was acceptable. However, both the navigation and user friendliness need further refinement of the interface for adults older than 70 years and people with dementia.
2. The participants appreciated the *chat* function as an easy way to get or stay in touch with each other. Most of them also liked the questionnaires in the *deciding together* function. The value of the decision-making steps was not clear enough to the participants.
3. The *DecideGuide* had added value for its users regarding decision-making and had a meaningful impact on them: it encouraged participants to communicate more frequently with each other, opened up difficult issues for discussion, took all perspectives into account, and led to more involvement of the other participants in the daily lives of people with dementia. Moreover, it offered a structured path to decisions.

Discussing the Results

The *chat* function was more meaningful than we expected to the users of the *DecideGuide* during the field study. We thought that the *deciding together* function would be the most important one. Nevertheless, our participants said that the chat was easy to use for their mutual communication. They shared more daily items with each other than they had previously. It helped them be more involved in others' daily lives, particularly when participants were living at a distance, and it improved the communication within the networks. Being more involved in the lives of others and sharing more about daily items seems to be a good, valuable, and even indispensable base for making shared decisions during a difficult phase of life: the dementia process. Elwyn et al. (2014) recent study appears to confirm this finding. As decision-making is often seen as a cognitive, individual activity that neglects mutual interaction, Elwyn and colleagues produced a model that emphasizes the importance of the interpersonal aspects in making decisions, which they call collaborative deliberation. The first requirement of this model is the "constructive engagement" of the people concerned in a dialog, the safe zone to be created, exploring the issues, curiosity about each other's views, and respect as a core value. The *chat* function facilitated all of these items; it is important and indispensable as a basis within the dementia-care networks for engaging with each other.

In the context of serious illness, Epstein and Street (2011) concur about the importance of relationships for making decisions, as we see in their concept of the "shared mind." Sharing thoughts, feelings, perceptions, meanings, and intentions creates new perspectives. The *chat* function seems to fit Epstein and Street's concept of the "shared mind" very well.

Our findings show that the *DecideGuide* helps informal caregivers and case managers grasp the wider view of the situation and the decision-making. Specifically, it improves the communication in the network and the structured way of reaching decisions. People with dementia said that the *DecideGuide* improved the communication in the network, but they did not say anything similar about the decision-making, either positively or critically. This surprised us a bit because we expected some critical remarks about the obtrusiveness of the *DecideGuide* with respect to ethical considerations. During the development of the *DecideGuide,* some case managers, informal caregivers, and researchers wondered how people with dementia would feel about the transparency that we had in mind. They were afraid that the tool would be too confronting and obtrusive for them. However, our people with dementia did not complain of this. What they did say was that they did not want to tell others everything and they wanted to keep some things to themselves; but such thoughts were also recognized in the statements of some informal caregivers.

Nevertheless, ethical values can be risked when assistive technology is implemented in the home environments of older people and people with dementia (Zwijsen et al., 2010). Obtrusiveness is a well-known negative characteristic of assistive technologies that influences acceptance, but it is often undefined (Zwijsen et al., 2010). However, older adults, who are the actual users of most assistive devices, show little ethical objection to these devices. Their objection might be overshadowed by their greater fear of living in a nursing home (Zwijsen et al., 2010), and this might have been the case in our study.

Some people with dementia tried very hard to learn to use the tool; they had a strong intrinsic motivation to participate. Such motivation is a key factor for the successful use of the tool and should therefore be cherished. Researchers should focus on how they can help people with dementia use IT tools like the *DecideGuide*. According to Malinowsky et al. (2013), assistance should be tuned to their individual capabilities to understand and use technologies rather than assuming that people with dementia as a group are non-users due to their diagnoses.

Lindqvist et al. (2013) recent study also addresses the importance of individual support for people with dementia to become users of assistive technology. Appropriate support is a prerequisite for encouraging the IT activities of people with dementia. However, the potential user must be able to identify difficulties and needs, and then make changes to overcome them.

Lindqvist et al. (2013) identified four junctures with significant decisions to identify how people with mild dementia could become users of assistive technology: whether to become a user, how routines are to be adjusted to incorporate them into daily life, whether the person with dementia trust the assistive technology, and when the person with dementia feels an increased sense of ability while using the assistive technology.

In our study, two of the four people with dementia and three of the four spouses were enthusiastic and motivated to learn to use an iPad and the *DecideGuide*. They made a decision to become users, according to Lindqvist. Some of them tried very hard to become familiar with the iPad and *DecideGuide*, but most of them, and all our people with dementia stated that use did not become routine during the field study. Moreover, due to technical errors, their initial trust in the *DecideGuide* decreased. This influenced their sense of ability, although they were very proud when they logged in, sent a message, or responded to others. The technical failures that occurred influenced the older participants' attitude toward the use of the *DecideGuide*. Technical failures were mentioned by most of the participants as an important barrier in using IT applications, such as the *DecideGuide*. This is a well-known phenomenon and robustness, absence of technical failures, is therefore an important prerequisite for the image of user-friendly IT applications and their uptake.

Our study initially achieved three of Lindqvist and colleagues' four significant decisions for helping older adults and people with dementia become users of assistive technology. Later on, our study only succeeded in evoking one of the four significant decisions: to become a user. More attention should be paid to the other three decisions: how routines in daily life really can be adjusted, how to promote ongoing trust in the assistive technology, and what increases their sense of ability when people are using the assistive technology.

Limitations and Strengths

This study has some methodological limitations. First, a small and select but diverse sample was involved. Only four of the six care networks that initially consented to participate actually did participate and complete the 5-month field study. Second, the field study started in the summer. This delayed several informal caregivers who were late starting due to holidays. Third, although we tried to achieve diversity in the care networks beyond some diversity in age and gender, all our people with dementia were community dwelling and lived independently with their spouses. There was some diversity in informal caregivers regarding gender and living distance. Nevertheless, the strength of this study lies in its thorough and in-depth approach, the participation of all intended target user groups, the time that was spend to get familiar with the older participants, and the rich data provided by participants and diversity of data collection.

Conclusion

In a 5-month pilot study people with dementia, their informal caregivers, and case managers used the *DecideGuide*. The user friendliness of and navigation in the *DecideGuide* are sufficient for case managers and younger informal caregivers but need to be improved for older adults of 70 + and people with dementia. Moreover, the steps in the *deciding together* function need more explanation for and adjustment to all participants.

Most participants appreciated the *DecideGuide* as a valuable tool in decision-making. The *chat* function was particularly appreciated for its easy and mutual communication and information exchange between network members. This appraisal was better than we expected. The *chat* function seems to be a powerful function that helps participants engage constructively with each other. This engagement is a prerequisite for making shared decisions. The *DecideGuide* helped participants make decisions. Regardless of the participants' thoughts and use of the tool, they saw the added value of the *DecideGuide*: it offers a structured path to shared decisions.

Author Contributions

All authors contributed to the study design. MS supervised the data collection, analysis, and interpretation, and wrote the initial draft of the paper. LG, JJ, RJ, MH, and CS contributed to the data collection, analysis and interpretation of data, and commented critically on the work. CS, MH, MV, and JE critically revised the paper.

Acknowledgments

The Dutch Foundation Innovation Alliance [SIA RAAK (Regional Attention and Knowledge Circulation) PRO], Zorgpalet Hoogeveen (Residential care organization for older adults), and Windesheim University of Applied Sciences funded this study.

References

Alzheimer Europe. (2008). *Alzheimer in Europe Yearbook 2008*. Alzheimer Europe.

Bryman, A. (2008). *Social Research Methods*, 3rd Edn. New York, NY: Oxford University Press.

Corbin, J., and Strauss, A. (1990). Grounded theory research: procedures, canons, and evaluative criteria. *Qual. Sociol.* 13, 3. doi:10.1007/BF00988593

Coyne, I. T. (1997). Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? *J. Adv. Nurs.* 26, 623–630. doi:10.1046/j.1365-2648.1997.t01-25-00999.x

Dupuis, S. L., Gillies, J., Carson, J., and Whyte, C. (2011). Moving beyond patient and client approaches: mobilizing 'authentic partnerships' in dementia care, support and services. *Dementia* 11, 427–452. doi:10.1177/1471301211421063

Dutch Alzheimers's Association, and Vilans. (2013). *Dutch Dementia Care Standard [Zorgstandaard Dementie]*. Available at: http://www.alzheimer-nederland.nl/media/18837/Definitieve%20Zorgstandaard%20Dementie%20september%202013.pdf

Elwyn, G., Edwards, A., and Kinnersley, P. (1999). Shared decision-making in primary care: the neglected second half of the consultation. *Br. J. Gen. Pract.* 49, 477–482.

Elwyn, G., Kreuwel, I., Durand, M. A., Sivell, S., Joseph-Williams, N., Evans, R., et al. (2011). How to develop web-based decision support interventions for patients: a process map. *Patient Educ. Couns.* 82, 260–265. doi:10.1016/j.pec.2010.04.034

Elwyn, G., Laitner, S., Coulter, A., Walker, E., Watson, P., and Thomson, R. (2010). Implementing shared decision making in the NHS. *BMJ* 341, c5146. doi:10.1136/bmj.c5146

Elwyn, G., Lloyd, A., May, C., van der Weijden, T., Stiggelbout, A., Edwards, A., et al. (2014). Collaborative deliberation: a model for patient care. *Patient Educ. Couns.* 97, 158–164. doi:10.1016/j.pec.2014.07.027

Epstein, R. M., and Gramling, R. E. (2013). What is shared in shared decision making? Complex decisions when the evidence is unclear. *Med. Care Res. Rev.* 70(1 Suppl), 94S–112S. doi:10.1177/1077558712459216

Epstein, R. M., and Street, R. L. (2011). Shared mind: communication, decision making, and autonomy in serious illness. *Ann. Fam. Med.* 9, 454–461. doi:10.1370/afm.1301

Hsieh, H. F., and Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qual. Health Res.* 15, 1277–1288. doi:10.1177/1049732305276687

Koch, T., Iliffe, S., Manthorpe, J., Stephens, B., Fox, C., Robinson, L., et al. (2012). The potential of case management for people with dementia: a commentary. *Int. J. Geriatr. Psychiatry* 27, 1305–1314. doi:10.1002/gps.3783

Lindqvist, E., Nygard, L., and Borell, L. (2013). Significant junctures on the way towards becoming a user of assistive technology in Alzheimer's disease. *Scand. J. Occup. Ther.* 20, 386–396. doi:10.3109/11038128.2013.766761

Livingston, G., Leavet, G., Manela, M., Livingston, D., Rait, G., Sampson, E., et al. (2010). Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. *BMJ* 341, c4184. doi:10.1136/bmj.c4184

Malinowsky, C., Nygård, L., and Kottorp, A. (2013). Using a screening tool to evaluate potential use of e-health services for older people with and without cognitive impairment. *Aging Ment. Health* 18, 340–345. doi:10.1080/13607863.2013.832731

Menne, H. L., Tucke, S. S., Whitlatch, C. J., and Feinberg, L. F. (2008). Decision-making involvement scale for individuals with dementia and family caregivers. *Am. J. Alzheimers Dis. Other Dement.* 23, 23–29. doi:10.1177/1533317507308312

Murphy, K., Jordan, F., Hunter, A., Cooney, A., and Casey, D. (2014). Articulating the strategies for maximising the inclusion of people with dementia in qualitative research studies. *Dementia*. doi:10.1177/1471301213512489

Nijland, N. (2011). *Grounding eHealth: towards a holistic framework for sustainable eHealth technologies*. Enschede: University of Twente.

