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WHEN I SHOW THE BEATLES THEN YOU SAY: "RAMONES!": IMAGING SEMANTIC MEMORY IN ALZHEIMER'S DISEASE AND SEMANTIC DEMENTIA

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Stockholm 2012

Published by Karolinska Institutet. Printed by Larserics Digital Print AB.

Image on the front page by Petter Kallioinen.

ISBN 978-91-7457-759-4

In loving memory of Carl Olof Jonatan Tullus, who has carried me in his arms through all these years. A very strong angel.

ABSTRACT

Elderly people contacting the health care system because of suspected dementia very often report word forgetfulness, a clinical condition referred as anomia, often one of the first signs of cognitive decline. Considering the complexity of human language it is no wonder that dementia disorders can affect language processing, which in its turn relies heavily on the intactness of the semantic memory system. In an attempt to study language impairment in dementia, this thesis aimed to investigate semantic memory, from its normal degradation in healthy ageing, to its disruption in dementia, and from controlled to unconscious semantic processing. Moreover we chased the anatomical locus of semantic memory with the combination of several neurophysiological and neuroimaging techniques.

In **Study I** we investigated controlled semantic retrieval together with pattern of blood perfusion through the performance of verb fluency (VF) and animal fluency (AF), combined with Single-Photon Emission Computed Tomography (SPECT) in patients suffering from Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), and Subjective Cognitive Impairment (SCI).

In **Study II** we enquired automatic semantic retrieval in healthy young and healthy elderly, combining a novel semantic priming paradigm to Event Related Potential (ERP) Electroencephalography (EEG).

In **Study III** we used the same semantic paradigm and ERP EEG measurement as in Study II to investigate automatic semantic retrieval in AD, Semantic Dementia (SD), and an healthy elderly population. The result was then correlated to measure of blood perfusion by means of Pulsed Continuous Arterial Spin Labelling (PCALS) Magnetic Resonance Imaging (MRI).

In **Study IV** we chased the anatomical locus of semantic memory through the study of grey (GM) and white matter (WM) pathology in AD, SD, and healthy ageing, combining Voxel-Based Morphometry (VBM) MRI and Diffusion Tensor Imaging (DTI) MRI.

We could show that controlled semantic retrieval, and in particular VF is impaired in dementia and that this correlates to hypoperfusion in particular anatomical regions. Moreover, we could prove the automatic semantic retrieval remains stable under the span of healthy adulthood while controlled retrieval is not, and that this processes activates neurophysiologically comparable neural networks for healthy young as well as for healthy elderly. In addition we could show that automatic spread of activation is spared in mild dementia despite the deviant result in measures of controlled semantic processes and we found a possible early marker differentiating SD from AD and healthy ageing. We could even associate patterns of hypoperfusion to impairment in controlled semantic memory processing, this indicating that the altered electrophysiology of dementia patients is closely related to their structural and baseline blood degeneration. Finally we could detect different patterns of GM and WM loss in the AD compared to the SD group. In particular we could detect a specific area of WM disruption significantly separating AD from SD.

LIST OF PUBLICATIONS

I. Östberg P*, **Crinelli RM***, Danielsson R, Wahlund L-O, Bogdanovic N, Fernaeus S-E. A temporal lob e factor in verb fluency. Cortex, 2007, 43: 607-615. *equally contributing

II. Grieder M*, **Crinelli RM***, Koenig T, Wahlund L-O, Dierks T, Wirth M. Electrophysiological and behavioural correlates of stable automatic semantic retrieval in aging. Neuropsychologia. 2012, 50: 160-171. *equally contributing

III. Grieder M, **Crinelli RM**, Jann K, Federspiel A, Wirth M, Koenig T, Steirn M, Wahlund L-O, Dierks T. Topographic N400 anomaly correlates with reduced cerebral blood flow in the anterior temporal lobes of dementia patients. *Submitted.*

IV. **Crinelli RM**, Grieder M, Spulber G, Manzouri A, Östberg P, Dierks T, Wahlund L-O. A multimodal neuroimaing approach to Alzheimer's disease and Semantic Dementia: a study in grey and white. *Manuscript.*

