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31.05.2011, 18.00 CET

Please make sure that the number of pages prepared by you for each section corresponds to the maximum number indicated in brackets. Proposals exceeding the given limits will not be accepted!
Size of characters: 12 pt, Times New Roman

Project title: Virtual Environments as an early diagnostic and prevention tool for Alzheimer disease

Project acronym: VREDPAD

Name/institution of project coordinator:

Names/ institutions of other project partners:

A GENERAL INFORMATION

A1. Summary ***(max. 1 page)***
Summarise the objectives, give a short description of the research activities and expected results of the project.

Scientific and clinical research in the area of Alzheimer's disease (AD) during the last years have shifted their focus to earlier diagnosis and especially to the transitional phase between normal aging and dementia, named Mild Cognitive Impairment (MCI). Lately, the concept of MCI has been expanded to address observed clinical heterogeneity, and subtypes were recognized: amnesic (including memory impairment) and non-amnesic (including impairment in other non-memory cognitive domains), with the later including deficits in executive functioning Executive functions (EF) are defined as higher order functions that are needed for completing complex or non-routine tasks. Deficits in EF refer to a collection of deficits in attention, planning, problem-solving, multitasking, monitoring and behavioral control and persons who suffer from impairments in EF typically have difficulty in initiating or suspending activities, show impaired mental flexibility, as well as increased distractibility and have difficulty in learning novel tasks despite apparently intact cognitive abilities.

Lately, an increasing amount of studies suggest that persons with MCI might have deficits in EF, moreover, persons presenting a combination of executive deficits and memory deficits were found to be a high risk group for conversion to AD.

Procedures using VR are ideally placed to answer the need for ecologically valid tools for use in the functional assessment of memory impairments. Although behavioral experiments using real world environments provide useful data, it is often not feasible to test patients outside the clinic; computer-based VR tasks can provide a bridge between conventional neuropsychological tests and behavioral observation. One compelling strength of VR tests is that they can be constructed to simulate the demands of everyday life, which commonly require, for example, the ability to remember and initiate responses to more than one task (e.g., multitasking). Further, in everyday life there is typically no external agent (analogous to the tester) to elicit the appropriate response. Consequently, patients need to be able to recognize for themselves salient events or cues in the environment, and act accordingly, an important aspect of EF tasks. To simulate this, computers can be used to provide an interactive environment with prompts and cues for action that are administered independently of the tester.

Given the latest findings regarding EF and MCI, the aim of the current study is to examine the validity of virtual reality as a cognitive rehabilitation or decline prevention method by means of fMRI and Neuropsychological Assessment for the assessment of patients with MCI. More specifically, the objectives of the present study are:

(1) to assess the feasibility of virtual reality as a cognitive rehabilitation or decline prevention method by means of fMRI and Neuropsychological Assessment for the improvement of EF in MCI;

(2) to compare between the performance of patients with MCI and healthy matched controls in the virtual reality by means of Neuropsychological Assessment and fMRI, and

(3) to assess the relative importance of virtual reality by means of Neuropsychological Assessment and fMRI measures for the differentiation of the groups.

A2. Background and research objectives (max. 3 pages)
Give a detailed justification of the objectives of the project against the state-of-the art in the scientific area of the project:

Purpose:

The aim of the study is to investigate the feasibility of using a virtual environment as an assessment and intervention tool for overcoming deficits in executive function as well as enhancing IADL performance among persons with Mild Cognitive Impairment. The working hypotheses are that there will be improvement in executive functions, and the improvement in the executive functions will result in better performance in Instrumental Activities of Daily Living, both generally and especially in a fire evacuation task.

Key Words: *Alzheimer's disease, mild cognitive impairment, plasticity, functional magnetic resonance imaging.*

Detailed Description:

The dramatic increase in the number of persons with dementia expected in the next decades is accompanied by efforts to identify methods that will allow an easy and practical detection of the disease in its early stages and of MCI. Consequently, many computerized systems for cognitive assessment in the elderly are being developed and validated. However, although initially memory impairment was the focus of the diagnosis and research in MCI, lately the interest has concentrated on EF and on finding ecologically valid and easy-to-administer tools for the assessment and diagnosis of MCI.