O'Connor, A. M. (0000). *Evaluation Measures*. Available at: http://decisionaid.ohri.ca/eval.html

Peeters, J., de Lange, J., van Asch, I. P. S., Veerbeek, M., Pot, A. M., and Francke, A. (2012). *Landelijke evaluatie van casemanagement dementie*. Utrecht: NIVEL.

Prince, M., Bryce, R., and Ferri, C. (2011). *World Alzheimer Report 2011*. London: Alzheimer's Disease International (ADI). Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2011.pdf

Reamy, A. M., Kim, K., Zarit, S. H., and Whitlatch, C. J. (2011). Understanding discrepancy in perceptions of values: individuals with mild to moderate dementia and their family caregivers. *Gerontologist* 51, 473–483. doi:10.1093/geront/gnr010

Scholl, I., Koelewijn-van Loon, M., Sepucha, K., Elwyn, G., Legare, F., Harter, M., et al. (2011). Measurement of shared decision making – a review of instruments. *Z. Evid. Fortbild. Qual. Gesundhwes.* 105, 313–324. doi:10.1016/j.zefq.2011.04.012

Smebye, K. L., Kirkevold, M., and Engedal, K. (2012). How do persons with dementia participate in decision making related to health and daily care? A multi-case study. *BMC Health Serv. Res.* 12:241. doi:10.1186/1472-6963-12-241

Span, M., Hettinga, M., Smits, C., Groen-van de Ven, L. M., Jukema, J., Vernooij-Dassen, M., et al. (2014). "Developing a Supportive Tool to Facilitate Shared Decision Making in Dementia. Involvement of End Users in the Design Phase," in *Paper presented at the eTELEMED 2014: The Sixth International Conference on eHealth, Telemedicine, and Social Medicine* (Barcelona).

Span, M., Hettinga, M., Vernooij-Dassen, M. J. F. J., Eefsting, J., and Smits, C. (2013). Involving people with dementia in the development of supportive IT applications: a systematic review. *Ageing Res. Rev.* 12, 535–551. doi:10.1016/j.arr.2013.01.002

Span, M., Smits, C., Groen-van de Ven, L. M., Cremers, A., Jukema, J., Vernooij-Dassen, M., et al. (2014a). Towards an interactive web tool that supports shared decision making in dementia: identifying user requirements. *Int. J. Adv. Life Sci.* 6, 338–349.

Span, M., Smits, C., Groen-van de Ven, L. M., Cremers, A., Jukema, J., Vernooij-Dassen, M., et al. (2014b). An interactive web tool to facilitate shared decision making in dementia: design issues perceived by caregivers and patients. *Int. J. Adv. Life Sci.* 6, 107–121.

Stacey, D., Légaré, F., Col, N. F., Bennett, C. L., Barry, M. J., Eden, K. B., et al. (2014). Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst. Rev.* (1): CD001431. doi:10.1002/14651858.CD001431.pub4

Van Gemert-Pijnen, J. E. W. C., Nijland, N., Van Limburg, M. A. H., Kelders, S. M., Brandenburg, B. J., Ossebaard, H. C., et al. (2011). Introducing a holistic framework for eHealth technologies. *J. Med. Internet Res.* 13, e111. doi:10.2196/jmir.1672

von Kutzleben, M., Schmid, W., Halek, M., Holle, B., and Bartholomeyczik, S. (2012). Community-dwelling persons with dementia: what do they need? What do they demand? What do they do? A systematic review on the subjective experiences of persons with dementia. *Aging Ment. Health* 16, 378–390. doi:10.1080/13607863.2011.614594

Wolfs, C. A. G., de Vugt, M. E., Verkaaik, M., Haufe, M., Verkade, P. J., Verhey, F. R. J., et al. (2012). Rational decision-making about treatment and care in dementia: a contradiction in terms? *Patient Educ. Couns.* 87, 43–48. doi:10.1016/j.pec.2011.07.023

Zwijsen, S., Niemeijer, A., and Hertogh, C. (2010). Ethics of using assistive technology in the care for community-dwelling elderly people: an overview of the literature. *Aging Ment. Health* 15, 419–427. doi:10.1080/13607863.2010.543662

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 23 July 2015
doi: 10.3389/fnagi.2015.00141

"Are we ready for robots that care for us?" Attitudes and opinions of older adults toward socially assistive robots

Maribel Pino[1,2]*, *Mélodie Boulay*[1,2], *François Jouen*[3] and *Anne-Sophie Rigaud*[1,2]

[1] Department of Geriatrics, Assistance Publique-Hôpitaux de Paris, Hôpital Broca, Paris, France, [2] Faculté de Médecine, Université Paris Descartes, Paris, France, [3] Laboratoire Cognitions Humaine et Artificielle, Ecole Pratique des Hautes Etudes, Paris, France

Socially Assistive Robots (SAR) may help improve care delivery at home for older adults with cognitive impairment and reduce the burden of informal caregivers. Examining the views of these stakeholders on SAR is fundamental in order to conceive acceptable and useful SAR for dementia care. This study investigated SAR acceptance among three groups of older adults living in the community: persons with Mild Cognitive Impairment, informal caregivers of persons with dementia, and healthy older adults. Different technology acceptance questions related to the robot and user characteristics, potential applications, feelings about technology, ethical issues, and barriers and facilitators for SAR adoption, were addressed in a mixed-method study. Participants ($n = 25$) completed a survey and took part in a focus group ($n = 7$). A functional robot prototype, a multimedia presentation, and some use-case scenarios provided a base for the discussion. Content analysis was carried out based on recorded material from focus groups. Results indicated that an accurate insight of influential factors for SAR acceptance could be gained by combining quantitative and qualitative methods. Participants acknowledged the potential benefits of SAR for supporting care at home for individuals with cognitive impairment. In all the three groups, intention to use SAR was found to be lower for the present time than that anticipated for the future. However, caregivers and persons with MCI had a higher perceived usefulness and intention to use SAR, at the present time, than healthy older adults, confirming that current needs are strongly related to technology acceptance and should influence SAR design. A key theme that emerged in this study was the importance of customizing SAR appearance, services, and social capabilities. Mismatch between needs and solutions offered by the robot, usability factors, and lack of experience with technology, were seen as the most important barriers for SAR adoption.

Keywords: socially assistive robots, technology acceptance, older adults, Mild Cognitive Impairment, dementia

Edited by:
Valeria Manera,
University of Nice Sophia Antipolis, France

Reviewed by:
Roger Bemelmans,
Zuyd University of Applied Sciences, Netherlands
Anna Ozguler,
Raymond Poincaré University Hospital, France

****Correspondence:***
Maribel Pino,
Hôpital Broca, 54-56 rue Pascal, Paris 75013, France
maribel.pino@brc.aphp.fr

Received: *26 February 2015*
Accepted: *06 July 2015*
Published: *23 July 2015*

Citation:
Pino M, Boulay M, Jouen F and Rigaud A-S (2015) "Are we ready for robots that care for us?" Attitudes and opinions of older adults toward socially assistive robots. Front. Aging Neurosci. 7:141. doi: 10.3389/fnagi.2015.00141

Introduction

Increase in life expectancy and population aging has contributed to the rise of the number of elderly individuals living with an age-related disability or a chronic disease. In order to improve health outcomes, quality of life, and control the costs associated with health and social care in this age group, there is growing social and economic pressure to help older adults to live at home for as long as possible (Fujisawa and Colombo, 2009). However, cognitive disability can seriously compromise independent living in old age, particularly when it stems from progressive conditions, such as some forms of Mild Cognitive Impairment (MCI), Alzheimer's disease (AD) and related dementias. Persons with dementia often require a complex care approach combining medical, social and preventive services. With the progression of the disease, the help needed for the execution of daily tasks normally increases, leading to burden of informal caregivers, and in many cases to institutionalization (Alzheimer's Association, 2012). Despite the importance of efforts and policies to improve care delivery at home, living at home until the very end of life remains a promise, not a reality for many persons living with dementia. Dealing with this situation represents a current and future challenge for society that has been increasingly addressed by assistive technology.

Socially Assistive Robots (SAR) are an emerging form of assistive technology encompassing all robotic systems capable of providing assistance to the user by means of social interaction (Feil-Seifer and Mataric, 2005; Broekens et al., 2009; Flandorfer, 2012). SAR can deliver help at different levels (Rich and Sidner, 2009): (a) supporting user's cognitive or functional abilities (e.g., task reminding and monitoring, navigation aids); (b) offering the user opportunities to enhance social participation and psychological well-being (e.g., communication and social applications, telepresence, companionship); (c) providing remote and continuous monitoring of user's health status (e.g., blood pressure or fall detection sensors); and (d) coaching the user to facilitate the promotion of healthy behavior and achievement of health-related goals (e.g., improving nutrition. physical activity).

The therapeutic use of SAR in the context of dementia care has received increasing attention over the last decade as illustrated by a growing body of research in this area (Libin and Cohen-Mansfield, 2004; Robinson et al., 2013; Mordoch et al., 2013; Moyle et al., 2014). Most of these studies have focused on Paro (Shibata and Wada, 2010), a therapeutic animal-like robot modeled on a baby harp seal, mainly employed to encourage social behavior and/or alleviate stress among persons with dementia. In the broader context of mental health interventions, Rabbitt et al. (2015) have recently described a number of roles for SAR, including: a companion (e.g., SAR that work in an analogous way to trained therapy animals), a therapeutic play partner (e.g., SAR used to help children build clinically relevant skills), and a coach or instructor (e.g., SAR provide instruction, encouragement and supervision to users in activities such as weight loss or physical exercise).

SAR cover a wide range of design solutions: *machine-like robots*, which have an unequivocal mechanical and computer-like aspect; *human-like robots*, whose form resembles a human body and/or have human facial features (e.g., eyes, nose, mouth, eyelids, etc.); *androids* or very realistic human-like robots; *mechanical human-like robots* which combine human-like and machine features; *animal-like robots* that simulate animal behavior and morphology; and *mechanical animal-like robots* which combine animal-like and machine features. These categories were defined by DiSalvo et al. (2002), MacDorman and Ishiguro (2006), and Walters et al. (2009). Mobility is another common feature of these systems although it is not mandatory. Locomotion, when available, allows the robot to move around in a particular environment, follow or locate a user or an object either by being operated at distance or autonomously guided.

Studies conducted on SAR acceptance among elderly people have shown that several robot-related variables appear to positively influence technology acceptance and intention to use these systems, for instance: perceived usefulness (e.g., facilitating care delivery, enhancing safety at home) (Arras and Cerqui, 2005; Scopelliti et al., 2005; Boissy et al., 2007); perceived enjoyment (e.g., pleasure associated with its use); robot appearance (e.g., having a small size and friendly aspect); perceived sociability (e.g., robot being caring, empathic, intelligent, exhibiting human-like communication capabilities) (Dautenhahn et al., 2005; Broadbent et al., 2010; Heerink et al., 2010; Wu et al., 2012); perceived adaptivity (e.g., robot being controllable and having a predictable behavior) (Dautenhahn et al., 2005; Scopelliti et al., 2005).

