MIND GAMES do they work?

Last week a government report highlighted that the number of people in England with dementia is set to rise by 30% over the next 15 years. **James Butcher** investigates whether programs such as Nintendo's Brain Age, which claims to improve cognitive function, could help elderly users

For millions of people who are approaching old age, developing dementia, particularly if there is a family history of the disease, is a frightening prospect. Many of them are asking their doctors for advice on how to slow memory loss, as well as searching the internet for preventive strategies. As a result, over the past two years, the “grey gamer” has become a powerful market force and computer games like Nintendo's Brain Age, which claim to improve users' cognitive performance with repeated use, have sold tens of millions of units.

Celebrity endorsements have been a major part of the marketing campaigns, with stars such as actress Nicole Kidman and quiz show host Chris Tarrant appearing in television adverts to promote Nintendo's brain training programs. But the Brain Age products, which were developed with the help of neuroscientist Ryuta Kawashima, are beginning to face serious competition.

In the United Kingdom, Susan Greenfield, a professor of pharmacology at the University of Oxford and director of the Royal Institution, has been promoting MindFit, a computer program sold by MindWeavers that says it is “based on science, proven in practice, fun to play.” And in the United States the Brain Fitness Program, sold by Posit Science, a company cofounded by neuroscientist Michael Merzenich, claims to be “clinically proven to help people think faster, focus better, and remember more.”

Real benefits?

However, some independent experts are uneasy about the claims some of these products make. “I have some concerns about the way Nintendo is marketing the game in the United States,” says Michael Marsiske, a clinical and health psychologist at the University of Florida. He cites a television advertisement in which a middle aged man has difficulty remembering the name of a colleague whom he would like to introduce to his wife; he goes and buys Brain Age and as a result his memory gets better. Dr Marsiske notes that all the available data on cognitive training show that when a person practises something—for example, short term memory retrieval—the person can get better at doing that test but that the improvement does not necessarily generalise into the real world.

“There is a physical exercise analogy that anyone can understand,” says Dr Marsiske. “If you work on your biceps, your legs do not get stronger. The exercises in Brain Age, which are things like the speed of responding, visual search, and some memory items are only likely to improve the things that are being practised. I think people may believe that they are doing some mental cross-training and that they will generally improve their cognitive efficiency. That may be true, but there is no evidence for that just yet,” he says.

Observational evidence

What is clear from numerous observational studies, however, is that keeping mentally

active throughout life reduces the risk of developing dementia. In particular, the evidence is compelling that receiving a good education in the first two decades of life reduces the risk of developing dementia later on. But doing challenging work during mid-life is also helpful, as is engaging in leisure activities during old age, says Laura Fratiglioni, professor of medical epidemiology at the Karolinska Institute in Stockholm. “People with low education, but who have engaging jobs, have reduced risk of developing dementia,” she says. “This seems to me very interesting because it seems that we can modulate the risk that you may have with a bad starting point in life.”

Importantly, engaging in physical, social, and mental activities contributes equally to decrease dementia risk, says Professor Fratiglioni, who published a paper in 2006 examining the relative importance of these three types of activities in protecting 776 healthy elderly people from dementia.¹

Data from the five year follow-up of one of the largest cohort studies to investigate the relation between cognitive activity and the risk of developing Alzheimer's disease was published last June.² The Rush memory and ageing project, a clinical-pathological study of risk factors for common chronic conditions of old age, enrolled more than 1000 people living in retirement communities and subsidised housing facilities in the Chicago area. Over five years, 90 of the participants developed Alzheimer's disease.

“The level of cognitive activity in old age

EVIDENCE BEHIND THE CLAIMS

Karp et al 2006. Study of the protective effect of social, physical and mental activity in 776 healthy people aged 75 and older over three years suggested a broad spectrum of activity is more beneficial than one aspect alone¹

Wilson et al 2007. Five year follow-up of 1000 older people, of whom 90 developed Alzheimer's disease. Greater cognitive activity was associated with decreased risk of disease²

Willis et al 2006. Randomised controlled trial of 10 sessions of memory, reasoning, or speed training programmes in 2832 healthy adults with mean age of 74. Benefits were seen with all three programmes and maintained at five years³

Unpublished

Zelinsky and colleagues. Controlled trial of Brain Fit Program in 465 people aged over 65 over 8-10 weeks showed benefit on auditory memory

Korczyn and colleagues. Comparison of Mindfit with other computer games in 121 elderly volunteers. After 24 sessions the Mindfit group improved more than the control group

Ryuta Kawashima, a neuroscientist who has helped to develop Nintendo's brain training products, is the face of Brain Age

predicted who would get Alzheimer's disease years later," says Robert Wilson, one of the investigators. "The level of activity prior to old age was also predictive, but not after controlling for activity levels in old age," he explains. "This is an observational study, so we have not proved causation, but the evidence from observational studies is extremely consistent. Nearly every prospective study of this type has found this association despite widely varying ways of measuring how mentally active people are. The correlation is quite robust."

Professor Wilson and his colleagues have obtained consent from the participants to do a post-mortem examination of their brains to determine the level of amyloid burden, the density of neurofibrillary tangles, and the presence of Lewy bodies, as well as the number of chronic cerebral infarctions. "This allows us to ask why a risk factor is related to memory and clinical Alzheimer's disease," says Professor Wilson. "Is it working through an effect on the accumulation of the pathology that we associate with the disease or is it working through some other mechanism that somehow is helping us to tolerate the pathology?"

Professor Wilson says that it looks as though some of the lifestyle factors that are associated with reducing the risk of developing dementia are working through the second mechanism. "There is certainly evidence that we can affect the risk of this disease through behaviour and the trick is going to be understanding precisely what the behaviours are and how they work."