The virtual reality tool might, therefore, provide an additional tool to improve the early diagnosis of MCI while avoiding the difficulties of neuropsychological tests. The rationale guiding the present study was the accumulation of knowledge about the relationship between EF and MCI and the need to find a valid and non-threatening way of diagnosing MCI.

The first steps in exploring the usefulness of constructing VEs for use in the assessment and rehabilitation of persons with EF deficits have been taken, and shown to hold considerable promise. Creating an artificial world through computer technology has a number of advantages for the measurement of a complex ability such as EF, as it allows a patient to be observed completing a practical memory task, administered in a standardized and ecologically valid manner.

There are two potential objectives for future research and development of measures of PM using VR in clinical practice. The first is to develop a standardized assessment procedure. For this to happen it would be necessary to establish the psychometric credibility of a test procedure in a systematic manner, that is, to show it met conventional standards of reliability and validity. As Uttl (2008) has observed, many researchers have ignored the psychometric characteristics of their methods, and consequently procedures of unknown reliability, difficulty levels, and discriminatory power have been compared and contrasted, adding to the difficulty of reconciling inconsistent findings. Of primary importance is evidence that the VR tests accurately predict real world PM abilities, and that scores are stable and internally consistent. Consideration of the attributes of a 'gold standard' for PM, which could be used as a criterion against which the sensitivity and specificity of a VR test might be measured, would help in defining the meaning of the construct.

The second objective concerns the use of VEs in training PM skills. It is commonly a

significant rehabilitation goal to teach patients specific memory skills and to make them aware of the boundaries of their competence. Building VEs in which they can learn to do this safely and repeatedly, without physical fatigue, has been shown to be feasible and useful. Once again, to achieve widespread acceptance of virtual reality in rehabilitation it will be necessary to demonstrate that performance in the virtual world validly mirrors performance in the actual world. Then research will be needed to show that rehearsal of skills in a VE leads to changes in behavior, and that these transfer and generalize to increased competence outside the clinic.

In constructing VR applications, it is important to bear in mind that uptake amongst clinicians will depend on constructing portable and inexpensive computer-based platforms. Although it is possible to create ever more sophisticated immersive environments, the gains in the reality of the simulated presentation need to be balanced against the gains in clinical utility, and the costs of those gains. Indeed complex immersive environments are likely to be bewildering for some patients — for example, older adults with cognitive impairments — and no more effective than cheaper and more portable 2-D di-plays. In the long term the marketplace will decide whether VR procedures have a substantial place in the practice of clinical neuropsychology. The widespread dissemination of computer games shows that VR applications can have wide appeal if they are portable, relatively cheap, and easy to set up and use. Although measures using VEs can bridge the gap between tests developed in the laboratory and behavioural experiments in the real world, they currently have limits in their applicability in clinical practice. Difficulty adapting programs to specific rehabilitation needs, problems with technical issues, and the reluctance of many clinicians to engage in the use of computer-based technology need to be overcome before widespread use of VR will become an actuality.

Functional MRI (fMRI) is a valuable method for use by clinical investigators to study task-related brain activation in patients with neurological or neuropsychiatric illness. Despite the relative infancy of the field, the rapid adoption of this functional neuroimaging technology has resulted from, among other factors, its ready availability, its relatively high spatial and temporal resolution, and its safety as a noninvasive imaging tool that enables multiple repeated scans over the course of a longitudinal study, and thus may lend itself well as a measure in clinical drug trials. Investigators have used fMRI to identify abnormal functional brain activity during task performance in a variety of patient populations, including those with neurodegenerative, demyelinating, cerebrovascular, and other neurological disorders that highlight the potential utility of fMRI in both basic and clinical spheres of research. In addition, fMRI studies reveal processes related to neuroplasticity, including compensatory hyperactivation, which may be a universally-occurring, adaptive neural response to insult. Functional MRI is being used to study the modulatory effects of genetic risk factors for neurological disease on brain activation; it is being applied to differential diagnosis, as a predictive biomarker of disease course, and as a means to identify neural correlates of neurotherapeutic interventions. Technological advances are rapidly occurring that should provide new applications for fMRI, including improved spatial resolution, which promises to reveal novel insights into the function of fine-scale neural circuitry of the human brain in health and disease.