Conversely, other robot-related factors have been identified as having a negative impact on SAR acceptance: lack of trust in the robot (e.g., safety concerns) (Scopelliti et al., 2005); robot conveying a negative representation of prospective users because of a stigmatizing aesthetic (e.g., presupposing the user is isolated, dependent, and/or frail) (Hirsch et al., 2000; Neven, 2010); space requirements for the robot (e.g., important size or mass of the system) (Scopelliti et al., 2005; Young et al., 2009); robot appearance (e.g., reluctance toward humanoid robots) (Arras and Cerqui, 2005; Dautenhahn et al., 2005; Wu et al., 2012); accessibility issues (e.g., technology perceived too complex, high costs) (Young et al., 2009); and ethical concerns (e.g., reduction of social contact, replacement of human presence) (Arras and Cerqui, 2005; Dautenhahn et al., 2005; Harmo et al., 2005; Scopelliti et al., 2005; Sparrow and Sparrow, 2006; Wu et al., 2012). The influence of individual factors such as age, gender, cognitive abilities, education level, technology experience, cultural background, on SAR acceptance has also been addressed in some studies (Scopelliti et al., 2005; Broadbent et al., 2010; Flandorfer, 2012).

Many of these factors have been examined by different Technology Acceptance Models (TAM) developed to explore aspects that contribute, or hinder, the acceptance and use of robot technology. Such is the case of the Unified theory of acceptance and use of technology (UTAUT) model (Venkatesh et al., 2003) applied to the use of home healthcare robots (Alaiad and Zhou, 2014), or the Almere model (Heerink et al., 2010), also based on the UTAUT, suggested to assess the acceptance of assistive social agent technology by older adults. These models are built on the assumption "usage intentions" of the potential consumer regarding a particular technology are strongly correlated with subsequent use. In the field of assistive technology TAM may be valuable for guiding technology design because they allow understanding of variables that influence the acceptance of assistive devices. With this information, designers in the field of SAR may be able to conceive systems that are more likely to be adopted (Beer et al., 2011). **Figure 1** presents determinants of technology acceptance and key moderators included in the two aforementioned models.

Concerning SAR, one of the factors that has been found to influence technology acceptance is the stakeholder category to which the potential user belongs: this means being either a patient, a professional or a person outside the healthcare environment (Broadbent et al., 2010; Alaiad and Zhou, 2014). Indeed, when used within the care context of a condition involving multiple care providers, such as dementia, SAR may serve different purposes depending whether the user is the person with cognitive impairment, a formal or an informal caregiver. Research in this field has shown that needs vary greatly among these stakeholder groups (Orrell et al., 2008; van der Roest et al., 2008). Therefore, it can be expected that specific needs in each stakeholder groups influence how these actors accept and adopt assistive technology (Topo et al., 2007; Topo, 2009). In the same line of ideas, it seems reasonable to expect that the severity of symptoms, or the stage of the disease, influences patients and caregivers' needs, and subsequently the intention to use SAR as any other support service. In this respect, Hawkey et al. (2005) noted that the interests of persons with dementia and those of informal caregivers might compete regarding both, a problematic situation and a potential solution. These authors conducted a needs-assessment study for an assistive technology device designed to store and automatically deliver information to address repetitive questioning in dementia. Results showed that some persons with dementia preferred to be given detailed information regarding un upcoming event a week or two ahead of time, whereas some caregivers preferred to limit the amount of information provided, and shorten the time to give this information, in order to avoid further repetitive questions (e.g., half hour or less before the event). The study confirmed the importance of interviewing both, the caregiver and the person with dementia, to have a good understanding of the impact of assistive technology on the dyad. Information collected from both sides should be useful to define systems requirements and increase its acceptability.

Most studies on SAR conducted in the dementia care context have only focused on one stakeholder group (For a review see Mordoch et al., 2013). Thus, little is known about how the views of persons with cognitive impairment and caregivers converge or diverge regarding the acceptance of SAR. A more comprehensive approach should include both groups' perspectives to better understand technology acceptance and usage intention of SAR in the general context of dementia care. In this study we seek to obtain data that will help to address this research gap.

The aim of this exploratory study was to clarify several aspects related to the acceptance of SAR by older adults. In particular, we were interested in examining if opinions and attitudes toward SAR differed among three groups of older adults living in the community: healthy elderly individuals, persons with MCI, and informal caregivers of persons with dementia. Different technology acceptance questions related to (a) robot features, (b) user characteristics, (c) potential applications, (d) feelings about technology, (e) ethical issues, and (f) facilitating or hindering factors for SAR acceptance, were addressed in a mixed-method study. The role of individual factors on SAR acceptance was examined as well (e.g., age, gender, education, health status, technology experience). Results from this study are expected to contribute to a better understanding of users' needs and system requirements for the development of SAR intended to support older adults with cognitive impairment at home and their informal caregivers.

Materials and Methods

Participants

A total of 25 elderly individuals living in the Paris area (France) were enrolled in this study. Among the participants were 10

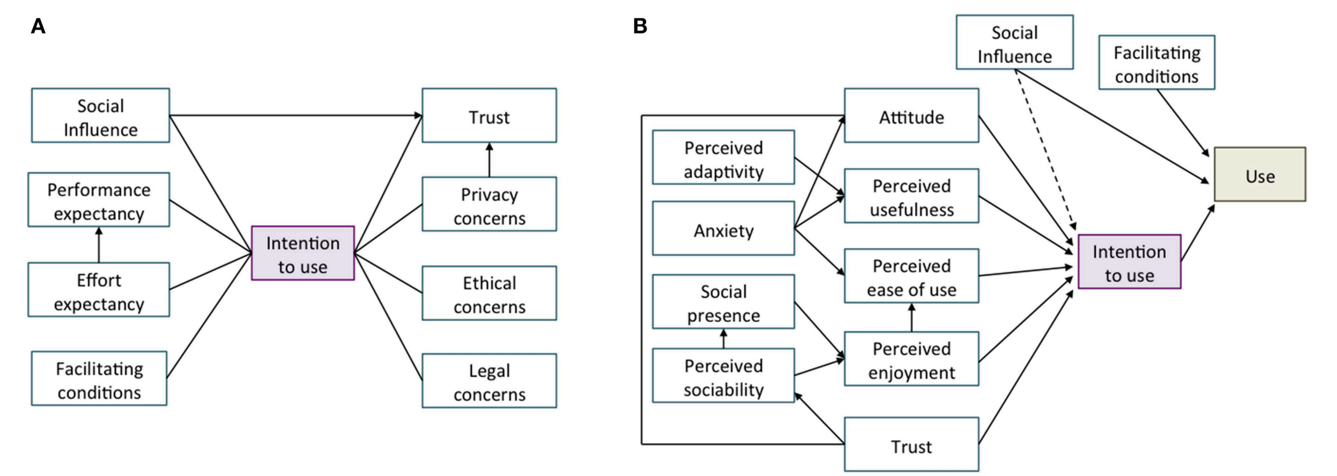

FIGURE 1 | Technology Acceptance Models applied to the context of SAR. (A) Structural model of determinants of home healthcare robots adoption (Alaiad and Zhou, 2014); **(B)** The Almere model for assessing acceptance of assistive social agent technology by older adults (Heerink et al., 2010).

individuals with MCI, seven informal caregivers of persons with dementia, and eight healthy older adults (HOA). The group of HOA was included in order to contrast their opinions with those of participants confronted to cognitive impairment and/or dementia. **Table 1** summarizes characteristics of the sample.

Inclusion criteria for the MCI group were: being 65 years old or older, having received a clinical diagnosis of MCI according to the European Consortium on Alzheimer's Disease Working Group on MCI (Portet et al., 2006), living in the community, and not having any other medical condition or psychiatric disorder severe enough to preclude participation in the study. Cognitive status in this group was evaluated by the Folstein Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and a battery of neuropsychological tests targeting memory, language, visuo-spatial capacities, and problem-solving skills. Persons with MCI also underwent a complete physical and neurological examination, including laboratory tests as well as cerebral imaging.

Inclusion criteria for the group of informal caregivers were: living in the community, being primary caregiver (spouse, adult children, other relative or friend) who cared, at least once a week, for an older adult who had been diagnosed with mild-to-moderate dementia, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria (American Psychiatric Association, 1994). For HOA inclusion criteria were: being 65 years old or older, having a general preserved cognitive functioning, and living in the community. Caregivers and HOA with severe illnesses or psychiatric disorders were also excluded.

TABLE 1 | Summary of the sample characteristics.

Participants	MCI	Caregivers	HOA	All
Number (female, male)	10 f (6), m (4)	7 f (5), m (2)	8 f (6), m (2)	25 f (17), m (8)
Mean age Range	71.5 65–83	68.28 58–81	77.75 69–86	72.6 58–86
Education level (*n*)	Elementary (0) Secondary (6) Higher (4)	Elementary (0) Secondary (1) Higher (6)	Elementary (1) Secondary (3) Higher (4)	Elementary (1) Secondary (10) Higher (14)
Volunteer work (*n*)	Yes (4) No (6)	Yes (4) No (3)	Yes (8)	Yes (16) No (9)
Health-status (0–12) (*SD*)	7.7 (4)	5.82 (1.79)	3.25 (2.37)	5.59 (3.06)
Technology use score (0–15) (*SD*)	10.5 (3.59)	11.28 (3.45)	11.12(3.04)	10.92(3.26)
Attitudes toward new technologies (0–6) (*SD*)	3.3 (1.88)	4.14 (1.67)	4.25(1.28)	3.84 (1.65)

Volunteer work was rated "yes" for older adults who performed regular volunteer work for a church, charity or other community group and "no" for those who did not engage in this kind of activities, all the participants except for one caregiver were retired or had never been employed; Health status, number of health problems (0, excellent; 1–4, good; 5–8, fair; 9–12, poor); Technology use, number of current technologies used (0–5, scare; 6–10, moderate; 11–15, regular); Attitudes toward new technologies is a composite score built from two measurements: interest in new technologies (0–3) and reactions to new technology-related products or services (0–3); SD, Standard Deviation.

Participants in the MCI group and informal caregivers were recruited through the AP-HP Broca Memory Clinic (Paris). HOA were recruited through local senior associations in the Paris region. All participants volunteered for the study. The University Paris Descartes ethical committee approved the study protocol.

Study Design and Data Collection

A mixed-method approach, including a short self-administered questionnaire and a series of focus groups, was used for data collection and analysis. The questionnaire was structured in two sections: Part A covered socio-demographic information including age, gender, education, volunteering status, self-rated health status, use of current technologies, and interest in new technologies. Part B covered a number of domains assessing the global appreciation of SAR: (a) robot's appearance, (b) potential applications, (b) robot social ability, (d) perceived usefulness, and (e) current and future intention to use (See Supplementary Material, Appendix 1). These factors were selected based on constructs included in the Almere model (Heerink et al., 2010) and previous studies on SAR acceptance (Beer et al., 2011; Flandorfer, 2012). Content and usability of the instrument were first tested and refined through a pilot assessment among seven healthcare professionals working in the area of assistive technology for dementia care. Based on their feedback some items and the general structure of the questionnaire were reviewed in order to keep it easy to understand and complete. A booklet containing the pictures and descriptions of different SAR was distributed with the questionnaire as support material (See Supplementary Material, Appendix 2).

Participants were allocated to one of the seven focus groups that were purposefully heterogeneous (i.e., MCI, informal caregivers of persons with dementia, and HOA) (**Table 2**). Focus groups were digitally recorded, fully transcribed and subjected to content analysis using principles described by Strauss and Corbin (1998). Dedoose version 4.3.87 (Dedoose, 2012), a web application for mixed methods research, was used for qualitative data analysis. Data from the questionnaires were analyzed using descriptive and non-parametric statistical techniques and R statistical package version 2.13.2 (R Development Core Team, 2011).

Material

The RobuLAB 10 robot (**Figure 2A**) was used for a live demonstration of the robot. RobuLAB 10 is a mobile platform intended to provide cognitive and social support to older adults. Robot input devices include a voice-based control system and a touch-screen. For high-level control and user interfaces, the robot uses a Tablet PC with a 12.1" Premium WXGA (1280 × 800) display running Windows 7 (Dupourqué, 2009).