Interventional studies

Many of the companies that are marketing cognitive training software are also sponsoring trials to try to prove that their program's strategy is effective. One of the largest trials done to date has been the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study, which was sponsored by Posit Science and tested the company's Brain Fitness Program. The initial data from the trial were presented at the sixtieth annual meeting of the Gerontological Society of America in November.

The researchers from three US academic centres randomly assigned 468 healthy adults aged 65 and older to either 40 hours of the computer based Brain Fitness Program or to 40 hours of a computer based educational training program.

The Brain Fitness Program is intended to improve memory by increasing the speed

and accuracy of processing of aural information. The participants who were assigned to the Brain Fitness Program group used the program for at least 60 minutes a day, five days a week, over 8-10 weeks. "In one of the exercises people hear sounds that either go up or go down and they have to identify the sequence that a pair of sounds operates," explains Elizabeth Zelinski, a cognitive scientist from the University of Southern California who helped run the study.

Professor Zelinski and her colleagues found that after 10 weeks of training, participants in the intervention group improved more in the auditory memory score on the repeatable battery for the assessment of neuropsychological status test (the primary end point) than did participants in the control group. Professor Zelinski believes that some people may benefit from as little as 20 hours of training, whereas others may need as much as 60 hours. Future work will investigate this further, she says. And Posit Science has already conducted small trials in patients with mild cognitive impairment, to see whether the program can help ward off progression to Alzheimer's disease.

Another trial that was presented publicly for the first time last year, at the eighth international conference on Alzheimer's and Parkinson's diseases in March, tested the effectiveness of the MindFit training program. In that trial, 121 healthy elderly people were randomly assigned to either the training group, which was given MindFit and asked to use it

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for 20 minutes every two or three days for 24 sessions, or to a control group, which was given a CD with computer games and asked to play them for similar durations.

The researchers, led by neurologist Amos Korczyn from Tel-Aviv Sourasky Medical Center, found that both groups improved on most outcome measures but that people who used MindFit improved significantly more. "We are very confident that the data are very strong and that MindFit is in fact working quite well," says Professor Korczyn, who is also chief scientist at NexSig, which developed the computerised neuropsychological assessment software (NexAde) that was used as the main outcome measure in the trial.

Five year follow-up data from the largest independent trial done to date, the advanced cognitive training for independent and vital elderly (ACTIVE) study, were published at the end of 2006.³ The trial was sponsored by the US National Institute on Aging and the US National Institute for Nursing Research. Dr Marsiske and his colleagues randomly assigned 2832 healthy people with a mean age of 74 years to one of four groups: memory training, reasoning training, speed training, and a "no contact" control group that was used to see what the effects of repeated testing would be. Participants in each of the training groups received 10 sessions of training.

"All three training programmes were initially highly effective at improving the target of their training," explains Dr Marsiske. Impressively, those people who received one of the three training regimens continued to perform significantly better five years later than people who received no training. "That does not mean that there wasn't any decline

or loss of training effects—of course, after five years some of it washes away—but we see persistent differences between those who were trained and those who weren't and persistent advantages for those who were trained," he says.

However, the improvements in training were highly specific—for example, people who were assigned to the memory training group improved in memory but did not improve in reasoning or speed of processing.

"There are limitations to the generalisability of what we did to other kinds of mental intervention, but the generalisable proposition that you can take from these data is that people who are in later life—mid-60s to mid-80s and older—can in general continue to improve even when cognitive training is introduced in late life.

"We're at a very early stage in the development and evaluation of these training programs, and if we were developing new medications we would have many trials and at least some of those trials would be independently conducted by people who did not also design the training program," says Dr Marsiske. "We would look at a wide variety of outcomes and we would do very long term follow-up studies, and in general those studies that are claiming successes for their training programs, and that even includes the Posit Science group, have not yet had the opportunity to look at broad outcomes over long periods of time."

Clinical recommendations

In the absence of clear data on the effectiveness of brain training programs, should doctors recommend these products to patients

who are worried about their memory? Ken Rockwood, a leading dementia researcher and clinician based at Dalhousie University, Canada, says that he does not prescribe cognitive training programs to his patients. "But I do encourage my patients, particularly with mild Alzheimer's disease or the worried well with

mild cognitive impairment, to adopt a healthy brain strategy, and that includes not just things with reasonable data—like controlling blood pressure and cholesterol, and being physically active—but also to engage their brains in a variety of ways."

One benefit of this empowerment strategy, he says, is that patients with memory problems feel as though they are able to take control of their lives again. Dr Marsiske agrees that a feeling of empowerment is crucial: "We know from decades of research that higher levels of life engagement can really be a very protective factor not just for mental functioning but also for things like depression," he says. "The caveat is that there is some slight worry that if you have a brain that is at the limits of its capacity, it is losing reserve, then if that brain suddenly starts to practise things that are not so relevant to everyday life will that cost capacity that would be better used for maintaining everyday functions? There is no evidence for that at this point, it is purely speculative, but we don't have clear evidence that these training programs won't do any harm yet."

However, most researchers believe that the risk of harm is low, even if the clinical benefit of brain training products is unproved. "Strictly speaking, as an evidence based practitioner, you would caution against the nature of the trials and that there are a lot of observational studies and so on," says Professor Rockwood. "But talking as a doctor with a patient in front of me it's a very reasonable thing to encourage people to use cognitive training programs and to incorporate them as part of an overall package of lifestyle changes that they might wish to undertake once the diagnosis of cognitive impairment of some sort has been made. But I'd be very careful to explain what the evidence for that part of the prescription might be," he notes.

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