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International Conference

Memory in the Diseased Brain

Abstracts

27 January 2015 - Casina Pio IV - Vatican City

ESI

THE PONTIFICAL ACADEMY OF SCIENCES

International Conference

Memory in the Diseased Brain

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VATICAN CITY 2015

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RIVISTA QUADRIMESTRALE - SUPPLEMENTO al Vol. 9 n.1 - Gennaio/Aprile 2015

SOMMARIO

Program

9:00 – **Welcome Addresses: H.E. Msgr. Marcelo Sánchez Sorondo - Stefano M. Zuccaro**

Introduction: H.E. Msgr. Jean-Louis Brugues

Chairman: Paolo M. Rossini (Rome, I)
Scientific Director of AFaR, Professor and Director. Institute of Neurology, Policlinico A. Gemelli, Rome

9:30 – 10:00 Opening Lecture: What is Memory
Eric R. Kandel (New York, Usa)
Co-Director Mind Brain Behavior Institute, Columbia University, New York
Nobel Prize For Medicine 2000

Chairmen: Roberto Bernabei (Rome, I)
Director Department of Geriatrics, Neurosciences and Orthopedics, Policlinico A. Gemelli, Rome
Gabriele Miceli (Trento, I)
Professor of Neurology, University of Trento, Director of CeRiN (Centre for Neurocogitive Rehabilitation)

10:00 – 10:30 The Clinical Neuropsychiatry Of emory Disorders
Michael D. Kopelman (London, Uk)
Professor of Neuropsychiatry, King's College, London

10:30 – 11:00 The Importance Of Vascular Changes In Memory Deficits: Alzheimer's Disease And Vascular Dementia
Gabriel Gold (Geneva, Ch)
Physician/Head of Division, Dept. of Internal Medicine, Rehabilitation and Geriatrics, Trois-Chene Hospital, Geneva

11:00 – 11:30 Break

11:30 – 12:00 Memory Is on the First Line of Attack of Alzheimer Disease
Bruno Dubois (Paris, F)
Head of Dementia Research Center (IM2A), Department of Neurology, Salpêtrière Hospital, University of Paris

12:00 – 12:30 Treatment of Memory Deficits in Neurodegenerative Diseases
Ezio Giacobini (Geneva, Ch)
Professor at Department of Internal Medicine, University of Geneva

12:30 – 13:00 Memory Deficits in Parkinsonian Patients
Clive Ballard (London, Uk)
Professor of Age Related Diseases, Co-Director Biomedical Research Unit for Dementia, Institute of Psychiatry, King's College, London

13:00 – 14:30 Break

Chairmen: Mario Maj (Naples, I)
Ph Professor,/Director, Department of Psychiatry, University of Naples
Stefano M. Zuccaro (Rome, I)
Vatican Health Officer

15:00 – 15:30 Memory and Cognitive Dysfunction in Depression
Philippe H. Robert (Nice, F)
Director of the Nice Memory Center, C.H.R.U., University Sophia Antipolis, Nice

15:30 – 16:00 New Updates on the Pharmacological Treatment of Depression, with Reference to Memory and Cognitive Dysfunction
Marco A. Riva (Milan, I)
Associate Professor of Pharmacology, Univesity of Milan

16:00 – 16:30 Memory and Cognitive Dysfunction in Schizophrenia
Philip D. Harvey (Miami, Usa)
Professor of Psychiatry and Behavioral Sciences, Univesity of Miami School of Medicine

16:30 – 17:00 Break

17:00 – 17:30 Memory Aging and Brain Maintenance
Lars Bäckman (Stockholm, S)
Professor in Cognitive Neurosciences, Aging Research Center, Karolinska Institute

17:30 – 18:00 The Role of Cognitive Training and Exercise in the Prevention of Memory Disturbances
Laura Fratiglioni (Stockholm, S)
Professor/Director, Aging Research Center, Karolinska Institute

Chairman: Ezio Giacobini (Geneva, Ch)
Professor at Department of Internal Medicine, University of Geneva

18:00 – 18:45 General Discussion

International Conference Memory in the Diseased Brain

Introduction

In human physiology, memory is the process by which information from the outside world is encoded, stored and later retrieved. Borges said that "we are our memory".

Memory is such an important process that, historically, it has been assigned a fundamental value to individual and social life of man.

Herodotus reports that the Egyptian priests kept the memory of 341 previous generations, that means over 11,000 years. The Greeks worshiped a deity called Mnemosyne, attributing a divine property to memory, to guarantee the preservation of culture and history of populations.

Papa Francesco, commenting on the reading from the Book of Nehemiah (8, 1-4, 5-6, 7-12), about the discovery of the book of the law that had been lost, he said that we all have the memory of salvation and that feel close the memory of our salvation warms the heart and lights up inside us the joy and concluded by stating to ask the Lord for the grace to always have his memory next to us.

But, if memory is a tool of human physiology of such a great historical, cultural and even religious value, what is actually memory and what happens when it fails?

This is what the International Conference "Memory in the Diseased Brain" to be held under the auspices of the Pontifical Academy of Sciences on January 27, 2015 at the Casina Pio IV, Vatican City, aims to clarify.

The conference will be opened by a keynote lecture by Prof Kandel, Nobel Prize for Medicine in 2000 for his research on the physiological basis of memory storage in neurons, which will present the state of the art of what is memory and what we actually know about it.

It will be followed by a first morning session, focusing the differences between normal and pathological memory and memory disorders in the course of the most important neurological and geriatric diseases, such as vascular dementia or Alzheimer's dementia, neurodegenerative disorders and Parkinson's disease.

In the afternoon, memory disorders in the course of some of the most severe psychiatric disorders will be dealt with, particularly emphasizing the topics regarding major depression and schizophrenia.

The final section covers the most recent therapeutic advances in memory disorders, both on the psychological and organic treatments aspects.

Prof. Stefano Maria Zuccaro
Vatican Health Officer

H.E. Msgr. Marcelo Sánchez Sorondo
Chancellor of the Pontifical Academy of Sciences

Prof. Roberto Bernabei
Director Dept. of Geriatrics, Neurosciences
and Orthopedics, Pol. Gemelli, Rome

Chiesa e memoria

Bruguès J.L.

Prefetto biblioteca Apostolica Vaticana

1. «Fate questo in memoria di me». Ben poche frasi nel testo evangelico hanno peso specifico uguale a questa espressione, ripetuta in due pericopi, entrambe riferite all'istituzione dell'Eucarestia (Lc 22, 19 e 1 Cor. 11, 24-25). Questa stessa frase ci invita a cogliere la stretta relazione che intercorre fra Chiesa e memoria: relazione a cui vorrei far riferimento in questo mio breve intervento.

2. L'atto del ricordare ricopre una doppia funzione. Da una parte permette di accedere all'identità: se il mio interlocutore non mi riconosce, gli ricordo fatti passati, le circostanze di un incontro precedente, che permettano di collocarmi e identificarmi. La lingua francese ha una felice espressione per sciogliere le incertezze dovute a un vuoto di memoria: «Vous me remettez?», si chiede alla persona che sembra averci dimenticato. D'altro canto, l'atto del ricordare istituisce un patto di reciproca fiducia: è infatti proprio perché Dio ha liberato il suo popolo dalla schiavitù dell'Egitto che il popolo può dar credito alle sue richieste – l'obbedienza alla Legge – e alle sue promesse. Ma questa osservazione ha valore anche per la vita sociale: è proprio perché conservo la memoria della benevolenza ricevuta da qualcuno, che mi posso fidare di lui.

3. La coesione di un gruppo sociale, sia politico che religioso, e più ancora il suo futuro, dipendono in gran parte dalla capacità di ricordare le proprie origini. L'attaccamento all'Europa, ad esempio, non sarà certo lo stesso, a seconda se ci si riferisca ai «padri fondatori», Robert Schumann e Alcide De Gasperi, a coloro cioè che l'hanno voluta e allo spirito con cui hanno operato, oppure se si ritenga che l'Europa non abbia bisogno di porsi domande sulle proprie origini, perché essa è un'idea da reinventare continuamente. E così si mette in gioco l'identità.