Support material for the focus group included a PowerPoint presentation with pictures and public available videos from different SAR projects that were projected during the discussion (**Figure 2**). The presentation covered a range of design solutions for SAR: machine-like, mechanical human-like, human-like, androids, mechanical animal-like, and animal-like. Other material included a video projector, a screen, a computer, and a video camera.

Procedure

Potential participants were contacted by telephone and given information about the purpose and nature of the study. If interested, they were scheduled to participate in a focus group. The day of the meeting, participants read and signed an informed consent form prior to the beginning of the discussion. The meeting began with the introduction of the participants and a summary of the procedures that will be followed. Participants received the booklet with the robots' description and the questionnaire. They were then asked to complete Part A of the survey related to demographic information.

Two trained moderators led the focus groups. One of them made a live demonstration with the RobuLAB 10 and presented the scenarios. The second moderator conducted the discussion, raised questions and kept the conversation on the subject ensuring that all participants expressed their views. Sessions lasted between 1.5 and 2 h. The focus groups had a semi-structured format involving four sections:

(1) *Demonstration of predetermined applications:* The demonstration robot was brought to the room using remote-controlled navigation. General robot's features, such as size, autonomy, weight, and interaction modalities (i.e., touchscreen and voice command), were presented. Seven short use-case scenarios, describing the interactions between a fictional character (Mr A, 81 years old, living alone, memory complaints) and the robot, were presented to illustrate a number of tasks that may nowadays be accomplished by SAR. The presentation did not restrict potential usages of SAR to dementia care in order to avoid excluding HOA to represent themselves as potential users. Participants were invited to give their views on these SAR scenarios:

- *Communication and social support:* using the e-mail or the video-call applications of the robot, Mr A

TABLE 2 | Focus groups composition.

Focus group	*n*	Mean age (range)	Group	Gender composition (female, male)
1	3	72.6 (65–83)	MCI	f (3)
2	3	73 (65–81)	Caregivers	f (3)
3	3	72.66 (65–81)	MCI	f (1), m (2)
4	4	79.25 (69–86)	HOA	f (3), m (1)
5	4	64.75 (58–72)	Caregivers	f (2), m (2)
6	4	76.25 (69–86)	HOA	f (3), m (1)
7	4	69.75 (68–73)	MCI	f (2) m (2)

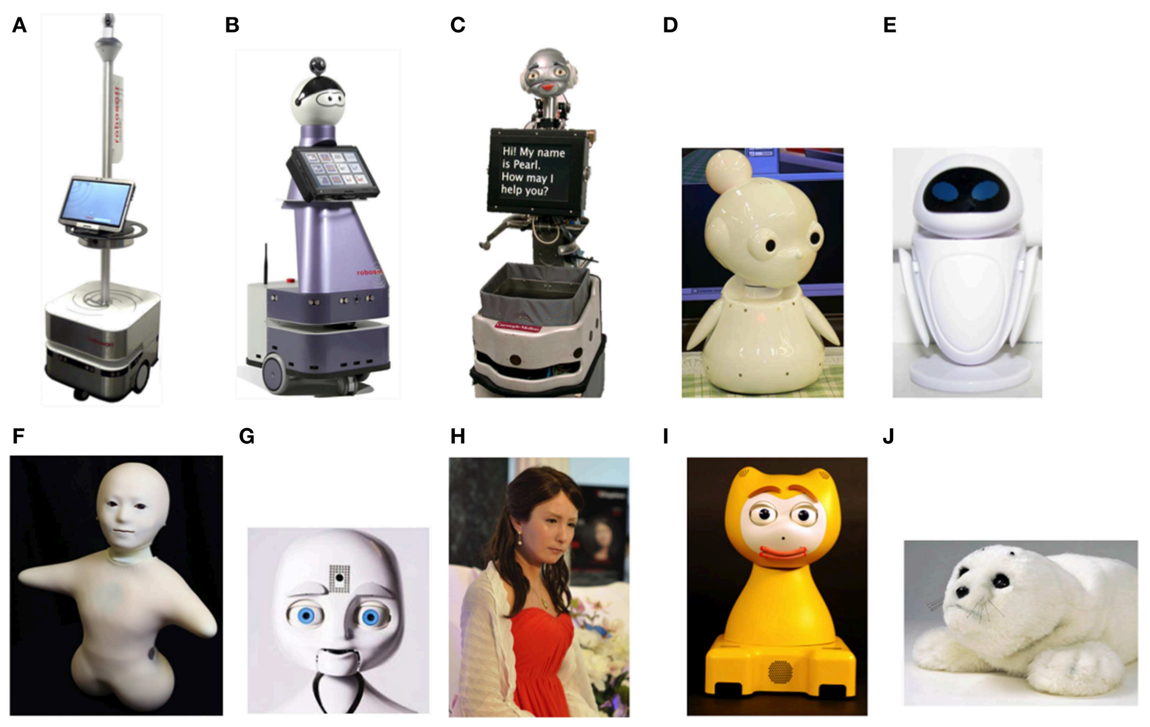

FIGURE 2 | Robots presented in the focus groups and design category. *Machine-like:* **(A)** RobuLAB 10; *Mechanical human-like:* **(B)** Kompaï, **(C)** Pearl, **(D)** Mamoru-kun (little protector), **(E)** Eve (from Wall-E a Pixar film); *Human-like:* **(F)** Telenoïd, **(G)** Nexi; *Android:* **(H)** Geminoid F; *Mechanical animal-like:* **(I)** iCat: *Animal-like:* **(J)** Paro.

can communicate with health professionals, distant caregivers, relatives and friends.

- *Compensate cognitive impairment:* to compensate Mr A's memory problems the robot can look around for him in his home and remind him of specific events (e.g., drug intake, appointments, finding lost items).
- *Affective computing applications:* by using sensors and algorithms, the robot can gather information about Mr A's emotional state. The robot can also exhibit emotional responses to enrich the interaction with the user.
- *Detection of emergency situations:* by using sensors and algorithms, the robot is able to detect emergency situations and alert Mr A's caregiver and/or health professionals (e.g., fall detection).
- *Health monitoring:* by using sensors and algorithms, the robot can monitor and analyse Mr A's physiological signs or behavioral patterns (e.g., sleep patterns, physical activity) alerting healthcare services in the case of atypical activity.
- *Cognitively stimulating and entertainment applications:* the robot includes a number of applications allowing Mr A to take part in stimulating activities alone or in a group (e.g., electronic games, online courses, virtual tourism).
- *Support for daily tasks:* through different applications the robot can assist Mr A with daily activities (e.g., journey planning, weather forecast, online grocery shopping).

(2) *Discussion on potential applications for SAR:* participants were encouraged to give examples of problematic situations they face in their everyday life. Regarding caregivers, challenging situations evoked should involve the person they care for or their caregiver role. People were asked to imagine possible applications of SAR to make it easier to care for themselves, or for a relative in the caregivers group, and in a general way to improve their quality of life.

(3) *Discussion on SAR design:* the moderator gave a brief introduction about different design solutions of SAR. Participants were asked to express their perceptions and opinions for 10 robots, described in Section Material Corresponding pictures and videos were projected on a screen. Other topic brought up in the discussion was the match between a robot's appearance and its functions.

(4) *Discussion on conditions for the adoption of SAR:* in the last part of the meeting, individual, societal and ethical issues that could be considered to facilitate or hinder SAR adoption were addressed. Participants were invited to express anything that they thought was important and that was not discussed throughout the session. Finally, they were asked to complete the Part B of the questionnaire on general appreciation of SAR, including robot's design, perceived usefulness and intention to use.

Results

Questionnaires

Preferences Regarding SAR Design

As far as the general design of the robot was concerned, most participants preferred a mechanical human-like robot integrating some anthropomorphic facial features within a global mechanical-looking design. Mechanical animal-like, animal-like and machine-like robots received a similar percentage of votes. Android robots received only a few votes, and human-like robots did not get any at all (**Figure 3**). Regarding group preferences, participants in the HOA group rated highest the machine-like design, caregivers preferred the mechanical human-like design, and persons with MCI preferred the animal-like design.

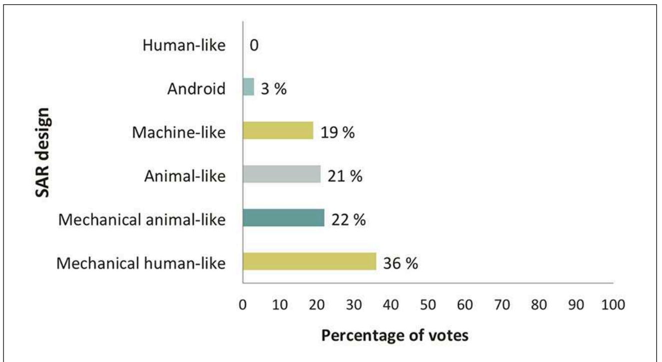

FIGURE 3 | Preferences regarding SAR design.

Overall results showed that the degree of human likeness in the robot design was not considered a fundamental feature. Concerning the facial expressions of the robot, results showed that HOA were little interested in a design with realistic human-like features (0.75/3), while participants in the MCI and caregivers group were moderately interested in this kind of design (1.22/3 and 1.86/3, respectively). The representation of emotional capabilities through facial expressions obtained a moderate score in the MCI and caregivers groups (1.4/3 and 1.5/3, respectively), whereas HOA were less enthusiastic about this aspect (0.86/3).

Services and Functionalities

The most preferred functionalities for SAR, when considering all the participants, were: (a) cognitive support applications to compensate cognitive impairment (e.g., locating lost items, task reminding); (b) communication services to keep an active social life (e.g., video calls, email); (c) risk prevention and healthcare applications (e.g., falls detection, management of critical situations), and (d) applications for supporting everyday tasks (e.g., online grocery shopping, journey planning, simplified Internet access) (**Figure 4**). Other functionalities mentioned were entertainment (e.g., music, poetry, and reading) and information and news applications, for keeping the user up to date with current events (e.g., broadcast news sources). In the group of informal caregivers, it was suggested to develop a "life memory album" available via the robot, to support autobiographic memory in persons with memory loss and encourage communication with caregivers and/or family members. This application could include multimedia material, such as a genealogical tree, pictures and/or videos of significant moments of the life of the person. Regarding differences between groups, HOA rated preferred functionalities for SAR in order of preference: (a) communication and social support,

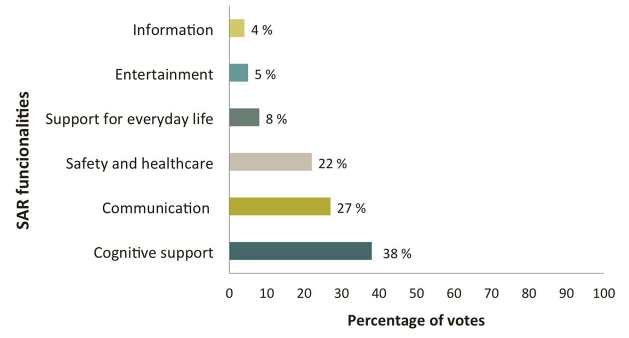

FIGURE 4 | Preferred functionalities for SAR.

(b) entertainment, (c) information. In the caregivers group applications were rated as follows: (a) safety and healthcare for care recipient, (b) compensation for cognitive impairment, (c) communication and social support. Finally, in the MCI group the rating observed was: (a) compensation for cognitive impairment, (b) communication and social support, (c) safety and health care.