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Eligibility

Ages Eligible for Study:	60 Years to 90 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

- Age 60+
- Diagnosed as suffering from MCI
- No impaired judgement
- Normal or corrected-to-normal vision and hearing ability
- Independent in ADL function
- Lives in the community

Exclusion Criteria:

- Suffering from other coexistent neurological diseases (e.g. stroke, muscular dystrophy)
- Has acute arthritis
- Poorly controlled hypothyroidism
- Suffering from physical or sensory limitations, as by self-report or noted by the investigator, that may limit the use of a computer
- Defined as suffering from depression as determined by the rating scale for depression
- Diagnosed as suffering from dementia as defined by Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV)

A3. Project Description (max. 10 pages)
Give an overall description of the research project and justify the methodology chosen to reach the objectives.

1. INTRODUCTION

VEs (Virtual Environments) are particularly suited to the assessment and rehabilitation of EF because of the ease with which a standardized procedure can be constructed that tests the dynamic coordination of multiple cognitive abilities. Further, in clinical practice, such an assessment or rehabilitation is most use-fully constructed using a real world task. As Brooks et al. (2004) have observed: 'The probable reason for the paucity of executive function and memory assessment material is that it is difficult to devise a comprehensive assessment that does not require testing in real-life situations with all the logistic problems that entails. Such an assessment would be impossible in a rehabilitation unit but can be devised using virtual reality' (p. 392). Any comprehensive examination of a patient's ability to complete an everyday EF task requires the assessment of a range of cognitive abilities, including both memory and nonmemory skills. In what follows, we briefly review the research methodology that focuses on the use of fMRI to assess the processes implicated in assessing the performance of VEs, and especially consider those studies that have directly focused on EFs in persons with dementia or related neurodegenerative brain impairments.

Whether or not there is a discrete, macroscopically visible structural lesion, many neurological disorders are characterized by abnormal brain function. The neurologist frequently relies on behaviorally observable abnormalities during the performance of a task in the clinical evaluation of patients. Although a number of diagnostic testing modalities provide information on resting brain function, including electroencephalography, positron emission tomography (PET), and single photon emission computed tomography, there are relatively few tools available to probe regional brain activity during task performance. One of the most readily available tools at present is functional MRI (fMRI).

For approximately the past decade, fMRI has undergone rapid growth in its use as a technique to study functional brain abnormalities in patients with neurological diseases. The use of fMRI in studies of patients with neurodegenerative diseases illustrates a number of applications of this technology. Beyond traditionally recognized neurodegenerative diseases, studies in neurodevelopmental disorders (such as autism[1]) and in neuropsychiatric disorders (such as schizophrenia[2] or individuals at genetic risk for schizophrenia[3]) have also begun to provide fundamental insights into the neural processing abnormalities that characterize these disorders. Functional MRI has also revealed novel observations in investigations of stroke and other cerebrovascular diseases, multiple sclerosis, head injury, and other neurological disorders. Ultimately, fMRI may prove to be useful as an imaging biomarker for use in the development of neurotherapeutic interventions for many of these disorders.[4]

2. fMRI: ADVANTAGES AND DISADVANTAGES

Because the functional neuroimaging tools assess inherently dynamic processes that may change during short-time intervals in relation to a host of factors, these measures have unique characteristics that may offer both strengths and weaknesses as potential biomarkers of neurological disease. Functional neuroimaging measures may be affected by transient brain and body states at the time of imaging, such as arousal, attention, sleep deprivation, sensory processing of irrelevant stimuli, or the effects of substances with pharmacological CNS activity. Imaging measures of brain function may also be more sensitive than structural measures to constitutional or chronic differences between individuals, such as genetics, intelligence or educational level, learning, mood, or medication use. Although these may be effects of interest in certain experimental settings, they need to be controlled when the focus is on disease-related changes and differences between subject groups or within individuals followed over a period of time.