Lo abbiamo ben sperimentato poco tempo fa nel dibattito sulla costituzione europea, che non ha ancora visto la luce… Se si considera l'Europa, secondo la visione liberale, solo un mercato comune, chiamato ad allargarsi oltre le frontiere geopolitiche e culturali del continente, sarà più opportuno orientarsi verso una costituzione molto leggera, una costituzione soft, fermandosi a far riferimento alle regole essenziali del libero scambio delle merci. Se invece l'Europa è chiamata a dotarsi di istituzioni forti, per acquistare nel contesto internazionale un ruolo politico significativo – non solo quindi economico – cosa che implica per natura sua una certa continuità d'azione, è essenziale che essa faccia riferimento alle proprie origini, alla volontà dei padri fondatori, quindi alle radici cristiane.

4. Il cristianesimo pratica quattro tipi di atti di memoria.

I. Vi è ciò che si potrebbe definire la memoria dei luoghi. Il credente sente il bisogno di ritrovare gli ambienti stessi nei quali il Cristo è vissuto, di respirarne la stessa aria, di vederne la stessa luce, di percorrere quegli stessi itinerari, toccare le pietre, guardare gli edifici che certamente lo hanno visto passare… Questo tipo di desiderio da parte del credente rimanda a qualcosa che si potrebbe chiamare strategia della memoria dell'amore: quando colui che amiamo ci ha lasciato, non proviamo forse anche noi il bisogno di ritrovare i luoghi e le cose che ancora ci parlano di lui o di lei, malgrado la sua assenza?

II. Per estensione, la memoria cristiana – memoria cattolica e ortodossa – cerca un contatto che va inteso in senso quasi fisico con coloro che hanno conosciuto da vicino il Cristo. Chiameremo questo seconda tipologia memoria di vicinanza (o di prossimità). Ci avviciniamo infatti a Gesù anche quando ci accostiamo a persone che lo hanno avvicinato perché suoi contemporanei (la Vergine Maria e i suoi discepoli), o per il grado di santità che ha trasformato alcune persone in immagini particolari e particolarmente coinvolgenti della santità del Cristo.

III. La preoccupazione per la memoria spiega infatti la cura con cui il cristianesimo ha conservato gli scritti che trattano del Cristo nel suo passaggio tra gli uomini, e quelli che analizzano e commentano i suoi acta et passa. In tal caso si parla di una memoria degli scritti. Nessuno si meravigli se l'Archivista e Bibliotecario di Santa Romana Chiesa manifesta una predilezione per questo terzo modo di "fare memoria"!

IV. L'ultimo atto di memoria è quello ancor più originale e riguarda la Chiesa che si definisce Corpo di Cristo. Poiché essa fa memoria delle parole e dei gesti del suo fondatore, la Chiesa non cerca solamente una fedeltà alla lettera, o l'esattezza storica, come andrebbe fatto per ogni personaggio del passato. La Chiesa desidera mostrare ciò che Egli continuamente dice e opera nell'oggi, perché lo proclama vivente. La sacramentalità rappresenta infatti l'essenza stessa della Chiesa, che si impegna così a rendere il Cristo presente e attivo tra gli uomini di tutti i tempi e di ogni civiltà. E questa è la sua missione essenziale. Un sacramento infatti non è solo un memoriale, ma permette di accedere alla vita stessa del Cristo risorto e rende coloro che vi si accostano capaci di partecipare alla stessa natura divina. In una parola: è fonte di grazia. E questa è ciò possiamo definire di memoria sacramentale.

5. Così ci si dovrà prima o poi scontrare con questa evidenza: chi ha perduto la propria memoria, ha perduto di colpo anche la propria identità e diventa incapace di guidare se stesso. Ma chi è affetto da amnesia non ha futuro. E questa constatazione emerge dagli indivi-

dui per i quali la perdita di memoria è studiata a livello di patologia, come nel caso del morbo di Alzheimer; ma la constatazione vale anche per i gruppi sociali e per le nazioni. Ed è proprio perciò che si istituiscono anniversari e festività civili; ma la loro efficacia può essere messa a rischio, se le generazioni più giovani non si trovano più in sintonia con la ricchezza di un passato condiviso, e se le generazioni che le precedono non si preoccupano di trasmettere il patrimonio che esse stesse hanno ereditato. In questo senso la crisi del '68 va letta non come un semplice avvenimento storico, ma come una vera rottura di civiltà di cui noi porteremo ancora a lungo le conseguenze: essa infatti può essere interpretata come una crisi della memoria. Con certezza per la prima volta nella Storia una generazione ha deciso di far tabula rasa del passato. Lucidamente e volontariamente si è deciso di non trasmettere.

Colui che ha dimenticato il proprio passato è condannato a ripeterlo. «Chi non ricorda non vive», così afferma il filologo italiano Giorgio Pasquali.

The clinical neuropsychiatry of memory disorders

Kopelman M.

Professor of Neuropsychiatry, King's College, London, U.K.

Clinical memory disorders can be classified as giving rise to a transient or discrete episode of amnesia, and those that give rise to a more persisting memory disorder. They can also be subdivided into those that have a neurological and those which have a psychological basis. In this talk, I spoke about examples of transient neurological, persistent neurological, and transient psychogenic amnesia. I mentioned that the amnesic syndrome mainly affects episodic memory; semantic dementia is an example of semantic memory disorder; and Alzheimer dementia affects both these components of memory. I distinguished between definitions of primary or working memory, autobiographical/episodic memory, semantic memory, and implicit memory. By definition, episodic/autobiographical memory is severely impaired in amnesic disorders, whereas semantic memory is more variably affected. Primary memory and implicit memory are often spared. I also distinguished between anterograde amnesia and retrograde amnesia.

Transient neurological ('discrete') episodes of memory loss can arise from such causes as toxic confusional states, head injury, alcoholic 'blackouts', hypoglycaemia, post-ECT, transient global amnesia (TGA), and transient epileptic amnesia (TEA). These various syndromes characteristically affect episodic memory, and important recent investigations have highlighted the clinical characteristics of TGA and TEA, including overlapping and contrasting features. I gave an example of a man who suffered from transient epileptic amnesia, having experienced approximately 9 episodes during the course of a year. Standard EEGs were normal, but a sleep EEG showed bilateral mid-temporal sharp and slow waves. He responded very well to anticonvulsant medication, having only one more (equivocal) episode during the course of the next 12 years. He was fairly typical of the transient epileptic amnesia syndrome, in which attacks occur more commonly in men, who are often in their 50s or 60s. There are often recurrent attacks of short duration (30 to 60 minutes). They may occur on arousal from sleep, and there is a variable severity of anterograde and retrograde amnesia. They respond well to anticonvulsant medication.

Persistent, neurological memory disorder occurs in the amnesic syndrome, in which episodic memory is predominantly affected (out of all proportion to other cognitive functions), arising from disorders such as herpes encephalitis, cerebral hypoxia, thiamine deficiency (the alcoholic Korsakoff syndrome), limbic encephalopathies, head injury, and the amnesic form of mild cognitive impairment (aMCI).

The true incidence, prevalence, and morbidity of (non-dementia) memory disorders is probably underestimated, because these diagnoses fall across a wide range of ICD (International Classification of Diseases) categories. In these disorders, the common feature is damage to the 'anterograde memory circuits', involving the mammillary bodies, the mammillo-thalamic tract, the anterior thalamus, the fornix, retrosplenium, and hippocampi. Controversies exist regarding the critical site of damage causing the anterograde amnesia in the Korsakoff syndrome, and the nature of the neuropsychological deficit in focal hippocampal lesions (as in some cases of cerebral hypoxia). Examples were presented of patients who had suffered severe herpes encephalitis, a cardiac arrest giving rise to hippocampal atrophy and profound amnesia, and the alcoholic Korsakoff syndrome. It was noted that herpes encephalitis can cause widespread damage in the medial temporal lobes.