Perceived Usefulness and Intention to Use

Concerning the intention to use the robot, results revealed that participants were more ready to use SAR in the future ($M = 1.96$. $SD = 0.88$), than at the present time ($M = 0.84$. $SD = 0.98$). This difference between current and future acceptance scores was observed in all user subgroups regardless of the variable used as a distribution factor (**Figure 5**). A Wilcoxon Signed-ranks test indicated that this difference was significant ($z = -3.08$. $p < 0.002$, two-tailed test).

Participants with MCI and caregivers had a more positive perception of the usefulness of SAR than HOA. Regarding the intention to use the robot, participants in the MCI and caregivers groups were more likely to accept to use the robot at the present time than HOA, although these scores were rather low in all groups, since they did not reach the average score of 1.5 of 3.0 (**Table 3**). Future intention to use was positively rated in all the three groups. However caregivers expressed less interest in using the system in the future compared to participants in the two other groups. A series of Fisher's exact tests were performed to examine the difference between groups regarding perceived usefulness, current and future intention to use, but no statistically significant difference was observed.

With respect to the difference between current and future intention to use SAR, within each group, a series of Wilcoxon signed-rank tests were carried out. This difference was significant in the MCI ($W = -36$, $p < 0.02$, two-tailed test) and the HOA group ($W = -36$, $p < 0.02$, two-tailed test) but not for the caregivers group ($W = -4$, $p > 0.05$, two-tailed test). Some of the arguments given by participants in the different groups to explain their position regarding perceived usefulness and usage intentions for SAR are presented in **Table 4**. Finally, a summary of findings by group for each criterion assessed in the questionnaire is presented in **Table 5**.

Focus Groups

The content of the discussions was transcribed and assigned to the 25 participants, taking into account the individual characteristics as descriptors (e.g., age group, gender, technology experience). An open coding system was used to identify, analyse, and categorize excerpts (i.e., relevant segments of speech) into parent codes (i.e., major themes), then into sub-codes, referring to secondary topics within major themes. Categories were compared with published literature on SAR acceptance (Heerink et al., 2010; Flandorfer, 2012). Two researchers conducted coding and differences were discussed until an agreement was reached. Throughout the coding process six parent-codes and 27 sub-codes were defined. A total of 373 excerpts were extracted from focus groups and assigned at least one of these codes. Parent codes, sub-codes and the number of excerpts and transcripts (i.e., each participant's discourse) associated to each theme are summarized in **Table 6**.

Content Analysis and Individual Factors

Excerpts were coded using parent codes and sub-codes and tagged with relevant individual factors pertaining to each participant (e.g., gender, technology experience). For each specific theme percentages indicate the proportion of relevant occurrences found in a particular group (i.e., MCI, HOA, informal caregivers). Occurrences by group were previously normalized based on the relative number of cases. This section presents some key trends observed in the data and excerpts of verbatim illustrating relevant statements for each theme.

With regard to robot characteristics, personalization was a topic of much discussion (HOA 44.2%, MCI 33.4%, caregivers 22.4%) mainly with respect to the appearance of the robot, its behavior, and the choice of services: *"An interest thing could be to let people put whatever they want as the robot's head and that it has meaning for the person. Customization is important to make the robot more personal"* (MCI, 72 y/o). Customization was also considered a key aspect to make the robot usable by persons with physical disabilities: *"It is important to be able to set the height of the robot. You have to consider that there are tall people, small people, people who are seated, or bedridden"* (MCI, 64 y/o).

Caregivers were more concerned about usability issues (55.5%), including ergonomics, training, and support, than participants with MCI (16%) and HOA (28.5%). In general, most caregivers agreed that SAR involving computer interfaces would be inaccessible for persons with dementia and little technology experience: *"I think persons with dementia will be unable to use the robot. Somebody else would have to do it for him. Otherwise, training must be provided at the first stages of the disease. My husband now has difficulties using the telephone, even if he's used it for over 70 years. How can you expect him to learn to use an appliance that is completely new for him? This is completely utopian"* (Caregiver spouse, 72 y/o).

With respect to the robot form and appearance, strong negative opinions on giving a human appearance to the robot came from HOA (75%). In general, persons in this group considered that a robot was just a machine and should therefore have a machine-like appearance: "*I'm against humanoid robots. If you have a scientific mind, you may ask yourself, what is the*

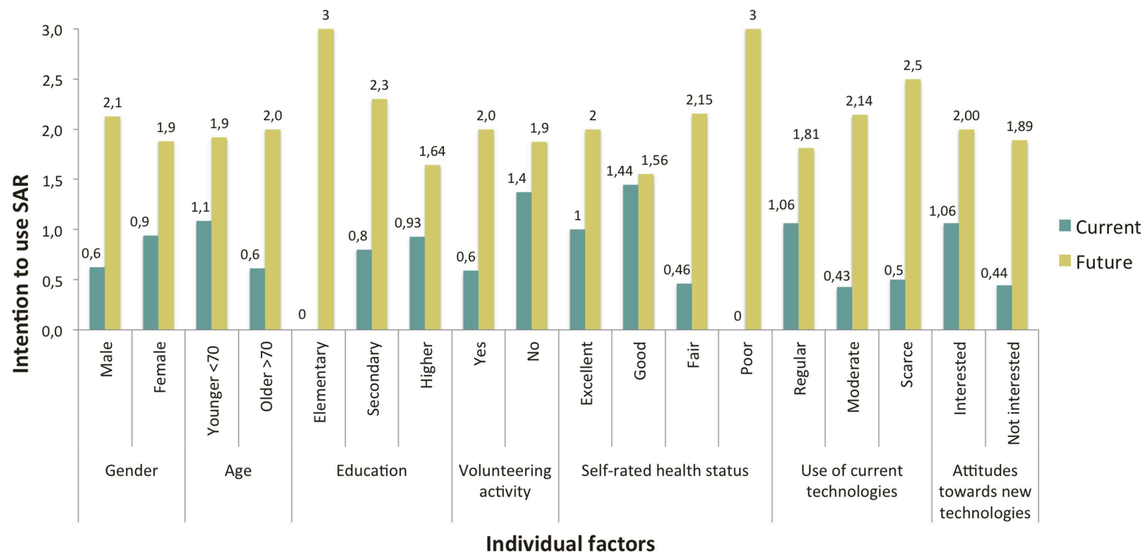

FIGURE 5 | Current and future intention to use SAR analyzed by individual factors.

TABLE 3 | Perceived usefulness, current and future intention to use SAR.

Attitudes toward SAR	MCI (0–3) (*SD*)	Caregivers (0–3) (*SD*)	HOA (0–3) (*SD*)	*F*-test *p*-value
Perceived usefulness	1.9 (1.1)	1.86 (0.9)	1.13 (1.13)	0.41
Current intention to use	1.1 (0.99)	1.29 (1.11)	0.13 (0.33)	0.20
Future intention to use	2.2 (0.63)	1.67 (1.21)	2.13 (0.64)	0.29

purpose of this ventriloquist dummy anyway?" (HOA, 79 y/o). Participants in the MCI and caregivers group had more positive opinions toward human-like robots. In these groups, a robot being capable of human-like communication was welcomed: "*If the robot is going to be part of my life it must be capable of communicating with me, being helpful is not enough*" (MCI, 83 y/o). The use of anthropomorphic forms by robot designers was appreciated to a certain degree, but a too realistic human appearance was considered problematic. For instance, caregivers argued that hyper-realistic representations could lead persons with dementia to confusion. These opinions also reflected the influence of media representations of robots and the field of robotics itself: "*There was this film [Blade runner] in which robots resembled humans so closely that they were confused with them. It was beautiful, but it was terrible at the same time*" (Caregiver children, 81 y/o). Participants in the MCI group claimed that they would have the feeling of being deceived: "*I don't like a humanoid robot because it gives you the illusion of being with someone and in reality you are still alone*" (MCI, 73 y/o).

User's characteristics were a matter of overall concern. Participants in the caregivers and MCI groups considered that user-friendly SAR could be particularly helpful to people with cognitive limitations (43.2 and 37.8%, respectively). These perceptions were in line with their opinions about the potential applications of SAR. Indeed, participants in both groups considered that SAR could provide cognitive support for everyday tasks (caregivers 46%, MCI 36.8%), for instance, helping the user to locate lost items, remind events and memories, or be oriented in time. There was also a positive perception of entertainment applications that could be implemented in the robot. However, a particular concern was raised about the conformity of these activities with the preferences and habits of the potential user: "*You say the robot could offer some electronic games. But you have to recognize that people who are in their eighties now are from a generation that is not used to play. They were taught to work, that's all. It seems difficult to ask people to do something that they have never done in their entire life*" (Caregiver spouse, 79 y/o).

Caregivers globally agreed that SAR could support them in their caregiving duties and alleviate their burden (87.5%). Participants in the HOA considered that SAR would be particularly helpful to support people with physical limitations (73.3%), or sensory impairment (71.4%). These opinions were consistent with the fact that in a general way HOA did not perceived the robot as being useful for themselves at the present time. Potential applications mentioned by HOA were also in agreement with the representation they had of prospective users of SAR (e.g., being frail, disabled, or isolated): "*I've met many young people, who are in their forties or fifties, who would be interested in a robot like this because they are paralyzed. People who have multiple sclerosis would be much more interested in it than an older person who has no experience with technology*" (HOA, f, 79). Most preferred functionalities for SAR in the HOA group were risk prevention and healthcare (55.6%), support for caregivers (55.6%), and communication and social life services (54.4%).

Robotic companionship was considered an interesting feature for participants in the MCI group (39.5%) followed by caregivers

TABLE 4 | Factors explaining usage intention for SAR among groups.

MCI	Caregivers	HOA
ARGUMENTS FOR		
Provides global support *"It will take care of my needs"* *"It could be like a personal assistant"* **Provides companionship** *"It will be an amusing companion"* *"I will not feel lonely"* **Supports independent living** *"It will delay my entry into a retirement home"* *"It will allow me to continue to do my errands if I can not leave my home"* **Supports social life** *"It will help me to have social contact outside of my home"* **Supports safety at home** *"It will ensure my domestic security"*	**Provides global support** *"It can help the patient and his/her entourage"* **Supports social life** *"It could help my wife to have social contact outside of my home"* *"I'm really interested in having a robot like this because I think it could influence our relationship (with the care-recipient) in a positive way"* **Supports safety at home and alleviate caregiver's stress** *"The robot would contribute to alleviate my stress, when my husband will not longer be able to stay alone at home and I have to go out"*	**Provides cognitive stimulation** *"The robot could allow me to exercise my brain"* **Useful for other people** *"A robot may be useful for disabled people"* *"I'd have loved that my mother, who had dementia, had it"* *"Perhaps, in the future I will be needing some help"* *"When I'll be older, it could allow me to maintain my autonomy for as long as possible"*
ARGUMENTS AGAINST		
Negative effect on autonomy *"I believe the use of the robot will restrict my autonomy"* **Size of the robot** *"It could interest me after reducing its size"* **Privacy concerns** *"The idea of surveillance does not appeal to me"* **Fear of robots replacing humans** *"With robots like those, pretty soon real people won't be needed anymore. Robots will take the place of teachers, of everyone"*	**Suitability for persons with dementia** *"It seems difficult to adopt it because my relative is seriously affected by dementia"* *"This robot will be difficult to adopt because my relative does not have the capacity to adapt to new things"* *"At the current state of my wife's illness, we are not yet concerned"* **Negative attitudes toward technology** *"This type of robot will be a total stranger for my relative"* *"My relative is hostile to this type of technology"*	**Generational gap** *"This robot addresses a younger generation that is more familiar with new technologies"* **Perceived usefulness** *"Not useful to me because I am too young"* *"Not useful to me because I am still active"* **Superfluous** *"I already have a computer which gives me access to the same services"* **Difficulty to project oneself into the future** *"I prefer to avoid the question. I am afraid of what is coming next [in life]"* *"It is difficult to know in which state I will be in in the future, to estimate its usefulness"*

TABLE 5 | Summary of findings by group.