Among functional neuroimaging techniques, fMRI has many potential advantages in studying neurological patients, because it is a noninvasive imaging technique that does not require the injection of contrast agent. This technique can be repeated many times during the course of a longitudinal study; therefore, it has potential as a measuring tool for use in clinical drug trials. It has relatively high spatial and temporal resolution, and the use of event-related designs enables the hemodynamic correlates of specific behavioral events to be measured.[5]

However, there are significant challenges to performing fMRI studies in neurologically impaired patients. This technique is particularly sensitive to even small amounts of head motion. Differences in task performance between patient and control groups complicate data interpretation.[6] Finally, it is critical to complete further reliability experiments if fMRI is to be used in longitudinal or pharmacological studies. Although there are now a few studies of fMRI test-retest reliability in young subjects,[7-9] reproducibility studies are only beginning to be performed in neurological patients.

3. CLINICAL APPLICATIONS OF fMRI IN NEURODEGENERATIVE DISEASES

Functional MRI has been applied in a number of ways in studies of patients with neurodegenerative diseases, and many of these applications are illustrative of how this technology can be applied to other neurological disorders. Given the growing body of evidence that alterations in synaptic function are present very early in the pathophysiological process of AD and related disorders, possibly long before the development of clinical symptoms and even significant neuropathology,[10–12] fMRI may be particularly useful in detecting alterations in brain function that may be present very early in the course of AD or related dementias. The fMRI is already beginning to reveal novel insights into functional abnormalities in particular brain regions in MCI, which in many cases is the earliest clinical phase of AD prior to dementia.

Functional MRI has been used to investigate abnormalities in patterns of regional brain activation during a variety of cognitive tasks in patients diagnosed with mild AD compared to control subjects. It is important to keep in mind that the particular abnormalities found in an fMRI study of an AD or other patient group are heavily dependent on the type of behavioral task used in the study; if the task does not engage a particular circuit, functional abnormalities will not likely be observed (see FIG. 1). Moreover, even brain regions not usually thought to be affected by AD (sensorimotor areas) have been shown to exhibit abnormal function in AD patients. [13,14]

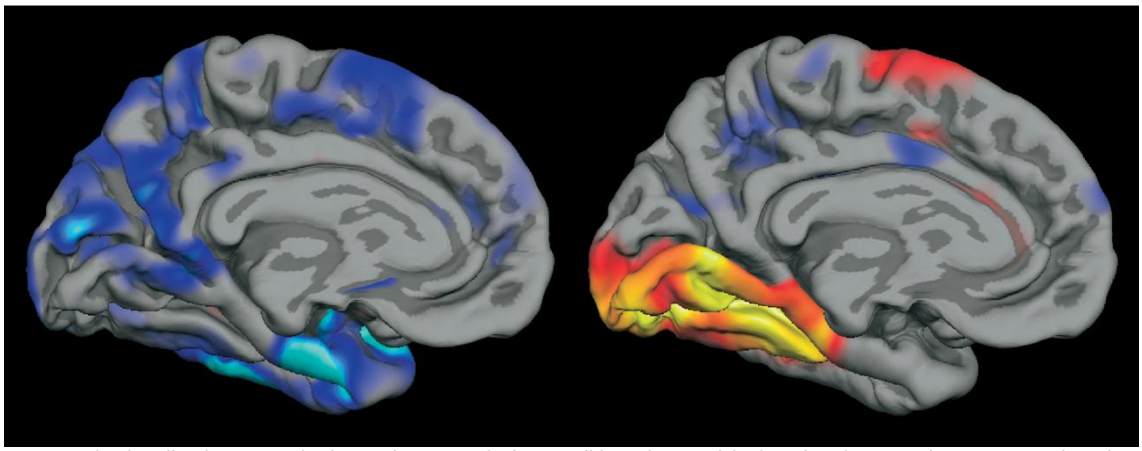

FIG. 1. The localization, magnitude, and extent of abnormalities observed in functional magnetic resonance imaging (fMRI) studies of patients with neurological diseases depend on both localization and severity of pathology and on functional networks engaged by the particular fMRI task, as well as participant performance on the task. In this illustration, regions of cortical thinning in Alzheimer's disease from structural MRI (left) are compared with cortical areas activated, as measured with fMRI, in normals during an event-related study of successful learning of new information that was later able to be freely recalled (right).