Cerebral hypoxia also causes hippocampal atrophy, together with reduced glucose metabolism in the thalami and retrosplenium. In the alcoholic Korsakoff syndrome, signal alteration can be seen within the anterograde memory circuits during the Wernicke phase, followed by atrophy in the thalami and mammillary bodies. There is also reduced glucose metabolism in the thalami, hypothalami, mammillary bodies, basal forebrain, on PET studies of Korsakoff patients.

There is also considerable controversy concerning the neuropsychological and pathophysiological basis of retrograde amnesia, and of spontaneous confabulation. Ribot (1882) described a 'law' which stated that recent memories are more vulnerable to the effects of brain damage – what is now known as a 'temporal gradient'. This can be demonstrated using modern neuropsychological tests.

There is also some evidence that, whereas the severity of anterograde memory impairment relates to the degree of atrophy of brain structures within the 'anterograde memory circuits', the severity and extent of retrograde amnesia relates more closely to performance on executive tests and the degree of frontal lobe atrophy, suggesting differing underlying mechanisms for these two components of memory disorder.

Spontaneous confabulation consists of the persistent, unprovoked outpouring of (unintentional) erroneous memories. There is now some evidence that this often results from damage in a different area of the brain – namely the ventro-medial frontal cortex and/or the orbito-frontal cortex. One theory, propounded by Korsakoff, suggested that confabulation results from so-called temporal context memory confusions, in

which real memories are retrieved inappropriately and out of temporal sequence. Another theory states that there is a problem with specifying the trace to be retrieved and with editing out errors. A third theory emphasises a motivational bias in what is recalled during confabulation. An example of a confabulating patient was presented.

Semantic memory is particularly affected in so-called semantic memory (progressive fluent aphasia). In this, there is disproportionate atrophy of the lateral and inferior temporal lobes, particularly on the left. This results in a specific impairment in naming, word-finding, and comprehension with relatively well-preserved orientation, visuo-spatial and number skills, reasoning and problem-solving, and executive skills. I presented the example of a man whose autobiographical (episodic) memory was relatively well preserved, but he struggled to express his memories, because of his word-finding difficulty.

Psychogenic amnesia can be 'global' or 'situation-specific'. The global form affects the whole of a person's previous life, and is commonly accompanied by a loss of the sense of personal identity, as in the case of Piano Man. This form of amnesia is usually transient, but, if it becomes persistent, it is better labelled as 'psychogenic focal retrograde amnesia'. Situation-specific amnesia involves a discrete gap in a person's memory, usually related to a traumatic episode, as in post-traumatic stress disorder (PTSD) and (more controversially) in the perpetrators and victims of certain types of offence.

Both transient neurological amnesia and transient psychogenic amnesia can be preceded by a precipitating stress/significant life event; and, in both, standard investigations (e.g. brain imaging) can be normal. Differences are that the loss of the sense of personal identity occurs in some cases of psychogenic amnesia, but very seldom in neurological amnesia (except in profound dementia).

Repetitive questioning is characteristic of transient neurological amnesia, but is not seen in psychogenic amnesia. The 'temporal gradients' of retrograde amnesia differ with relative sparing of early memories in neurological amnesia, and often 'reversed' gradients in psychogenic amnesia.

There are now neuroimaging findings concerning the correlates of psychogenic amnesia, which demonstrate activation of what might be called 'frontal inhibitory pathways'.

In summary, I contrasted transient versus persistent amnesia. I also contrasted anterograde amnesia, in which there is damage within the 'limbic circuits' (including medial temporal structures and the anterior thalamus) versus retrograde amnesia, in which more diffuse pathology (including frontal lobe damage) may be implicated. We contrasted episodic memory, which is profoundly affected in amnesic disorders with implicit or procedural memory, which is relatively spared.

I contrasted episodic or autobiographical amnesia (including confabulation) with semantic memory disorders (where the damage is principally in the inferior and lateral temporal lobes).

Finally, I contrasted neurological and psychogenic amnesia. The latter appears to involve the activation of frontal inhibitory circuits.

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The importance of vascular changes in memory deficits, alzheimer's disease and vascular dementia

Gold G.

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The relationship between cerebrovascular pathology and cognitive impairment is well established. The first descriptions associating dementia with "softening" of the brain (stroke) date back to the XIXth century. The concept has continuously evolved since then.

The clinical description of vascular dementia includes an abrupt onset, stepwise deterioration, history of stroke, focal neurologic signs and symptoms, and neuroimaging findings consistent with ischemic or hemorrhagic vascular events. It is based on the multi-infarct dementia concept (dementia due to multiple strokes) described in 1974. Clinical criteria based on this concept proved relatively specific but suffered from low to very low sensitivity suggesting that the multi-infarct concept should be enlarged to include other causes of cerebral ischemia and in particular small vessel disease. Progress in neuroimaging revealed the very high frequency of white matter changes in older brains and community based autopsy studies reported the presence of some type of vascular pathology in over 70% of all older individuals regardless of the presence or absence of dementia.

Clinicopathological studies carried out at the beginning of the XXIst century to sort out the clinical consequences of the various types of vascular pathology encountered in aging brains, showed that basal ganglia and thalamic lacunes and most importantly cortical microinfarcts had a powerful effect on cognition (1). This was not the case for focal and diffuse gliosis orm lacunes in the frontal, parietal and temporal white matter. The clinical effect of demyelination was weaker and inconsistent. Further research confirmed the strong correlation between cognitive changes and microinfarcts in vascular and mixed dementias, even in the oldest-old (2).

Many neuropathological studies of aging brains have recently focused on microinfarcts and reported a high prevalence (16 to 48% of all cases). A meta-analysis revealed that the presence of microinfarcts more than doubled the risk of developing dementia (odds ratio 2.31, 95% confidence interval 1.40-3.82) (3). This risk is also related to the quantity of lesions since dementia was 4 times more common in cases with multiple microinfarcts compared to cases with a single microinfarct (4).

Microinfarcts are sharply delimited regions of cell death or tissue necrosis and are not visible to the naked eye. Several efforts to detect them in vivo using magnetic resonance imaging (MRI) with special sequences or very high magnetic fields (7 tesla) have identified very small lesions (approximately 1 mm) but have been unable to visualize microinfarcts (500 microns or less) (5).

As a result, it is highly likely that many cases of mixed or multifactorial dementias with a microscopic ischemic component remain undiagnosed.

The origin of microinfarcts remains unclear. Although some have reported an association with atherosclerosis, arterial hypertension or a history of heart attack, others have found no relation between microinfarcts and vascular risk factors (including hypertension, atrial fibrillation, diabetes mellitus and tobacco use) or other vascular pathology (coronary artery disease, peripheral arterial disease). Studies exploring the association between cerebral amyloid angiopathy and microinfarcts have shown conflicting results.

In conclusion, cortical microinfarcts are closely related to cognitive function in aging brains, including the oldest-old. They represent an important therapeutic target for the prevention and treatment of memory disorders. The pathophysiological mechanisms leading to the occurrence of cortical microinfarcts should be further explored.

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Alzheimer disease: from biomarkers to the diagnosis

Dubois B.

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The discovery of biomarkers, considered as surrogate markers of the underlying pathological changes, led an international work group (IWG) to propose a new conceptual framework for AD in 2007 (Dubois, Feldman et al. 2007). According to the IWG, AD is now defined as a dual clinicobiological entity that can be recognized in vivo, prior to the onset of the dementia syndrome, on the basis of: i) a specific core clinical phenotype comprised of an amnestic syndrome of the hippocampal type and ii) supportive evidence from biomarkers reflecting the location or the nature of Alzheimer type changes. Therefore, AD is diagnosed with the same criteria throughout all symptomatic phases of the disease based on the biologically-based approach to diagnosis independent of clinical expression of disease severity. The definitions were further clarified in 2010 (Dubois, Feldman et al. 2010).