Criteria	MCI	Caregivers	HOA
Preferred design	Animal-like design	Mechanical human-like design	Machine-like design
Interest in human-likeness of robot's design	Moderate	Moderate	Low
Representation of emotional capabilities through SAR expressions	Moderate	Moderate	Low
Preferred applications	1) Compensate cognitive impairment 2) Communication and social support 3) Safety and health care	1) Safety and healthcare for care recipient 2) Compensate cognitive impairment 3) Communication and social support	1) Communication and social support 2) Entertainment 3) Information/ news
Perceived usefulness	Moderate	Moderate	Low
Current intention to use	Low	Low	Very low
Future intention to use	Moderate-High	Moderate	Moderate-high

(32.3%). Nevertheless, it must be specified that his idea was found attractive as long as the primary goal of SAR was not to replace human contact: *"For some people it can be more pleasant to be with a robot than to be alone. It would also allow the caregiver to have some time away from the patient. But its use should not be generalized. For a person that still has a social life, seeing a human face is better than looking at a screen"* (Caregiver spouse, 65 y/o). Persons with MCI tended to perceive a robot companion as a distraction, a confidant, and a company for lonely people: *"This robot could be like a friend. The person wouldn't have the impression of being completely alone…24 hours it's a long time when you're alone"* (MCI, 73 y/o). Participants in the HOA group who agreed on the interest of the robotic companionship function (28.2%) estimated that it could be helpful for isolated people or for those with depression, but they saw no benefit of this feature for themselves.

Participants in all groups discussed ethical issues associated to the use of SAR. Also, independently from the group to which they

TABLE 6 | Factors explaining SAR acceptance among groups.

Parent code	Excerpts *n* = 373	Transcripts *n* = 25	Sub-codes
Robot characteristics	159	25	Robot design Usability issues and accessibility Customization/ personalization Interaction modalities/ robot control methods
User characteristics	83	21	Cognitive and physical limitations Preferences and habits Technology experience Social and psychological needs
Potential applications	132	25	Cognitive support Communication and social life Robotic companionship Entertainment Risk prevention and healthcare Support for caregivers
Feelings about technology	199	25	Negative appreciation Positive appreciation Perceived usefulness Influence of media representations of robots
Ethical issues	68	20	Privacy Dignity Autonomy Vulnerability Risk of social isolation Fear of robots replacing humans
Facilitating conditions	15	18	Costs of the service Need of a supportive environment Promotion of intergenerational relationships

belong, those who reported a higher perceived usefulness of SAR, or being ready to adopt a robot at the present time, discussed ethical aspects to a greater extent (37.5 and 41.8%, respectively) than participants who reported no perceived usefulness (26%) or current intention to use a robot (24.4%). However, only participants in the MCI group expressed their concern about the stigmatization that could result from the use of SAR: "*Some work has to be done if you don't want people to think that if they are given a robot it's because they are not worth a human company. People should think that the robot is there to help. There must be a way to present it in a positive way*" (MCI, 70 y/o).

MCI participants were more sensitive to privacy issues (56%) than caregivers (16%) and HOA (28%). A common view in the MCI group was that surveillance applications could be a threat to their privacy: *"We can not accept to use a robot for surveillance purposes. It is awful to that to someone who has been free and independent during all his life. Human freedom is a wonderful thing, and we must keep it during our whole life"* (MCI, 68 y/o). Nevertheless, individuals with MCI did express their interest in services that could contribute to their safety (49.1%), as long as these services did not involve video data gathering, for instance fall detectors and emergency call systems. Caregivers had a more positive perception of these risk-prevention applications for their potential to improve safety at home: *"It may be intrusive but, at the same time, integrating a security camera in the robot could be useful. My mother is alone at home during the night. If there was a camera, I could check from time to time if everything is OK. Between privacy and safety, it is not better to give priority to safety?"* (Caregiver children, 58 y/o).

Concerns about dignity were mainly pointed out by HOA participants (47.9%). These apprehensions were mostly associated to the appearance of the robot, particularly to the use of human or animal-like robots: *"It is quite worrying. We're giving elderly people machine companions. It is undoubtedly much better to have human companionship. Perhaps in some cases there is not choice, and that's sad"* (Caregiver spouse, 65 y/o). Participants who expressed their concerns about infantilizing elderly people with SAR also indicated no perceived usefulness of SAR (70.2%), and no current (67.1%) or future intention (83.6%) to use them. A feeling of mistrust toward some applications of the robot was reported, especially among caregivers (44.4%) and participants with MCI (36.2%). These apprehensions were related to the following aspects: the effectiveness of the robot, the replacement of human caregivers by robots, and unemployment that could result from it, data confidentiality, and safe use of the system. Finally, of particular concern among participants with MCI and caregivers was SAR costs being prohibitively high (46.8 and 38.7%, respectively), factor that could hinder their acquisition.

Discussion

This study investigated SAR acceptance among three groups of older adults living in the community: healthy older adults, persons with Mild Cognitive Impairment, and caregivers of persons living with dementia. In this section, findings are discussed with respect to the main factors that were identified as having an influence on SAR acceptance, in particular those associated to group characteristics.

Personalization: Being Able to Adapt SAR to Users' Needs, Preferences, and Capabilities

One of the key themes that emerged in this study was the influence of personalization on SAR acceptance. Personalization may concern the general design of the robot (e.g., appearance, voice, gender), its behavior, the services it offers, or its social capabilities. These findings further support the idea of "customization needs," which has been previously addressed in the literature on assistive robotics for elderly people. For instance, Meng and Lee (2006) emphasized that considering the heterogeneity of older people, a successful robot design must give priority to the user's preferences and the accurate understanding of individual needs, technological issues being of secondary importance. Sharkey and Sharkey (2010) in their study on ethical issues and robot care in old age, also concluded that customization would be the best way to develop robots that contribute to the well-being of users without restricting their individual rights. Findings from our study revealed as well that a wide range of heterogeneous needs should be taken into consideration when designing SAR to be used in the context of dementia care. Based on the opinions gathered in this study this need for personalization may be analyzed at two levels:

(1) *Group-related interests:* each participant in this study belonged to a group sharing a role (e.g., being caregiver of a person with dementia), a health-status (e.g., experiencing memory loss, being in good health), or similar self-representations (e.g., being an independent and active person). The demand for personalized services partly responded to the search for solutions that meet the needs resulting from a particular circumstance: caring for a dependent person, experiencing cognitive decline, having some physical limitations, or feeling isolated. Consequently, there was a rather large heterogeneity among the three groups regarding the services expected from a robot.

Participants in the caregivers and MCI groups sought to identify solutions that could help them deal with the daily problems they faced. Participants with MCI focused on cognitive and functional support services intended to improve their autonomy. These findings are consistent with those of Gross et al. (2011) on how persons with MCI had a positive view on SAR functions related to cognitive support in daily life (e.g., cognitive stimulation, items locator, event reminder). For their part, caregivers expressed their interest in applications that could contribute to improve the living environment of persons with dementia (e.g., safety at home) and make it easier to care for them (e.g., cognitive support). Therefore, they perceived the robot as a tool for stimulating and supporting the person they cared for, as an extra assistant, or a potential mediator between them and their loved ones.

Our findings are in line with previous studies that have investigated needs of informal caregivers of persons with dementia that may be met by assistive technology (Topo, 2009). These needs include: improving safety at home, reducing caregiver's stress and burden, having access to stimulating and meaningful activities adapted to people with dementia, dealing with social withdrawal and apathy of care recipients. However, it is worth noting that in our study the severity of dementia symptoms appeared to be a modulating factor for the acceptance of SAR among informal caregivers. In accordance with the present results, Frennert et al. (2013) observed that some caregivers considered that SAR could be useful for other older people but not for their relative, who would not be cognitively able to use a robot.

Finally, participants in the HOA group did not ask for personalization of SAR, basically because they did not identify themselves as potential users of these systems. Even if in our presentation we did not put the accent on the use of SAR for supporting older persons with cognitive or physical impairment, HOA who took part in this study naturally considered that SAR should target isolated frail elderly or disabled people rather than healthy active people. These results confirm findings from previous studies in which healthy elderly persons have expressed their unwillingness to imagine having an assistive robot (Neven, 2010; Wu et al., 2012; Frennert et al., 2013). HOA considered priority services for a robot those that could meet the needs of people with various disabilities (e.g., compensation for disabilities, health monitoring, aid for mobility) and personalization requirements, when expressed, were formulated in this direction.

There are similarities between opinions of HOA in our research and those described by Neven (2010) in his study about the representations that elderly people and robot designers have of prospective users of SAR. This author found that for some older adults who took part in his research, having or needing a robot was a signifier of old age, loneliness, and physical and/or cognitive deterioration. Furthermore, he analyzed how these individuals dissociated themselves from the representation they had of prospective SAR users by presenting themselves as healthy, active, and independent persons, who were helping the "others" by taking part in research. It is possible that in our study, negative representations that HOA had of prospective users of SAR would have also led them to distance themselves from the group of potential users.

The identity-signaling approach to divergence proposed by Berger and Heath (2008) may prove helpful to interpret this finding. This approach claims that one of the reasons why people diverge from others, for example with regard to cultural tastes or practices, is to make sure that their identity is correctly recognized and avoid misidentification (e.g., being associated to low-status or disliked others). If we acknowledge that SAR convey a symbolic meaning, it is important to examine the connotations related to their use. In our study, the meanings that HOA attributed to prospective users of SAR were rather negative. It is therefore understandable that they have firmly avoided to be considered part of this group.

The analysis of ageism conducted by Nelson (2005), suggesting that for some persons, having a negative perception of elderly people is a way of denying the self-threatening aspects associated with old age (e.g., becoming frail, dependent, isolated) and reducing the anxiety associated with the idea of aging, offers an alternative interpretation for our findings. Within the field of SAR, Frennert et al. (2013) discussed how the refusal observed among older adults to imagine having an assistive robot at home could be explained, in a similar way, to their reluctance to accept physical and cognitive changes related to aging.

(2) *Individual preferences and self-representations:* Most participants agreed on the importance of being able to configure the robot according to their preferences to make it more personal. The need for personalization primarily concerned the robot appearance, its name, gender, personality, voice, interaction modalities, and the choice of services. Although most participants felt that physical attributes of the robot were a secondary aspect with respect to functionality, the frequency with which robot appearance

issues were raised allowed us to conclude that physicality might have a strong influence on SAR acceptance.

In our study, some robot designs caused rejection because they were associated with negative representations of aging or unethical care practices (e.g., stigmatization, deceptiveness). These findings confirmed that ethical issues described by Sharkey and Sharkey (2010), and Sparrow and Sparrow (2006), such as the risk of infantilization (i.e., disempowering effect associated with the conception of elderly with dementia reverting back to childhood) and deception (i.e., being induced to believe that robots are something that they are not) are issues of concern for older adults. On the contrary, several participants argued that appearance could have a positive influence on robot acceptance if it conveys pleasure, competence, and friendliness. Most of these positive features were related to the social capabilities of the robot and will be discussed later.