In addition to memory, aspects of language and attention have been studied in AD patients using fMRI. Altered patterns of frontal and temporal activation have been observed in AD patients performing language tasks.[15–17] Similarly, although temporoparietal activation was found to be diminished in AD during performance of semantic memory task, increased activation in temporal and frontal regions was also observed, suggesting possible compensatory processes.[18] During performance of a visual attention task, AD patients were found to have abnormal parietal activation; increased prefrontal activation was also observed compared with controls, again suggesting possible compensatory mechanisms.[19]

With respect to memory, a number of fMRI studies in patients with clinically diagnosed AD, using a variety of visual stimuli, have identified decreased activation in hippocampal and parahippocampal regions compared to control subjects during episodic encoding tasks.[20–25] Neocortical abnormalities in AD have also been demonstrated using fMRI, including decreased activation in temporal and prefrontal regions.[22] In addition to ADrelated differences in task-related blood-oxygen level dependent (BOLD) signal amplitude or spatial extent, the temporal dynamics of activation appear to be altered in patients with AD.[26] Interestingly, as has been observed in other types of tasks, increased activation in prefrontal and other regions has also been found in AD patients performing memory tasks.[23]

Whereas memory task-related fMRI data regarding medial temporal lobe (MTL) activation in individuals with MCI are less consistent than data from patients diagnosed with AD, with reports of both decreased and increased activation,[24,20,27] they do indicate that differences are present in comparison to older controls. Some of the variability in fMRI data in MTL activation appears to relate to degree of impairment along the spectrum of MCI, which suggests that fMRI may be sensitive to relatively subtle clinical differences in disease severity.[27]

Recent data suggest that there is a phase of increased MTL activation in MCI (see FIG. 2) that may represent an attempted compensatory response to AD neuropathology, given that greater activation is associated with better memory performance, as well as smaller hippocampal volume.[25,27–29] The use of event-related fMRI paradigms[30] may help determine whether increased activation in MCI patients is specifically associated with successful memory, as opposed to a general effect that is present regardless of success (possibly indicating increased effort). For example, the results of a recent Fmri study using an event-related paradigm suggest that MTL hyperactivation in MCI is specifically seen during the encoding of new material that is later successfully recognized, supporting the compensatory hypothesis.[31]

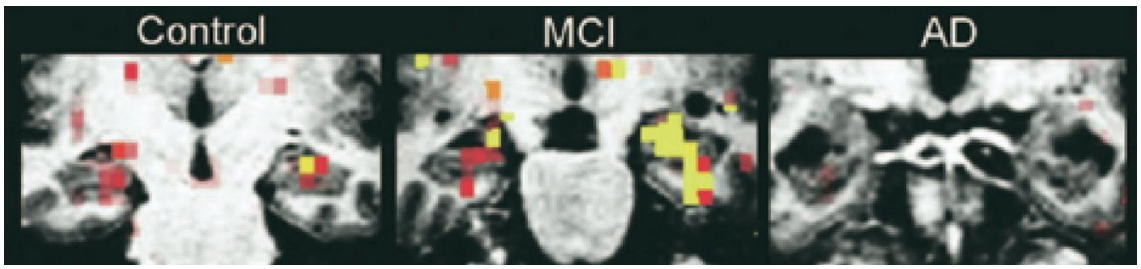

FIG. 2. A phase of compensatory hyperactivation appears to occur in the medial temporal lobe (MTL) in mild cognitive impairment, prior to the clinical onset of Alzheimer's disease (AD) dementia. Representative single subjects from each group, showing normal memoryrelated MTL activation measured with functional magnetic resonance imaging in normal older controls (left), hyperactivation and very mild atrophy in mild cognitive impairment (MCI) (middle), and hypoactivation and more prominent atrophy in mild AD (right).[28] Figure modified from published version.