Although the New Criteria are proposed for research purposes, we encourage expert centers with adequate resources to begin to use the proposed algorithm in order to move the field forward and facilitate translation into clinical practice.

A- The Conceptual Advances of the IWG Criteria:

The proposed revision of the Criteria for Alzheimer disease in 2007 and the subsequent proposal for a Lexicon revision in 2010 have induced significant changes in the conceptual framework of AD:

1) They first introduced biomarkers for the diagnosis of AD. The IWG proposed for the first time to divide biomarkers into pathophysiologic markers that identify AD pathology, i.e. makers of diagnostic, and **topographical markers** that reflect downstream damage, i.e. markers of progression. The first consist of: i) CSF changes in the level of amyloid beta [Aβ] and tau proteins; and ii) increased tracer retention on positron emission tomography (PET) amyloid imaging.

Topographical downstream markers consist mainly of: i) medial temporal atrophy on magnetic resonance imaging [MRI] and ii) parietal/temporal hypometabolism on fluorodeoxyglucose [FDG]- PET. Accordingly, CSF and MRI investigation are no longer proposed only for excluding other etiologies of brain dysfunction: the IWG Criteria have introduced a new diagnostic procedure based on positive evidence and not on excluding other causes of dementia. Recent data showed that pathophysiological markers are strongly correlated with post-mortem AD pathology (Tapiola, Alafuzoff et al. 2009), and can be considered as surrogate markers of the histopathological changes.

The IWG criteria have moved AD from a clinicopathological entity to the concept of AD as a **clinico-biological entity**. The use of biomarkers increases the dianostic accuracy, a major objective of the IWG. The aim of the 2007 Criteria was to propose algorithm that supports the high likelihood of the presence of AD because this is an imperative necessity for research purposes or clinical trials.

2) The IWG introduced the concept of 'prodromal AD".

The IWG Criteria have extended the concept of AD into a pre-dementia stage considering that there is no reason to link the diagnosis of the disease to a certain threshold of severity. In addition, the ambiguous nature of any boundary between prodromal AD and dementia of the AD type argues in favor of a unified diagnostic approach that uses the same criteria for diagnosis of AD regardless of the severity of the accompanying cognitive and functional deficits. Therefore, no reference to dementia is required. Biomarkers being a signature of the disease, they are not so much less linked to disease stages. They reinforce the diagnosis of the disease at any stage, even at the earliest prodromal ones.

3) AD is now considered as one clinical disease with a continuum through different stages.

The new approach established AD as a clinical disease with a spectrum of severity symptoms from very mild to severe. Its diagnosis relies on a simple and uniform procedure that applies for all stages based on the concept of a clinical-biological entity. The combination of a specific phenotype in typical AD (amnestic syndrome of the hippocampal type) and a biomarker supportive of the presence of Alzheimer pathology is the basis for diagnosis of AD at any stage of the disease.

4) The concept of "typical AD", defined by an amnestic syndrome of the hippocampal type, is opposed to that of atypical forms of AD.

The IWG Criteria have highlighted the importance of a specific pattern of episodic memory disorders in AD. It is the less studied among the markers although it is one of the most accurate (Landau, Harvey et al. 2010). Although memory disorders are common in AD and non-AD dementias a rather specific pattern of memory impairment is characteristic of AD: the amnestic syndrome of the hippocampal type. Memory disorders in AD can be viewed as a topographical marker of medial temporal lobe (and related structures) damage. With the added value of cueing paradigm, memory performance can make up to 90% of the diagnostic certainty for AD and can predict time of conversion to dementia (Sarazin, Berr et al. 2007). The amnestic syndrome of the hippocampal type, as evidenced by the Free and Cued Selective Reminding Test, was recently shown to be highly specific for AD pathology (Wagner, Wolf et al. 2012). Besides the memory disorders, several cognitive changes can be encountered in AD, even at a prodromal stage of the disease, but none

are specific of AD and their presence adds little for the diagnosis, except for the episodic memory impairment. Therefore, the IWG has introduced for the first time the concept of **"atypical forms of AD"** with specific clinical phenotypes that include nonamnestic focal cortical syndromes, such as logopenic aphasia, bi-parietal atrophy, posterior cortical atrophy, and frontal variant AD. With the advent of biomarkers providing in-vivo confirmation of Alzheimer's pathology, it is now possible to include these clinical disorders as atypical AD if there is convincing biomarker support. These disorders may develop an amnestic deficit later in the disease course.

5) The IWG proposed the existence of distinct preclinical stages of AD.

The IWG isolated for the first time the existence of preclinical states distinguishing:

- **"Asymptomatic at risk for AD" (**ASR-AD) with a normal cognitive condition and evidence of amyloidosis in the brain or Alzheimer type changes in the CSF. This neutral nomenclature was chosen to acknowledge that the percentage of persons who progress from this state to symptomatic clinical conditions is unknown
- **"Presymptomatic AD"** (PS-AD): with a normal cognitive condition and an autosomal dominant monogenic AD mutation. Because of the full penetrance of these mutations, these individuals will inevitably develop clinical AD.

B- The added value of the NIA/AA Criteria:

The NIA/AA criteria were published in 2011 and share many features with the IWG criteria including recognition of an asymptomatic biomarker positive phase and of a predementia symptomatic phase of AD. They also integrate biomarkers into the diagnostic process that were categorized into two types, one identifying amyloid abnormalities and one the downstream neurodegeneration. However, the NIAAA criteria differ from the IWG on several important points. They still consider 3 different stages of the disease and each stage has its own diagnostic criteria, creating the need to refer to 3 different sets of diagnostic criteria. Within the preclinical stages (Sperling, Aisen et al. 2011), the NIA-AA criteria support a diagnosis of AD in asymptomatic individuals with AP. This diagnostic stage is seen as being an "in situ" stage. The MCI stage of AD is formally distinguished from the dementia stage on the basis of the functional impairment severity.

C- Limitations of the IWG criteria:

The IWG Criteria are research criteria. They are particularly useful for research projects where a highly specific diagnosis is needed. The criteria should not be used in clinical settings for many reasons:

1) The criteria are not formally validated.

Complete validation and comparison of each biomarker in terms of its added value, either isolated or in combination, for the diagnosis or evolution of the disease is required. Laboratory standards for biomarkers must be established to improve their interpretability and reliability.

2) They cannot be applied everywhere.

They are more and more used in expert centers with facilities to assess a large spectrum of biomarkers, reliability of assessment procedures and with access to normative data: in these tertiary and expert centers, the criteria are applied for advanced diagnosis such as in case of young-onset AD or complex cases (posterior cortical atrophy, primary progressive aphasia…) where biomarkers may increase the diagnosis accuracy.

However, according to a report of Alzheimer's disease International (ADI, 2009) 58% of people with dementia lived in low and middle-income countries. Even in developed countries, there is still a lack of availability of the high-tech investigations required for the proposed diagnostic framework outside tertiary or research centers. Cultural acceptability of biomarkers should also be taken into account. Whereas the use of CSF biomarkers is well developed in European countries, it is not the case in many Asian countries (Chiu and Lam 2007).

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Treatment of memory deficits in neurodegenerative diseases

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The development of therapies that improve cognitive function and memory in particular, received special attention because of the cognitive decline inherent to aging and to neurodegenerative diseases. Among them, Alzheimer Disease (AD) occupies a prevalent position both for frequency and severity. Cholinergic mechanisms which have long been recognized for their involvement in learning and memory and selective degeneration of the cholinergic system constitute an early aspect of the pathophysiological process underlying this disease. Since acetylcoline exerts its effects at two receptor classes i.e nicotinic and muscarinic and each one mediates cognitive function, effort has been made to develop drugs targeting specific receptor subtypes of both. In particular, alpha-seven nicotinic acetylcholine receptors agonists have been clinically tested. One of them, EVP-6124, encenicline, a partial agonist, has shown promising results in phase II and III clinical trials in AD and in schizophrenia.