Results from this study suggests that it is important to allow potential users to customize robot's appearance because negative judgments about its design may affect compliance and be a reason for technology rejection. On the contrary, a "positive design" could improve technology acceptance, attachment to the system, and make the integration of the robot into the home environment easier. In this sense we could expect positive effects of personalization of SAR similar to those observed for mobile phones (Blom and Monk, 2003; Cui et al., 2007; Ho and Lee, 2011), PCs, or domestic vacuuming robots (Sung et al., 2009). In this respect, Broadbent et al. (2009) have pointed out that allowing the user to personalize the robot would help not only to accommodate individual differences but also to give users a sense of autonomy and control over the robot. Finally, it seems surprising that TAM in the field of SAR have not given enough attention to the influence of robot appearance on the acceptance and use of SAR. Research in this area should explore if robot design could be considered as a determinant of SAR acceptance.

Beyond Appearance and Functionality, Usage Intention Is Linked to Robot's Social Ability

Caregivers and participants with MCI agreed about the fact that the robot should not only be useful, but also pleasant and fun to use. These findings are consistent with those of Heerink et al. (2010) who observed that there was a strong correlation between "perceived enjoyment" and "intention to use" when assessing interactive robots among elderly users. In the same line of reasoning, Young et al. (2009) indicated that satisfying users' need for fun and entertainment increased the acceptance of SAR.

However, as pointed out by Heerink et al. (2006) one of the challenges of SAR design is to reach a balance between functionality, resulting from the technical configuration, and enjoyment, supported by the physical and "psychological" attributes of the robot (e.g., appearance, voice, social capabilities, personality). These authors have suggested that SAR acceptance combines both, a practical and a social dimension. The first refers to the perceived usefulness of the system, and the second to the willingness of end-users to engage in a social interaction with a robot. Indeed, potential users of SAR need to have a clear understanding of the practical gains that result from the use of these systems. The way perceived usefulness influences intention to use a technology, and subsequently, predicts its use, has been validated by different Technology Acceptance Models (Venkatesh et al., 2003).

The social dimension of technology acceptance is a complex factor since it involves several aspects that go beyond utility and design. In the present study, most participants in the MCI and caregivers group had a positive view of the social capabilities of the robot. Participants who were interested in robotic companionship also considered that some robot's features (e.g., human-like voice, subtle anthropomorphic traits, having a caring and empathic personality) could facilitate social human-robot interaction. These findings are in line with the view of Young et al. (2009) of successful domestic robotic interfaces as being somewhere in between a mechanical and a human-like appearance.

The higher perceived usefulness of robot social features (e.g., facial expressions) observed in the caregivers and MCI groups, compared to that observed in the HOA group, could be explained as follows. Caregivers are daily confronted with cognitive and psychological symptoms of dementia, such as apathy, social withdrawal, gradual loss of verbal communication abilities, or depressed mood. Therefore, it is understandable that they consider SAR as a potential tool to stimulate the person they cared for. In this scenario the robot social features would be a positive attribute. Also, we should consider that the highest acceptance of robotic companionship observed in our study was in the group of persons with MCI. Again, it seems plausible that for these individuals the social features of the robot were perceived as positive contributors to human-robot interaction.

Intention to Use and Level of Insight about SAR Possibilities

Participants in all three groups reported a higher intention to use the robot in the future than at the present time. This trend was less evident among caregivers, because they took in consideration the decline of cognitive and functional capacities observed over time in persons with dementia. Consequently, they believed that the use of a robot would no longer be possible in the most advanced stages of the disease.

People who felt more concerned by the need of support services, specifically caregivers and persons with MCI, seemed more disposed to discuss practical issues related to the use of the robot, for example, the costs of the service or the need of training and support to use the robot. This is understandable since these individuals had a more pronounced intention to use the system in the present time than HOA. In accordance, they could more easily project themselves acquiring it.

Finally one of the most striking results to emerge from the data was the significant difference observed between current and future intention to use SAR in the MCI and HOA groups. It would seem that these individuals, even those who considered themselves healthy and independent in the present time, were influenced by ageist conceptions and accordingly anticipated a future-self that corresponded to those stereotypes (e.g., being lonely, ill, dependent, or disabled) (Nelson, 2005; McGuire et al., 2008). However, reasons behind these results should be better addressed in future studies.

Methodological Considerations

The diversity and richness of the opinions expressed by participants in this study suggest that mixed-method approaches are particularly well suited to explore potential users' attitudes toward SAR (Dautenhahn, 2007). Questionnaires and focus groups appeared to be complementary approaches. The first one allows the identification of general trends in technology acceptance and the definition of users' profiles whereas the second one is useful to explore more in-depth views. However, combining these two methods poses the question of time and effort required to conduct simultaneously qualitative and quantitative research in terms of sampling and data analysis.

The use of multiple support materials for introducing SAR to participants was effective and could be of general interest for future studies in the field (e.g., live demonstrations, pictures, videos, scenarios). Proof of this is the fact that all participants actively discussed the scenarios for SAR that were provided and developed their own scenarios based on their own experiences. However, preferences regarding robot design and appearance were elicited using exclusively visual material from existing robots. Participants were not given the opportunity to suggest their own design solutions. Including a graphic designer or an artist to sketch the basic outline of ideas suggested by participants in a focus group might be a great brainstorming technique for addressing design issues in this kind of studies. Another drawback of this study is that there was no direct interaction between participants and SAR. Considering that research in the field has shown that familiarity with technology influence users' attitudes toward these systems and increases technology adoption (Young et al., 2009), conducting technology acceptance studies over several sessions and encouraging direct interaction between participants and SAR appears to be an interesting option to study the dynamics of technology acceptance including sequential patterns and attitudes change (Wu et al., 2014).

Some methodological issues limit the findings of this study. First, there is the small size of the sample. A small sample size reduces both, the chance of detecting true effects and the likelihood that a statistically significant result reflects a true effect (Button et al., 2013). For this reason, results from the inferential statistical analyses in this study may have a low predictive value and therefore, should be interpreted with caution. Small sample size also limited the possibility of studying the interaction between individual factors (e.g., education level) and SAR acceptance. Nevertheless, using a small number of subjects appeared to be appropriated to test the hypothesis of different attitudes toward SAR among stakeholder groups and lay the groundwork for future studies in this area.

Some considerations should also be given to the sampling method employed. This study involved exclusively people from the Paris region whose needs and views on SAR may not reflect the perspectives and needs of older people living in different environments (e.g., isolated and rural areas, deprived contexts). Another weakness of this study is that persons with a clinical diagnosis of dementia, one of the prospective primary-users of SAR, were not included in the sample. Although this choice was made to facilitate recruitment and participation in the focus groups, we could have considered adapting user-research methods for involving people with moderate or severe cognitive impairment in the study.

Finally, we summarize here some strategies which may counter some of the problems discussed above that may be useful for future studies on this area: (a) involving a number of participants in each relevant stakeholder group large enough to guarantee the representativeness of the sample and allowing the study of individual factors related SAR acceptance, for instance, performing an a priori power calculation to calculate sample size; (b) better implicating prospective users in SAR design, including persons with dementia, for instance, by organizing co-design workshops; (c) organizing technology acceptance studies over several weeks or months to allow familiarization of participants with SAR, which might show different and more robust behavioral trends.

Conclusions

It is expected that the field of SAR for dementia care will continue to develop. Still, despite the growing interest in robotics in this context, a specific model of robot acceptance has yet to be developed. This study confirmed that ensuring the design of acceptable and efficient SAR is a complex endeavor. The development of SAR for dementia care requires both, recognizing the needs, expectations and preferences of a range of stakeholders, and better understanding the influence of individual and social factors on technology acceptance. There is no SAR configuration that fits all scenarios. An implication of this is the demand for customizable and highly flexible systems.

Results so far have been encouraging in the sense that they showed that elderly people concerned by cognitive impairment recognize the potential of SAR for supporting health and social care at home. It is true that the current state of the research on SAR does not allow us to conclude that older adults are ready for robots that care for them, but the idea is no longer unimaginable. Nevertheless, many challenges must still be addressed before SAR can be proven reliable, useful, effective, and desirable enough to be introduced as home care assistants.

Author Contributions

MP and MB contributed to the conception and design of the study, data acquisition, analysis and interpretation. MP drafted the article, MB, AR and FJ participated in revising it critically and gave final approval of the version submitted. An earlier version of this study was presented as an oral communication at the Alzheimer's Association 2013 International Conference (AAIC, 2013), Boston (USA) 13-18 July 2013 (Pino et al., 2013).

Acknowledgments

We thank the French ≪ Fond Interministériel de Soutien aux Projets de Recherche et Développement Collaboratifs des

Poles de Compétitivé≫ (FUI9) for funding the PRAMAD (Plateforme Robotique d'Assistance pour le Maintien à Domicile) project. We also thank Romain Lardin and Laila Kamali who contributed to data transcription. Photo credits: "Robulab" and "Kompaï," courtesy of Vincent Duporqué (Robosoft, FR); "Pearl" Ken Andreyo (Digital and Creative Services, Carnegie Mellon Institute, USA); "Mamoru-Kun" (Tokio University, JP), courtesy of Philoo (robotblog.fr); "Eve," Wall-E ® (2008) Pixar Animation Studies film, (Milu, 2009) under creative commons license; "Telenoid" and "Geminoid F," courtesy of Pr. Hiroshi Ishiguro (Osaka University and Hiroshi Ishiguro Laboratories, Advanced Telecommunications Research Institute International, JP); "iCat" (Philips, NL), courtesy of Christoph Bartneck (Canterbury University, HIT Lab, NZ); "Nexi" (Personal Robots Group, M.I.T. Media Lab, USA), "Paro" (AIST, JP), courtesy of Cédric MAIZIERES (Inno3Med, FR).

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2015.00141

References

Alaiad, A., and Zhou, L. (2014). The determinants of home healthcare robots adoption: an empirical investigation. *Int. J. Med. Inform*. 83, 825–840. doi: 10.1016/j.ijmedinf.2014.07.003

Alzheimer's Association. (2012). Alzheimer's disease facts and figures. *Alzheimers Dement*. 8, 131–168. doi: 10.1016/j.jalz.2012.02.001

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders. 4th Edn.* Washington, DC: American Psychiatric Association.

Arras, K. O., and Cerqui, D. (2005). *Do We Want to Share Our Lives and Bodies with Robots? A 2000-People Survey.* Technical Report 0605-001. Autonomous Systems Lab (ASL), Lausanne: Swiss Federal Institute of Technology Lausanne.

Beer, J. B., Prakash, A., Mitzner, T. L., and Rogers, W. (2011). *Understanding Robot Acceptance.* Technical Report HFA-TR-1103. Atlanta, GA. Georgia Institute of Technology

Berger, J., and Heath, C. (2008). Who drives divergence? Identity signaling, outgroup dissimilarity, and the abandonment of cultural tastes. *J. Pers. Soc. Psychol*. 95, 593–607. doi: 10.1037/0022-3514.95.3.593

Blom, J. O., and Monk, A. F. (2003). Theory of personalization of appearance: why users personalize their PCs and mobile phones. *J. Hum. Comput. Int*. 18, 193–228. doi: 10.1207/S15327051HCI1803_1

Boissy, P., Corriveau, H., Michaud, F., Labonté, D., and Royer, M.-P. (2007). A qualitative study of in-home robotic telepresence for home care of community-living elderly subjects. *J. Telemed. Telecare*. 13, 79–84. doi: 10.1258/135763307780096195

Broadbent, E., Stafford, R., and MacDonald, B. (2009). Acceptance of healthcare robots for the older population: review and future directions. *Int. J. Soc. Robot*. 1, 319–330. doi: 10.1007/s12369-009-0030-6

Broadbent, E., Kuo, I. H., Lee, Y. I., Rabindran, J., Kerse, N., Stafford, R., et al. (2010). Attitudes and reactions to a healthcare robot. *Telemed. e-Health* 16, 608–613. doi: 10.1089/tmj.2009.0171

Broekens, J., Heerink, M., and Rosendal, H. (2009). Assistive social robots in elderly care: a review. *Gerontechnology* 8, 94–103. doi: 10.4017/gt.2009.08.02.002.00

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., et al. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci.* 14, 365–376. doi: 10.1038/nrn3475

Cui, Y., Chipchase, J., and Ichikawa, F. (2007). A cross culture study on phone carrying and physical personalization. *Usability and Internationalization. HCI Culture LNCS* 4559, 483–492. doi: 10.1007/978-3-540-73287-7_57

Dautenhahn, K., Woods, S., Kaouri, C., Walters, M., Koay, K. L., and Werry, I. (2005). "What is a robot companion—friend. assistant or butler?," in *Proceedings: International Conference on Intelligent Robots and Systems (IROS 2005)* (Edmonton. AB: IEEE Press), 1488–1493.