Evidence is accumulating that task-related regional brain hyperactivation occurs in a variety of neuropsychiatric disorders and conditions, including AD/MCI, Huntington's disease,[32] Parkinson's disease,[33] cerebrovascular disease,[34,35] multiple sclerosis,[36–38] traumatic brain injury,[39] human immunodeficiency virus (HIV),[40] alcoholism, [41] schizophrenia,[42] sleep deprivation,[43] and aging. [44] All of these studies provide behavioural evidence that greater activation in task-relevant brain regions serves, at least in part, to preserve task performance in the patient group, supporting the contention that hyperactivation may be compensatory for

neurological insults. It is possible, however, that hyperactivation reflects inefficient function of neural circuits in the face of injury, and that such a response may be deleterious in the long run. Thus, it will be critical to elucidate the relationships between behavioral performance, neural circuit function, and clinical course of disease, with the ultimate goal of determining how best to use these fMRI measures as biomarkers of putative therapeutic response in clinical trials.

In the last few years there has been an explosion of literature on imaging and genetics, primarily in psychiatric disorders[45] and regarding the basic science of genetic modulators of brain function.[46] This is an area that is ripe for study in neurological disease, with a number of studies having been done in populations at elevated genetic risk for AD. The APOE 4 allele is a major genetic susceptibility factor associated with increased risk for AD.[47] Several fMRI studies have investigated regional brain activation during task performance in cognitively intact subjects stratified by their APOE 4 allele status. Smith et al.[48] reported decreased activation in inferior temporal regions with a visual naming and a letter fluency fMRI paradigm (there was no hippocampal or other MTL activation reported with these tasks) in APOE 4 carriers. In a subsequent report, this group reported increased parietal activation in women with an APOE 4 allele.[49]

Bookheimer et al.[50] reported increased activation in left hippocampal, parietal, and prefrontal regions among APOE 4 carriers, compared to noncarriers, using a word-pair associative memory paradigm. In addition, an increased number of activated regions in the left hemisphere at baseline was associated with a decline in memory at the 2-year follow-up among the APOE 4 carriers. The authors hypothesized that this increase in activation in the APOE 4 carriers might represent the additional cognitive effort or neuronal recruitment required to adequately perform the task. Similarly increased activation in multiple brain regions was recently reported in cognitively intact APOE 4 carriers compared to 3 carriers, although the effect was lateralized to the right MTL region (left hippocampal activation was greater in 3 carriers).[51] Among a group of 29 controls, MCI subjects, and AD patients, we recently reported that 13 APOE 4 carriers demonstrated greater entorhinal activation than noncarriers, in the absence of genotype-related differences in the volumes of these regions.[28] Other studies suggest that decreased MTL activation may also be seen in APOE 4 carriers.[52]

The early detection and differential diagnosis of disorders causing cognitive impairment is a promising aim for further work using fMRI. Because clinical evaluation and neuropsychological testing are currently the most sensitive approaches to diagnosis, and fMRI is sensitive to both cognitive performance and clinical status, it seems reasonable to hope that the potential capability of fMRI to detect alterations in the pattern and degree of regional brain activation during task performance may provide additional useful data to complement clinical and psychometric evaluations. However, relatively little fMRI data have been published on differential diagnosis to date.

In elderly individuals with cognitive symptoms, it can be difficult to distinguish a neurodegenerative process from depression. Functional MRI may be helpful in this setting. In a study of individuals who had sought clinical evaluation for memory-related symptoms, Gron et al.[53] investigated the utility of fMRI to differentiate patterns of regional brain activation in those diagnosed with depression versus AD (as well as a control group). Hippocampal activation during the memory task was decreased in AD patients compared with controls and depressed patients. In contrast, orbitofrontal and cingulated activation were greater in depressed patients than in AD subjects and controls.

Furthermore, different forms of neurodegenerative dementias may be challenging to specifically diagnose early in their course. Functional MRI may provide helpful data to assist in differential diagnosis of the dementias. Rombouts et al.[54] compared regional brain activation during a working memory task in patients with frontotemporal dementia to that of AD patients. Although both groups activated similar fronto-parietal –thalamic regions, fronto-parietal activation was

diminished in frontotemporal dementia patients than in AD patients.

Further insights into the utility of fMRI in assisting with differential diagnosis may be potentially gained through prospective studies of patients presenting for clinical evaluation with subtle symptoms consistent with a degenerative dementia who do not yet have a clear clinical diagnosis. If such individuals are scanned using tasks they can still perform and then be clinically followed, it may be possible to determine whether fMRI has predictive power in differential diagnosis.