Muscarinic agonists selectively targeting M1 postsynaptic receptors have not been successful in AD and the only cholinergic drugs presently used for the treatment of cognitive deficits in AD are cholinesterase inhibitors (ChEI). Recently, the use of ChEI has been extended to disorders other than AD such as dementia in Parkinson Disease, Loewy body disease and vascular dementia (1). The question is still open whether ChEI in AD act primarily on memory or rather on attention (2).

Cholinesterase inhibitors are considered to be "disease stabilizers" with a symptomatic effect lasting generally 6 month to a year which extends itself in certain cases up to 3 years.

Another approach to cognition in AD has been to target beta-amyloid considered to be responsible for the synaptic damage. Four major pharmacological approaches have been tested in numerous clinical trial of phase 3 lasting up to 18-24 month using anti-aggregants, gama- and beta-secretase inhibitors and anti a-beta immunization. None of these attempts has resulted in a clinically significant cognitive effect (3).

Presently, drug targets for cognitive enhancement in clinical development include other receptors beside cholinergic ones, such as glutamatergic (particularly NMDA and AMPA receptors), serotonergic, histaminergic and GABAergic ones.

Memantine, a compound that moderately blocks NMDA receptors modulates excessive glutamate leading to improvement in cognition in AD patients. CREB, the cAMP response element binding protein, is a core component of the molecular mechanism which converts short to long term memory (Kandel et al 2014). According to this hypothesis, phosphodiesterases (PDE) have been considered as potential therapeutic targets for AD therapy.

Among them, only rolipram, a specific PDE4 inhibitor has shown some evidence to restore cognitive deficits in memory function. Modafinil, a drug blocking the recapture of noradrenaline and dopamine, used in the treatment of narcolepsia and hypersomnia, has also been considered as a candidate for treatment of cognitive deficits, mainly to improve attention.

Among serotoninergic drugs, a novel selective 5HT6 receptor antagonist, LU AE 58054 has been tested in the treatment of moderate AD together with a ChEI or alone resulting into a significant improvement in cognition. Ampakines, another group of preclinically promising nootropics compounds which are positive allosteric modulators of the glutamate receptors, stimulating both AMPA and NMDA receptors, have failed to demonstrate clinical efficacy.

Finally, among non receptor related targets is worth mentioning two series of clinical trials in AD patients using NGF either directly administered intracerebrally by mean of a viral technique (in vivo gene therapy) or via genetically modified fibroblasts to produce NGF (ex vivo gene therapy).

Both attempts have shown some positive results, however, this procedure is considered to be too invasive for a general use. Despite the fact that remarkable advances have been made in our understanding of the molecular basis of memory function, the treatment of memory dysfunction in neurodegenerative diseases still represents an unmet target.

In conclusion, beside ChEI and memantine, which are well established treatments in the symptomatic pharmacological arsenal of AD, it is difficult to predict which drug target will be most beneficial for memory improvement. To date, none has met with clinical success because of lack of efficacy or of good tolerability. At the preclinical level we still lack valid experimental animal models of memory impairment wich mimics the cognitive deficits at different stages of the disease typical of AD, Parkinson Disease, Down syndrome or of other neurodegenerative diseases.

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Memory in Parkinson's Disease and Related Dementias

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Cross section studies have indicated that at any one time 25-30% of people with Parkinson's disease have dementia, with 80% or more people developing dementia over longer term follow-up. In combination, Parkinson's disease dementia and the related condition of dementia with Lewy bodies account for 15-20% of people with dementia (Svenningsson et al 2012).

These conditions are characterized clinically by motor, sleep, and prominent psychiatric symptoms including hallucinations and other psychotic symptoms. The core areas of neuropsychological impairment include attention, executive function and visuo-spatial performance. Fluctuation of cognitive performance, and particularly fluctuation of attention is prominent (figure 1 – Walker et al 2000), and is related to variability in cortical arousal as measured by EEG.

Increasingly the focus has shifted to the identification of people with Parkinson's disease who have cognitive impairments at a "pre-dementia" stage. This concept has been given the name PD-Mild Cognitive Impairment, and operationalized criteria have been developed (Litvan et al 2012). It has been estimated that between 20 and 30% of people with PD have MCI.

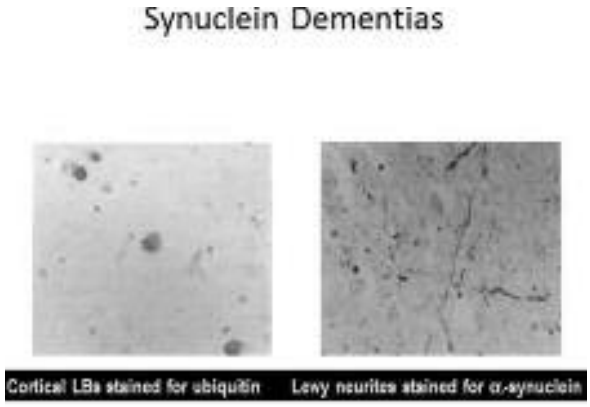
Neuro-pathologically, the core feature is alpha-synuclein depositions in brain-stem, limbic structures and the neocortex (figure 2) but they are usually accompanied by amyloid deposits and tau-pathologies. The alpha synuclein burden most closely relates to the magnitude and progression of cognitive impairment (Aarsland et al 2005), but concurrent amyloid pathologies are associated with the severity of memory deficits.

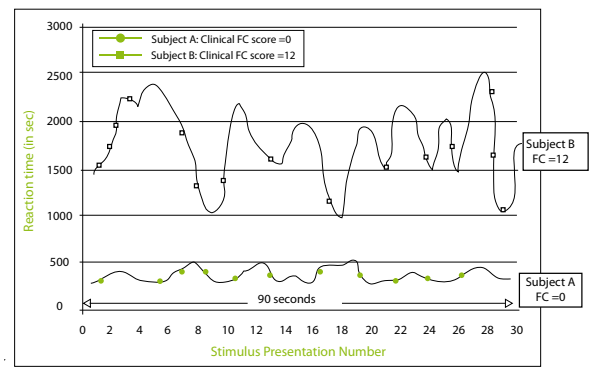
Ascending pathology from the brain stem to the cortex results in progressive monoamine deficits, including the typical loss of dopaminergic neurones leading to motor parkinsonism.

Cholinergic deficits are also prominent and involve ascending cholinergic pathways from the nucleus basalis to key cortical areas from an early stage of the disease. Post-mortem studies have indicated that these cholinergic impairments are closely related to deficits in attention and executive function, and are correlated to the presence of visual hallucinations (Ballard et al 2000, Svenningsson et al 2012).

Cholinesterase inhibitors confer significant symptomatic benefit in the treatment of cognitive impairment (particularly attention and executive function), activities of daily living and visual hallucinations in people with Parkinson's disease dementia and dementia with Lewy bodies and are licensed for the treatment of PDD. Preliminary case series indicate potential benefit in people with PD who have milder degrees of cognitive impairment. Clinical trial evidence also suggests that memantine confers modest but significant global clinical benefits, and may improve sleep disturbances. Emerging studies indicate possible benefit from the MAI B inhibitor rasagiline. The novel 5ht2a inverse agonist is effective in treating psychotic symptoms in people with PD, including those with dementia.

Work to develop disease modifying therapies are at a more preliminary stage of development, but immunotherapy, treatments targeting lysosomal and proteasome clearance of abnormal proteins and strategies to enhance endogenous neurogenesis are all under investigation.





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Cognition in schizophrenia: aging effects and the role of memory impairments

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Cognitive impairment in schizophrenia has been the focus of clinical and research attention for more than 100 years. These impairments are wide ranging and in many domains severe in their magnitude. Disability is also pervasive and spans domains of productive activities, social functioning, and maintaining independence in living. Cognitive impairments, likely through their influence on the ability to perform everyday functional activities, are a major cause of disability.