Dautenhahn, K. (2007). Methodology and themes of human-robot interaction: a growing research field. *Int. J. Adv. Robot. Syst.* 4, 103–108. doi: 10.5772/5702

Dedoose. (2012). *Web Application for Managing, Analyzing, and Presenting Qualitative and Mixed Method Data*. Los Angeles, CA: Socio Cultural Research Consultants; LLC.

DiSalvo, C. F., Gemperle, F., Forlizzi, J., and Kiesler, S. (2002). "All robots are not created equal: the design and perception of humanoid robot heads," in *Proceedings 4th Conference on Designing Interactive Systems: Processes, Practices, Methods, and Techniques* (London).

Dupourqué, V. (2009). RobuLAB 10, a service robot designed to Aging-in-Place. *Gerontechnology* 8, 183. doi: 10.4017/gt.2009.08.03.009.00

Feil-Seifer, D., and Mataric, M. J. (2005). "Defining socially assistive robotics," in *Proceedings of the 2005 IEEE 9th International Conference on Rehabilitation Robotics* (Chicago, IL).

Flandorfer, P. (2012). Population ageing and socially assistive robots for elderly persons: the importance of sociodemographic factors for user acceptance. *Int. J. Populat. Res*. 2012, 1–13. doi: 10.1155/2012/829835

Folstein, M., Folstein, S. E., and McHugh, P. R. (1975). "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Frennert, S., Eftring, H., and Östlund, B. (2013). What older people expect of robots: a mixed methods approach. *Soc. Rob. LNCS* 8239, 19–29. doi: 10.1007/978-3-319-02675-6_3

Fujisawa, R., and Colombo, F. (2009). The long-term care workforce: overview and strategies to adapt supply to a growing demand. *OECD Health Working Papers. No. 44. OECD Publishing*.

Gross, H. M., Schroeter, C., Mueller, S., Volkhardt, M., Einhorn, E., Bley, A., Langner, T., et al. (2011). "I'll keep an eye on you: home robot companion for elderly people with cognitive impairment," in *Proceedings: 2011 IEEE International Conference on Systems, Man, Cybernetics (SMC)* (Anchorage, AK).

Harmo, P., Taipalus, T., Knuuttila, J., Vallet, J., and Halme, A. (2005). "Needs and solutions-home automation and service robots for the elderly and disabled," *Proceedings: 2005 IEEE/RSJ International Conference on Intelligent Robots and Systems* (Edmonton, AB).

Hawkey, K., Inkpen, K. M., Rockwood, K., McAllister, M., and Slonim, J. (2005). "Requirements Gathering with Alzheimer's Patients and Caregivers," in *Proceedings of the 7th International ACM SIGACCESS Conference on Computers and Accessibility* (Baltimore, MD).

Heerink, M., Kröse, B., Evers, V., and Wielinga, B. (2010). Assessing acceptance of assistive social agent technology by older adults: the almere model. *Int. J. Soc. Robot*. 2, 361–375. doi: 10.1007/s12369-010-0068-5

Heerink, M., Kröse, B. J. A., Evers, V., and Wielinga, B. J. (2006). Studying the acceptance of a robotic agent by elderly users. *Int. J. Assist. Robot. Mechatronics* 7, 33–43.

Hirsch, T., Forlizzi, J., Hyder, E., Goetz, J., Kurtz, C., and Stroback, J. (2000). "The ELDer project: social, emotional, and environmental factors in the design of eldercare technologies," in *Proceedings on the 2000 Conference on Universal Usability* (Arlington, VA).

Ho, J., and Lee, C. S. (2011). Factors underlying personalisation adoption: case of mobile telephony. *IJSTM* 15, 281–297. doi: 10.1504/IJSTM.2011.040380

Libin, A., and Cohen-Mansfield, J. (2004). Therapeutic robocat for nursing home residents with dementia: preliminary inquiry. *Am. J. Alzheimers Dis. Other Demen*. 19, 111–116. doi: 10.1177/153331750401900209

MacDorman, K. F., and Ishiguro, H. (2006). The uncanny advantage of using androids in cognitive and social science research. *Interact. Stud*. 7, 297–337. doi: 10.1075/is.7.3.03mac

McGuire, S. L., Klein, D. A., and Chen, S.-L. (2008). Ageism revisited: a study measuring ageism in East Tennessee, USA. *Nurs. Health Sci.* 10, 11–16. doi: 10.1111/j.1442-2018.2007.00336.x

Meng, Q., and Lee, M. H. (2006). Design issues for assistive robotics for the elderly. *Adv. Eng. Inform.* 20, 171–186. doi: 10.1016/j.aei.2005.10.003

Mordoch, E., Osterreicher, A., Guse, L., Roger, K., and Thompson, G. (2013). Use of social commitment robots in the care of elderly people with dementia: a literature review. *Maturitas* 74, 14–20. doi: 10.1016/j.maturitas.2012.10.015

Moyle, W., Jones, C., Cooke, M., O'Dwyer, S., Sung, B., and Drummond, S. (2014). Connecting the person with dementia and family: a feasibility study of a telepresence robot. *BMC Geriatrics*. 14:7. doi: 10.1186/1471-2318-14-7

Nelson, T. D. (2005). Ageism: prejudice against our feared future self. *J. Soc. Issues* 61, 207–221. doi: 10.1111/j.1540-4560.2005.00402.x

Neven, L. (2010). 'But obviously not for me': robots, laboratories and the defiant identity of elder test users. *Soc. Health Ill.* 32, 335–347. doi: 10.1111/j.1467-9566.2009.01218.x

Orrell, M., Hancock, G. A., Liyanage, K. C., Woods, B., Challis, D., and Hoe, J. (2008). The needs of people with dementia in care homes: the perspectives of users, staff and family caregivers. *Int. Psychogeriatr.* 20, 941–951. doi: 10.1017/S1041610208007266

Portet, F., Ousset, P. J., Visser, P. J., Frisoni, G. B., Nobili, F., Scheltens, P., et al. (2006). Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. *J. Neurol. Neurosurg. Psychiatry* 77, 714–718. doi: 10.1136/jnnp.2005.085332

Pino, M., Boulay, M., and Rigaud, A.-S. (2013). Acceptance of social assistive robots to support older adults with cognitive impairment and their caregivers. *Alzheimers Dement.* 9, P342. doi: 10.1016/j.jalz.2013.04.205

R Development Core Team. (2011). *R: A Language and Environment for Statistical Computing.* Vienna: R Foundation for Statistical Computing. Available online at: http://www.r-project.org/

Rabbitt, S. M., Kazdin, A. E., and Scassellati, B. (2015). Integrating socially assistive robotics into mental healthcare interventions: applications and recommendations for expanded use. *Clin. Psychol. Rev.* 35, 35–46. doi: 10.1016/j.cpr.2014.07.001

Rich, C., and Sidner, C. L. (2009). Robots and avatars as hosts, advisors, companions, and jesters. *AI Magazine* 30, 29–41 (Accessed, October 12 2013).

Robinson, H., MacDonald, B. A., Kerse, N., and Broadbent, E. (2013). Suitability of healthcare robots for a dementia unit and suggested improvements. *JAMDA* 14, 34–40. doi: 10.1016/j.jamda.2012.09.006

Scopelliti, M., Giuliani, M. V., and Fornara, F. (2005). Robots in a domestic setting: a psychological approach. *UAIS* 4, 146–155. doi: 10.1007/s10209-005-0118-1

Sharkey, A., and Sharkey, N. (2010). Granny and the robots: ethical issues in robot care for the elderly. *Ethics Inform. Technol.* 14, 27–40. doi: 10.1007/s10676-010-9234-6

Shibata, T., and Wada, K. (2010). Robot therapy: a new approach for mental healthcare of the elderly-a mini-review. *Gerontology* 57, 378–386. doi: 10.1159/000319015

Sparrow, R., and Sparrow, L. (2006). In the hands of machines? The future of aged care. *Minds Machines* 16, 141–161. doi: 10.1007/s11023-006-9030-6

Strauss, A., and Corbin, J. M. (1998). *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory, 2nd Edn.* Thousand Oaks, CA: SAGE Publications.

Sung, J. Y., Grinter, R. E., and Christensen, H. I. (2009). "Pimp my Roomba: designing for personalization," in *Proceedings of the 27th International Conference on Human Factors in Computing Systems* (Boston, MA).

Topo, P., Saarikalle, K., Begley, E., Cahill, S., Holthe, T., and Macijauskiene, J. (2007). "I don't know about the past or the future, but today it's Friday"—Evaluation of a time aid for people with dementia. *Technol. Disabil.* 19, 121–131.

Topo, P. (2009). Technology studies to meet the needs of people with dementia and their caregivers: a literature review. *J. Appl. Gerontol.* 28, 5–37. doi: 10.1177/0733464808324019

van der Roest, H. G., Meiland, F. J., van Hout, H. P., Jonker, C., and Droes, R. M. (2008). Validity and reliability of the Dutch version of the Camberwell assessment of need for the elderly in community-dwelling people with dementia. *Int. Psychogeriatr.* 20, 1273–1290. doi: 10.1017/S1041610208007400

Venkatesh, V., Morris, M. G., Davis, G. B., and Davis, F. D. (2003). User acceptance of information technology: toward a unified view. *MIS Q.* 27, 425–478. doi: 10.2307/30036540

Walters, M. L., Koay, K. L., Syrdal, D. S., Dautenhahn, K., and Te Boekhorst, R. (2009). "Preferences and perceptions of robot appearance and embodiment in human-robot interaction trials," in *Proceedings: Symposium at the AISB09 Convention* (Edinburgh).

Wu, Y.-H., Fassert, C., and Rigaud, A.-S. (2012). Designing robots for the elderly: appearance issue and beyond. *Arch. Gerontol. Geriat.* 54, 121–126. doi: 10.1016/j.archger.2011.02.003

Wu, Y.-H., Wrobel, J., Cornuet, M., Kerhervé, H., Damnée, S., and Rigaud, A.-S. (2014). Acceptance of an assistive robot in older adults: a mixed-method study of human-robot interaction over a 1-month period in the Living Lab setting. *Clin. Interv. Aging* 9, 801–811. doi: 10.2147/CIA.S56435

Young, J. E., Hawkins, R., Sharlin, E., and Igarashi, T. (2009). Toward acceptable domestic robots: applying insights from social psychology. *Int. J. Soc. Robot.* 1, 95–108. doi: 10.1007/s12369-008-0006-y

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.