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
MCI	Mild Cognitive Impairment
SD	Semantic Dementia
SPECT	Single-Photon Emission Computed Tomography
SCI	Subjective Cognitive Impairment
ERP	Event-Related Potential
EEG	Electroencephalography
PCALS	Pulsed Continuous Arterial Spin Labeling
MRI	Magnetic Resonance Imaging
VBM	Voxel-Based Morphometry
DTI	Diffusion Tensor Imaging
CA1	Corno Ammonis region 1
CA3	Corno Ammonis region 3
SPI	Serial encoding, Parallel Storage, Independent retrieval
SFT	Sensory/Functional Theory
HIT	Hierarchical Interference Theory
OUCH	Organized Unitary Content Hypothesis
DSKH	Domain-Specific Knowledge Hypothesis
SMMSK	Sensory-Motor Model of Semantic Knowledge
CSA	Conceptual Structure Account
ATL	Anterior Temporal Lobe
PET	Positron Emission Tomography
fMRI	functional MRI
rTMS	repetitive Transcranial Magnetic Simulation
SOA	Stimulus Onset Asynchrony
MMN	Mismatch Negativity
SNR	Signal to Noise Ratio
RF	Radiofrequency Pulses
GP	Gradient Pulses
TR	Repetition Time
TE	Echo Time
PD	Proton Density

SE	Spin Echo
GE	Gradient Echo
FSE	Fast Spin Echo
FOV	Field of View
DBM	Deformation-Based Morphometry
TBM	Tensor-Based Morphometry
GM	Grey Matter
WM	White Matter
CSF	Cerebrospinal Fluid
GLM	General Linear Model
SPM	Statistical Parametric Mapping
ROI	Region of Interest
MNI	Montreal Neurologic Institute
CBF	Cerebral Blood Flow
CT	Computed Tomography
ASL	Arterial Spin Labeling
PLD	Post Labeling Delay
DICOM	Digital Imaging and Communication in Medicine
EPI	Echo Planar Imaging
PALS	Pulsed Continuous Arterial Spin Labeling
CASL	Continuous Arterial Spin Labeling
VS-ASL	Velocity Sensitive Arterial Spin Labeling
MF	Magnetization Transfer
FA	Fractional Anisotropy
DA	Axial Diffusivity
DR	Radial Diffusivity
MD	Mean Diffusivity
TBSS	Tract-Based Spatial Statistics
rCBF	Regional Cerebral Blood Flow
IPSP	Inhibitory Pre-Synaptic Potential
EPSP	Excitatory Pre-Synaptic Potential
GFP	Global Field Power
TANOVA	Topographic Analysis of Data
TCR	Topographic Component Recognition

FTD	Fronto-Temporal Dementia
FDG-PET	Fludeoxiglucose Positron Emission Tomography
aMCI	amnestic Mild Cognitive Impairment
nMCI	non amnestic Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
NF	Noun Fluency
VF	Verb Fluency
EC	Elderly Controls
YC	Young Controls
BNT	Boston Naming Test
GDS	Global Deterioration Scale
CDS	Cornell Depression Scale
RT	Reaction Time

1. A BEAUTIFUL HYPOTHESIS BY AN UGLY FACT

Elderly people contacting the health care system because of suspected dementia very often report word forgetfulness, a clinical condition referred as anomia. Anomia is clinically defined as the failure to name objects, concepts and people whether in response to a stimulus presentation or in spontaneous speech. It is now widely known that word retrieval and word usage depend causally on a neuronal network which must be activated in a fast and precise way for everyday use. Considering the complexity of human language it is no wonder that even mild brain disorders can affect language processing and thus lead to anomia. What is also known is that such an intricate and nevertheless intriguing phenomena as human language heavily relies on the intactness of semantic memory, a system considered the site of conceptual knowledge, thus an associative and organised network storing words, concepts, and their associations. The study of anomia and, consequently, the study of what semantic memory language relies on, is of particular interest in clinical practice as it is often one of the first signs of cognitive decline, even when no other objective evidence of memory deficit can be found. In an attempt to shed a light on language impairment and its neurological substrate, this thesis aims to investigate semantic memory, from its normal degradation in healthy ageing to its disruption in dementia. In particular our focus has been on neurodegenerative dementia disorders such as Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI), here considered as mirroring a cognitive impairment continuum, and Semantic Dementia (SD), a condition considered as characterised by semantic memory impairment only. In order to chase semantic memory impairment, from its clinical features, to its neural correlates, we have combined different techniques consisting of neuropsychological tests together with neurophysiologic and neuroimaging methods. We started with combining known techniques on subjects in different stages of dementia, to continue with the creation of novel tools and their evaluation on healthy subjects, to finally complete our model with the combination of those new methods on dementia patients. Moreover we went from investigating effortful semantic retrieval to disentangling automatic semantic processes.
In sum we aimed to:

1. Investigate explicit semantic retrieval together with pattern of blood perfusion through the performance in verb and noun fluency combined with Single-Photon Emission Computed Tomography (SPECT) measurements in patients suffering from AD, MCI, and Subjective Cognitive Impairment (SCI).