Cognitive deficits are not the result of other symptoms of the illness, treatments for the illness, or immediate environmental factors. These deficits appear similar in nature and severity in multiple different parts of the world and have been found to have similar correlations with disability worldwide. These findings suggest that cognitive impairments are a central feature of the illness and not an artifact of other influences.

Domains of impairment include processing speed, various aspects of memory functioning, reasoning and problem solving, and attention. Impairments are present prior to the development of the other symptoms of the illness and they appear quite stable over time. Other than in a limited subset of patients, there appears to be little change over time, both in terms of improvement associated with recovery or worsening with more severe symptoms or increasing age.

The limited exceptions to these findings will be described below. There are three aspects of memory functioning most impaired in schizophrenia. These include episodic memory, the processing of learning information with practice and exposure and recalling it after a delay, working memory, the process of maintaining and manipulating information in short term memory, and prospective memory, the process of recalling information that has to be used in the future.

Episodic memory can be measured with various learning paradigms. These include list learning and story learning. The ease of learning of the information can be manipulated by making it more or less challenging to encode. Further, interference effects can be induced, by interspersing information between learning and recall. Finally, retrieval can be manipulated as well, through either simply asking the participant to recall information (free recall) or by providing various prompts and cues (recognition or cued recall).

In people with schizophrenia, there is little evidence of rapid forgetting as seen in dementia. In contrast, the extent to which information is learned is an efficient predictor of the extent of delayed recall. However, rates of learning can be quite impaired.

Working Memory can include memory for verbal information, spatial locations, and actions.

Maintenance features include retention of information without rehearsal and information is lost from working either by simple decay processes or by being replaced in the limit-capacity store by new information. Manipulation involves the process of organizing the information in short term storage. This is often measured by asking the participant to organize information, such separating different types of information such as letters vs. numbers, or by recalling information in reverse order.

People with schizophrenia demonstrate deficits in both aspects of working memory, but have greater deficits in manipulation. Further, the overall capacity of working memory seems to be limited in people with schizophrenia. This limitation has been widely studied and impacts on the ability of people with schizophrenia to perform multi-tasking operations.

Prospective memory involves the ability to remember to do things in the future and is likely critical for organization of one's life and self-care. Recalling to take medication is a critical feature of prospective memory and other functional acts such as remembering what to buy when shopping or in what sequence to perform daily activities are also features of prospective memory.

Aging effects on cognition in schizophrenia appear relatively greater than healthy individuals only in a subset of cases with schizophrenia. These include patients with a lifelong course of treatment nonresponse and often who have experienced chronic institutional stay. These declines appear not to be associated with institutionalization itself, as impairment appears to continue to progress after discharge from long-stay hospitals.

Aging effects may be difficult to detect because of the substantial impairments seen earlier in life in people with schizophrenia. Studies comparing schizophrenia patients healthy controls have found that schizophrenia patients in their 40's perform more poorly than healthy controls in their late 70's.

Other aspects of cognitive functioning may be as important as memory for prediction of everyday outcomes. These include impairments in processing speed, the ability to rapidly and efficiently perform complex tasks. When abbreviated assessments of cognitive performance in schizophrenia are developed, processing speed appears to predict multiple outcomes most significantly. However, both episodic and working memory also contribute to the prediction of real-world outcomes. As different aspects of cognition in schi-

zophrenia appear to be quite intercorrelated, a common impaired circuit may be responsible for the occurrence of multiple different cognitive deficits.

Resting state studies have suggested that there is excessive resting activity in hippocampal regions and reduced adaptive response of these regions to cognitive demands.

Summary
Deficits in memory are central in schizophrenia, predicting disability ad being present over the course of illness from prior to the first psychotic symptom until later life. Treatment of cognitive deficits is a likely path forward to reduce disability and improve the quality of life of the millions of people with schizophrenia worldwide.

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Successful Memory Aging: The Brain Maintenance View

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Not all human memory systems are equally affected by advancing adult age. Specifically, a positive age gradient has been found for semantic memory, and other types of memory (i.e., primary memory, procedural memory, priming) change relatively little in old age.

By contrast, episodic and working memory are negatively affected in normal human aging. Episodic memory is considered to be the most age-sensitive long-term memory system (1). Working-memory performance is also typically reduced in old age. Studies in the cognitive neuroscience of aging have begun to link declining episodic and working memory to structural and functional brain changes. Recently, there has been much progress in this interdisciplinary area, reflecting increased availability of brain-imaging technology and a trend toward refined study designs with large sample sizes.

Although episodic and working memory decline in adulthood and old age, evidence on the onset of decline is mixed. Most cross-sectional studies suggest linear decline across the adult life span, beginning as early as in the 20s. Longitudinal studies tell a very different pattern, indicating that episodic memory remains relatively stable until 60-65 years of age, after which accelerated decline is typically observed. One source of this discrepancy is that cross-sectional estimates of age-related change are biased by cohort effects, including age differences in educational attainment (1): when age differences in educational level are statistically controlled in cross-sectional analyses, age differences in episodic memory are apparent at a much later age. Less is known about the average onset of decline in working memory. The reason for this lacuna is the absence of lifespan longitudinal studies on working memory. However, longitudinal evidence exists for some cognitive abilities, such as reasoning, that are highly related to working memory. Similar to episodic memory, this evidence suggests a relatively late onset of average age-related decline. For example, data on visuo-spatial reasoning indicate that decline starts after age 55. Taken together, the available longitudinal evidence does not support a view of an early onset of decline in episodic and working memory.

Findings from several large-scale population-based studies demonstrate substantial inter-individual differences in how episodic and working memory change in old age. These between-person differences increase as a function of advancing adult age. A more rapid than average decline for a certain individuals has attracted much interest, as it might be indicative of forthcoming diseases, such as dementia. Relatively less attention has been paid to individuals who display little or no memory decline. A main reason for this is methodological difficulties – identifying individuals with preserved memory functioning is a challenge and often involves testing large samples. In one study, cognitive and non-cognitive data from approximately 1500 adults in the Betula longitudinal study were analyzed with a factor-analytic technique in order to classify individuals in terms of 'usual' versus 'successful' aging. Results revealed substantial heterogeneity in levels of cognitive performance.

Of chief interest, almost 10% of the participants older than 70 years were categorized as meeting the criterion of successful cognitive aging, performing at levels comparable to those of younger adults.

Longitudinal studies provide additional evidence for heterogeneity in aging trajectories of cognitive performance, including identifying sub-groups of elderly individuals who maintain superior levels of cognitive performance over time.

Thus, evidence indicates substantial individual differences in both level and change of memory performance in old age, and that there are high-performing older individuals who display little or no performance decline.

The fact that some older adults show little evidence of cognitive decline have led researchers to propose general mechanisms that may protect against imminent age-related cognitive losses. One of these concepts is 'reserve'. The reserve concept captures properties of brain and cognition. In either case, the amount of reserve is assumed to determine the relation between age-related pathological alterations in the brain and behavioral manifestations, so that some individuals are more likely to tolerate a certain amount of pathology (e.g., amyloid plaques, neuronal loss) than others.

A key variable affecting such individual differences in reserve is educational attainment. According to this view, successful memory performance in old age is primarily determined by having reached high levels of performance prior to the onset of senescent decline than about minimizing decline itself; an individual with a larger brain reserve will have better memory performance and therefore reach the threshold for functional impairment (e.g., a dementia diagnosis) at a later age. The reserve concepts are undoubtedly of great heuristic value; they have informed the search for conditions that promote successful cognitive aging and continue to be refined and specified in neural terms.

Here we introduce brain maintenance as a complementary concept. Maintenance denotes the process of preserving a condition. That is, whereas the reserve concept seeks to explain why some individuals have

intact functioning in the presence of brain pathology, the maintenance concept focuses on the conditions that promote preservation of structural, functional, and neurochemical brain integrity in old age (2).