We recently pursued such a study of a group of 25 senior citizens spanning the spectrum of MCI, none of whom were demented at the time of baseline assessment, but who exhibited varying degrees of mild symptoms of cognitive impairment clinically (as measured using the clinical demensia rating (CDR) Sum-of-Boxes (CDR-SB) scale.[55] At baseline, subjects performed a visual scene-encoding task during fMRI scanning and were clinically followed longitudinally after scanning. During 4 years of follow-up after scanning, subjects demonstrated a wide range of cognitive decline, with some showing no change and others progressing to dementia (i.e., a change in CDR-SB that ranged from 0 to 4.5). The degree of cognitive decline was predicted by hippocampal activation at the time of baseline scanning, with greater hippocampal activation predicting greater decline ($p < 0.05$) (see FIG. 3). This finding was present even after controlling for baseline degree of impairment (CDR-SB), age, education, and hippocampal volume. These data suggest that fMRI may provide a physiological imaging biomarker useful for identifying the subgroup of MCI individuals at highest risk of cognitive decline for potential inclusion in disease-modifying clinical trials.

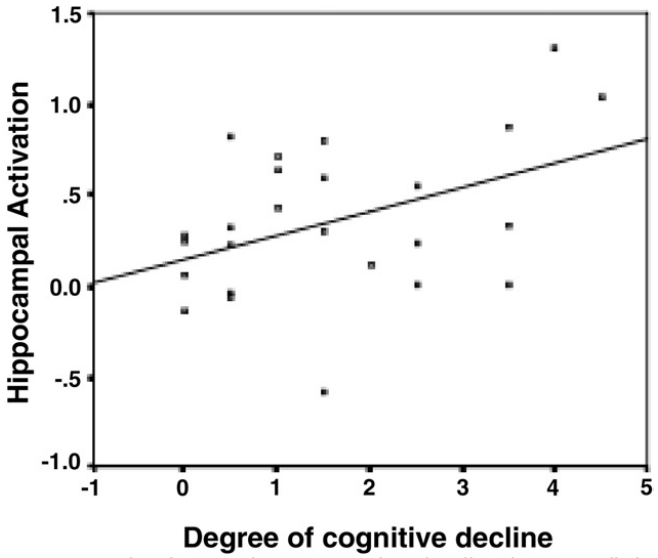

FIG. 3. Functional magnetic resonance imaging (fMRI) as a predictive quantitative imaging biomarker. In a group of mild cognitive impairment patients, hippocampal activation at baseline predicts the degree of cognitive decline during 4-year timeframe after scanning.[55] The Y axis indicates percent blood-oxygen level dependent (BOLD) signal change within hippocampal formation; X axis indicates relative clinical decline as measured by CDR Sum-of-Boxes (CDR-SB) scale, with higher numbers indicating greater decline.

Recent fMRI studies are beginning to reveal a link between disease-related hemodynamic alterations and the well-described resting perfusion/metabolic abnormalities in AD. Hypoperfusion/metabolism is typically seen with nuclear medical imaging techniques (such as FDG-PET or single photon emission computed tomography) in temporo-parietal/posterior cingulate cortical regions in AD patients during the "resting" state. The medial parietal/posterior cingulate cortex, along with medial frontal and lateral parietal regions, appear to compose a "default mode" network that is more active when individuals are not engaged in particular tasks, and which is thought to play a role in vigilance, readiness, or monitoring these regions "deactivate" (BOLD signal amplitude falls below baseline) during cognitive task performance.[56] Several recent studies in AD patients have demonstrated alterations in the deactivation and

functional connectivity of these regions, suggesting that this default mode network is disrupted by the disease.[25,57–59] Substantial overlap is present between these default mode areas and the localization of PET amyloid tracer binding.[60]

4. fMRI STUDIES OF BRAIN PLASTICITY

A growing body of fMRI literature has emerged that directly demonstrates correlates of regional brain plasticity in neurological disorders. Much of this work has been performed in patients who have suffered focal ischemic strokes.[61,62] This population is attractive because of the relatively rapid pace of functional recovery in many cases, such that studies can be performed during a period of months, minimizing the other variables that may potentially contribute to changes in fMRI signal in longitudinal studies (e.g., patient-related variables in those with progressive diseases; instrument-related variables resulting from scanner upgrades).