Thus, the focus is on the relative lack or postponement of senescent brain changes, including pathology, rather than on ways of coping with their presence. We define brain maintenance as follows: 'Individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline'. Maintenance underscores the perhaps obvious, but yet undervalued, notion that the primary characteristic of the brains behind successful memory aging is preserved structure, function, and chemistry.

Next, we review evidence from structural and functional MRI as well as PET-based molecular imaging targeting dopamine and amyloid in relation to the brain maintenance concept.

As with cognitive functioning, there are marked inter-individual differences in the extent to which the brains of older adults deviate from those of younger adults. Findings from structural MRI studies show that some older adults have larger hippocampal volumes and show less annual hippocampal volume change than younger adults. Similar cross-sectional and longitudinal patterns have been reported for other cortical and subcortical structures, including the caudate nucleus (3), as well as for the brain's white matter. Thus, aging individuals differ reliably in rate of structural brain changes and brain integrity is relatively well preserved in some older adults. Burzynska et al. assessed cortical thickness and executive functioning in samples of younger and healthy older adults. The Wisconsin Card Sorting Test (WCST) was administered as an indicator of executive functioning. On average, older adults showed lower performance on the WCST than younger adults and also had a thinner cortex than their younger counterparts. A thicker cortical mantle in the fronto-parietal network, critical to WCST performance, was related to better performance. Importantly, positive associations between cortical thickness and WCST performance were stronger in older than in younger adults. This suggests individual differences in rates of performance-related cortical thinning in aging. Specifically, executive functions seem to be more likely to be maintained into old age if cortical thinning progresses at a slow pace. Further, a longitudinal study investigated the association between changes in white matter integrity, measured with diffusion-tensor imaging, and cognition. Fewer alterations in whole-brain white-matter microstructure were linked to less working-memory decline. Thus, evidence supports the notion that less structural brain changes are associated with better memory performance in old age.

Additional evidence for brain maintenance in aging is provided by fMRI studies. A particularly intriguing pattern of results from such studies in relation to brain maintenance is that of comparable recruitment of functional networks in younger and older adults. Such observations have been made when high-performing older adults have been compared with younger adults.

Nagel et al. examined individual differences in BOLD signal responsivity during spatial working memory in younger and older adults. Initial analyses showed that the BOLD signal is less responsive to increasing working-memory demands in old age. However, these overall age group differences were qualified by differences between high and low performers within each of the two age groups.

The dose-response functions across load of old high performers resembled those of the young, suggesting that similarities in functional activation patterns were related not only to chronological age, but even more so to performance level. Similarly, Nagel et al. investigated whether individual differences in performance also contribute to adult age differences in BOLD signal responsivity during verbal working memory. As in the previous study, older adults as a group showed compromised BOLD signal responsivity to increasing working memory load. At the same time, BOLD responsivity, as well as load-dependent functional connectivity in frontoparietal regions predicted working-memory performance at high load for both younger and older adults, indicating that modulation of brain activity contributes to proficient performance regardless of adult age. These two fMRI studies indicate that older adults with relatively high levels of performance increase brain activity in task-relevant brain regions as a function of load, whereas low-performing older adults show flat or inverted-U shaped activation profiles. Hence, the patterns of brain activity associated with high working-memory performance look strikingly similar across age groups: Older adults with more 'youthful' brain responsivity to increasing task demands show higher levels of working memory performance than older adults whose brain responsivity differs from younger adults.

An fMRI study of episodic memory addressed brain changes in relation to different cognitive aging trajectories.

Twenty-six 55-79-year-old individuals were followed behaviorally over 20 years and assessed with fMRI at two occasions spaced six years. All participants had stable levels of episodic memory performance up until the first fMRI session. However, thereafter some persons remained stable or even increased slightly, whereas others declined. Critically, the longitudinal fMRI analysis revealed that BOLD signal in left hippocampus showed a time-related decrease for individuals with declining, but not for those with stable, memory performance.

Also, individuals with declining performance had declining hippocampus volume. Additional evidence for brain maintenance in episodic memory comes from an fMRI study of brain activity patterns associated with encoding processes. Those older adults whose activation patterns during encoding resembled those of the young had well preserved recollection.

Thus, successful aging of episodic memory appears to reflect preservation of a functional memory network characteristic of younger adults.

Research on how aging influences neurotransmitter systems, notably the dopamine (DA) D1 and D2 systems, provides additional evidence for brain maintenance underlying successful cognitive aging. Numerous PET and SPECT studies have linked DA losses to age-related deficits in multiple cognitive domains, including episodic and working memory (4). It is evident that individual differences in DA binding are pronounced. Of particular relevance here are findings that such differences persist in old age. Rieckmann et al. examined the links between different DA D1 pathways in younger and older adults.

They found that the associations of nigrostriatal to mesolimbic and mesocortical DA pathways were reduced in aging along with slower responding in an interference resolution task. This pattern suggests that aging is associated with reduced connectivity among DA pathways. Of key significance, however, some older adults showed preserved relationships of D1 binding in sensorimotor and frontal regions and these individuals were as fast as their younger counterparts in the cognitive task. Thus, corroborating the MRI work, preserved DA functioning in aging was associated with preserved cognitive performance.

Brain maintenance in aging may manifest itself in other ways than in the MR- and molecular-imaging applications discussed above, including vascular influences. On a more microscopic level, brain autopsy can reveal dementia-related neuropathological lesions, and it has been shown that neurofibrillary tangles, cerebral infarction, and neocortical Lewy bodies contribute to age-related cognitive decline. Critically, consistent with the concept of brain maintenance, little age-related cognitive decline has been observed in the absence of such lesions. Further, PET can be used to provide in vivo information on pathological processes that underlie Alzheimer's dementia (AD), including amyloid burden. In keeping with the brain maintenance view, several studies have found that high memory performance is related to low amyloid burden in frontal and parietal areas. In a large sample of 137 adults, Rodrigue and colleagues observed that many adults even in their 80s had modest levels of amyloid and high amyloid burden was related to working-memory performance. A longitudinal study showed that high amyloid deposition predicted transition from normal to impaired cognition, whereas low amyloid deposition predicted cognitive stability.

Taken together, a wide range of findings provides converging evidence for marked heterogeneity in brain aging.

Of critical import, some older adults show little or no brain changes relative to younger adults, along with intact cognitive performance, supporting the viability of the brain maintenance concept. In other words, maintaining a youthful brain, rather than responding to and compensating for changes, may be the key to successful memory aging.

An intriguing question, then, is whether there are factors that may promote brain maintenance in old age. Genetic factors represent a case in point. Some genetic variants may be especially conducive to maintaining high levels of brain functioning, thereby contributing to the large heterogeneity of memory functioning in old age. It has been hypothesized that losses in neurochemical and structural brain resources associated with aging magnify the influence of common genetic variations on cognitive functioning. This hypothesis rests on the assumption that the function relating brain resources to cognitive performance is nonlinear, such that genetic variability is more likely to result in performance differences when resources move away from close to optimal levels, as in aging. In line with this notion, twin studies suggest that individual differences in the acceleration of cognitive decline from adulthood to old age are strongly influenced by genetic factors.

Furthermore, age-comparative studies linking allelic variations in single nucleotide polymorphisms to memory performance show increasing genetic effects with advancing adult age, thereby supporting the hypothesis that common genetic variations contribute to heterogeneity of memory functioning in old age. Examples include genes related to dopaminergic (e.g., COMT, DRD2, DAT1) and glutamatergic (NR3A) neurotransmission, synaptic plasticity (e.g., BDNF, KIBRA, CLSTN2) as well as to vascular integrity and neural repair (e.g., APOE), as reviewed by Papenberg et al.. This pattern of data is in line with the view that maintenance of memory functioning in aging depends, in part, on genetic factors.

In addition, environmental factors and lifestyle choices play a role in maintaining brain integrity and cognitive performance in old age. In the literature on brain and cognitive reserve, education has been a much discussed factor in this context. Evidence consistently shows that education is associated with level of memory performance in old age, but not with inter-individual differences in rate of change. Thus, the association between education and cognitive functioning in old age likely reflects individual differences in cognitive functioning that have survived since early adulthood. In contrast, engagement in socially, mentally, and physically stimulating leisure activities reliably predicts change in cognitive performance in old age; greater engagement in socially and mentally stimulating activities predicts less subsequent cognitive decline. Moreover, higher complexity of main lifetime occupation is associated with higher cognitive performance, but these effects are reduced after retirement, supporting the 'use-it-or-lose-it' adage. These findings suggest that preserving level of late-life cognitive functioning (i.e., avoiding negative change) is more a matter of what you do in old age than what you did in earlier periods of the life-span.

Even though the empirical evidence of an association between an enriched lifestyle and cognitive perfor-

mance in aging is convincing, the brain mechanisms mediating this association are largely unknown.

Nonetheless, some evidence suggests that brain integrity is modifiable by experience and learning. For example, motor learning and the acquisition of abstract knowledge are associated with alterations in gray-matter morphology in early adulthood. Such experience-dependent plasticity of brain volume extends into old age. Similarly, white matter integrity of the brain is modifiable by experience in younger and older persons alike. Thus, lifestyle factors such as engagement in stimulating leisure activities may affect cognitive performance by preserving the brain's grey and white matter.

Hence, both genetic and lifestyle factors support brain maintenance in aging. In addition, preserving the brain may not only be a matter of avoiding negative influences on brain integrity, such as cerebrovascular conditions (3), but also reflect direct positive influences on brain plasticity. Some individuals may show reliable decline as early as in their 50s. Conversely, and of main concern here, others may show relatively preserved memory functioning well into their 70s. Preserved memory functioning in old age may reflect the fact that the brains of some older adults age less rapidly and show little or no pathology. According to the maintenance view, the brains of individuals whose cerebral anatomy and neurochemistry is relatively well preserved are more likely to show functional brain activation patterns that resemble those of younger adults and that are germane to proficient performance.

Thus, the maintenance concept focuses on relative lack or postponement of senescent brain changes as the key to preserved cognition in old age.

As noted, specific genetic and life-style factors are related to brain maintenance. A related issue concerns the influence of various forms of training and intervention. An important implication of the maintenance view is that cognitive interventions should aim at maintaining, and possibly restoring, youthful brain structures and functions (2). That is, rather than expecting that training will evoke novel brain responses in older adults, interventions may improve performance by reducing or remediating age changes in various aspects of brain physiology. Support for this position comes from functional imaging studies, where both cognitive and physical interventions served to make the activation patterns of older adults more similar to those of younger adults.

Similarly, structural brain imaging work has provided evidence for restoration after both cognitive and physical intervention programs. Thus, maintaining the integrity of the brain is a critical determinant of preserved memory and other forms of cognition in late life. That said, maintenance should not be viewed in absolute terms. Rather, even successful aging is associated with some negative brain changes.

There are several intriguing issues for future research on brain maintenance in aging.

These include work on how measurements of memory and cognition should be optimized to index brain maintenance? Can latent factor models be used to compensate for limited reliability and validity of individual cognitive tasks, and hence better capture subtle age-related decline? Will a multimodal imaging approach provide a more comprehensive account of inter-individual variability in brain maintenance? Will future longitudinal PET data confirm cross sectional estimates of marked average age-related decline in dopamine system integrity? Can brain maintenance, similar to liability to diseases, be quantified? Are some aspects of brain integrity more critical than others in relation to brain maintenance?Are there genetic and lifestyle determinants of brain maintenance still to be discovered? What is the potential for restoring a youthful brain signature in aging after negative changes have commenced and how durable are potential reversals? Finally, at a conceptual level, what is the relation among brain reserve, cognitive reserve and brain maintenance? Are reserve and maintenance related, such that some individuals show fewer age related brain changes (maintenance) as well as less vulnerability to brain pathology when it eventually manifests (reserve)?

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The role of cognitive activity and physical exercise in the prevention of memory disturbances

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It is estimated that one third of all health-related expenses in Europe are caused by brain disorders, of which dementia is one of the most relevant. As dementia is strongly associated with age, and the number of elderly people is increasing worldwide, we will face an epidemic of dementia in the coming decades. Alzheimer disease (AD) is the most frequent type of dementia, accounting for up to 75% of all dementia cases. However, autopsy and neuroimaging studies have revealed that mixed dementia characterized by brain lesions of both cerebrovascular and degenerative etiology accounts for the majority of dementia cases among old individuals (age 75+).

Dementia is a complex disorder and the main cause of disability among elderly. It affects not only patients themselves, but also people close to the patients, such as family and friends, and has huge societal impact due to the patients' need for informal and formal professional care. For all those reasons, dementia challenges all societies worldwide and their health care systems. Thus, the identification of strategies to decrease dementia risk is a relevant scientific goal with important clinical and public health implications.

There is growing recognition that the development and clinical manifestation of dementia in old age may be determined not only by individual differences in genetic susceptibility but also environmental and social factors experienced over the life course. The life-course approach provides the possibility of determining whether accumulative exposures could have integrative or additive effects over the life course. It allows also identifying possible time windows when exposures might have their greatest effect on dementia risk, which could lead to better specify interventions targets relevant for chronic disorders with a long latent time period such as dementia and AD (1).

All population-based studies up to the present have shown that 40% to 50% of people who reached the age of 90 are free of dementia, suggesting that dementia is not an unavoidable event when people get older. Who are these dementia-free people? Why and how do they escape dementia? It is already possible to provide some answers to these questions. Several epidemiological studies support the hypothesis that vascular and psychosocial factors play a role in the pathogenic processes and clinical manifestations of the dementing disorders, over and above genetic susceptibility. Moderate to strong evidence from multidisciplinary research (epidemiologic, neuroimaging, and neuropathological studies) supports the hypothesis that vascular risk factors (such as smoking, obesity, and high total cholesterol) and vascular morbidity (such as high blood pressure, diabetes, silent brain infarcts, and white matter lesions) are associated with an increased risk of dementia, including AD (2). A systematic review reported that psychosocial factors and an actively integrated lifestyle over the lifespan may reduce the risk of AD and dementia (3). These factors include early-life high educational attainment, adult-life high work complexity, late-life rich social network and high levels of social engagement, and frequent participation in physically and mentally stimulating activities.

The role of these factors in dementia has been indirectly confirmed by recent reports concerning time trends in prevalence, survival, and incidence of dementia and AD in several countries. In a population-based study from Central Stockholm, Sweden, we found that prevalence of dementia was stable from the late 1980s to the early 2000s, whereas survival of patients with dementia increased, which suggests that incidence of dementia may have decreased during this period (4). Similar results have been detected in the Netherlands, United Kingdom, and United States and indirectly confirmed by a Danish study concerning prevalence of physical and cognitive impairment in two groups of nonagenarians born ten years apart.

The decrease in dementia risk over the last two decades may be due to 1) the preventive and therapeutic interventions for major vascular risk factors that have substantially decreased the risk of major cardiovascular disease since the 1980s, and 2) increased brain reserve linked (for example) to higher educational level.

This evidence provides a strong argument for the view that strategies to maintain cardiovascular health and to promote active lifestyles from midlife onward could represent the most promising approach to protecting the brain from cognitive decline, thus benefiting cognitive function in ageing (5). Currently, several multi-domain intervention studies are ongoing, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Healthy Ageing Through Internet Counselling in the Elderly (HATICE), and the Multimodal preventive trials for Alzheimer's Disease (MIND-AD). These studies will clarify the extent to which multi-domain interventions that include cognitive training, physical exercise and control of vascular burden will delay the onset of cognitive impairment and dementia among

people at increased risk.

We can conclude that aging without dementia is already a reality today. By applying our increasing knowledge, more people may remain free of memory disturbances such as dementia in the future. When results from the ongoing interventions will be available, our possibility to promote a healthy aging will be potentiated.

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