Functional MRI studies of stroke patients have shown that, for example, the laterality of primary sensorimotor cortex activation may shift after an infarct from typical contralateral organization (which would be ipsilesional during movement of the body part affected by the stroke) toward the side ipsilateral to movement. Furthermore, the manner by which a behaviour is normally organized influences how that behavior is organized after a stroke. Thus, for example, face motor representation (i.e., normally bilaterally organized at a neural level) is more likely to be shifted to the hemisphere ipsilateral to movement than a movement that is less bilaterally organized in the normal state.

The ready availability of instruments for fMRI studies, their safety in longitudinal studies, and the ability to combine fMRI measures with other brain mapping tools has contributed to the explosion of plasticity research in stroke and other neurological disorders. This will likely be an area in which findings from **our proposed** imaging studies will be translated quickly into assessment tools and imaging biomarkers useful for prognostication.[63]

5. CONCLUSIONS

Functional MRI is a particularly attractive method for use by clinical investigators of Virtual Reality to study task-related brain activation in patients with neurological or neuropsychiatric illness. Despite the relative infancy of the field, there have already been a number of promising fMRI studies in neurodegenerative, demyelinating, cerebrovascular, and other neurological disorders that highlight the potential uses of fMRI in both basic and clinical spheres of investigation.

Functional MRI prior and after Virtual Reality treatment may provide novel insights into the neural correlates of EF, cognitive and other abilities,[64] and how they are altered by neurological disease and medications.[65] The technique may help elucidate fundamental aspects of brain-behavior relationships, such as the genetic influences on task-related brain physiology.

Functional MRI measures hold promise for multiple clinical Virtual Reality applications, including the early detection and differential diagnosis, predicting future change in clinical status, and as a marker of alterations in brain physiology related to neurotherapeutic agents. The greatest potential of fMRI likely lies in the study of very early and preclinical stages of progressive neurological diseases at the point of subtle neuronal dysfunction, prior to overt anatomic pathology.[66] There is a great need for this project as further validation and reliability studies and continued technical advances to fully realize the potential of Virtual Reality and fMRI.

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B TEAM INFORMATION (max. 1 page per partner)

For each team, the following information should be given:

- *Give the total number of team members. The size of each team should be limited to those people actually needed for performing the tasks.*
- *Describe the background and particular expertise of the team against the tasks to be performed. Describe how the teams complement each other in the performance of the project.*
- *If relevant, a maximum of five references of relevant, recent scientific publications, patents which best show the capability of the research team to perform the work proposed. Indicate for each the name of the authors, the title of the article, the journal or other publication, the date and place of issue. If a publication exists on a website, give its address.*
- *Describe the relevant instrumentation and infrastructure available in view of the tasks assigned to the team.*

C PROJECT MANAGEMENT (max. 2p.)

- *Describe how the overall coordination, monitoring of the project will be implemented. Provide if possible a project organisation chart. Indicate the decision schemes foreseen in the project (decision boards, coordination meetings).*
- *If appropriate set up a detailed diagram giving the time schedule of the tasks and mark their interrelations; add milestones where important goals will be reached and/or decisions on further approach will have to be made; indicate a critical path marking those events which directly influence the overall time schedule in case of delays.*
- *Explain how information flow and communication will be enhanced within the project (e.g. collaboration and task meetings, exchange of scientists).*
- *Risk management: Indicate where there are risks of not achieving the objectives and fall-back positions, if applicable.*

D IMPACT OF PROJECT RESULTS (max. 1p)

- *Describe the expected results of your project and the utilization potential.*
- *Describe the expected impact of the research project results in terms of economical and societal needs of Russia and the EU.*
- *Sketch out a result exploitation plan which explains:*

i.how the new knowledge generated through the project and other deliverables of the project such as data bases, problem solving concepts, computer codes, technical solutions etc.) will be exploited;

ii. if relevant: how innovative technologies/concepts will be further exploited through an implementation plan for the projects´ results;

iii. How intellectual property, including foreground knowledge, patents, copyrights, license agreements and any other arrangements will be managed.