2. Investigate age effects in speed stability of implicit semantic retrieval in healthy young and healthy elderly combining a novel semantic priming paradigm to Event- Related Potential (ERP) Electroencephalography (EEG).

3. Investigate implicit semantic retrieval in AD, SD, and elderly healthy subjects combining a novel semantic priming paradigm to ERP EEG and Pulsed Continous Arterial Spin Labelling (PCASL) Magnetic Resonance Imaging (MRI).

4. Investigate patterns of grey and white matter pathology in AD, SD, and healthy elderly combining Voxel-Based Morphometry (VBM) MRI and MRI Diffusion Tensor Imaging (DTI).

2. WITHOUT YOUR BRAIN YOU WOULD BE HEARTLESS

2.1 Born in a cab: how the mind emerges from the brain

It's the end of the 70s in New York City and in the back seat of a cab, George Miller and Michael Gazzaniga give name to the scientific discipline explaining how the mind emerges from the brain. Cognitive neuroscience is born and has apparently an American passport.
This is quite true as the quest for the mind started already in ancient Greece with Hippocrates (460-377 BC), now widely considered the father of Western medicine. "Some people say that the heart is the organ with which we think and that it feels pain and anxiety. But it is not so. Men ought to know that from the brain only arises our pleasures, joys, laughter, and tears" Hippocrates wrote after an extensive experience of human dissections (Penfield, 1975). In other words he claimed that without your brain you would be heartless, a cerebrocentric view that he also shared with Plato. The one who was instead not sharing this view was Plato's student Aristotle (384-322 BC), who claimed the heart to be the organ of intelligence (Spillane, 1981) and thus was in favour of a cardiocentric view in which the brain's main role was to cool the heat-producing heart.
It is not a wonder that Aristotle is considered one of the greatest minds of all times cause his (erroneous) cardiocentric view of the dualism brain-heart was the doctrine taught in medical schools all over the world until the 16th century, even if defied by anatomist Herophilus (335-280 BC) who claimed the brain was the seat of intellect, and after him, Galen (130-200), the physician of the Roman gladiators. Galen, observed that the gladiators sustaining a severe brain damage lost most of their mental faculties. Moreover, after having experimented that the breath ceases after cutting the medulla, he postulated that the brain controls respiration (Spillane, 1981). Nevertheless we have to wait until the 19th century to get more sophisticated investigations of the brain, even though still not based on empirical evidence. Two of the pioneers in this direction were the German physician Franz Joseph Gall (1758-1828) and his adept Johann Gaspar Spurzheim (1776-1832) who founded and developed the field of phrenology in an attempt to localize mental functions in the

brain. Phrenology, whose meaning comes from Greek φρήν, *phrēn*, "mind" and λόγος, *logos,* "knowledge", was never considered a knowledge in the scientific meaning of the term we use today, and was eventually rejected, but not before having made a great impact on both psychiatry and neuroscience. The whole theory was based on the concept that the brain is the organ of the mind and certain functions are localized in specific areas. The summed work of Gall and Spurzheim can be read in Spurzheim's Anatomy of the Brain, published in London in 1826 (Spurzheim, 1826).

Studying hundreds of brains, and only helped by his intuition, Gall made a list of 27 personality traits, each associated with a specific brain area which can be in its turn recognized and palpable as a cranial protuberance. Of these 27 traits, 19 were assigned as common to humans and animals while 8 were defined as peculiar to humans. Spurzheim, then, after ending his collaboration with Gall in 1814, increased them to 35 and made those traits and their corresponding areas more precise (Simpson, 2005).

Despite the fact that Gall's and Spurzheim's recognized that the grey matter in the brain is "the source and the nourishment of the nerve fibers", this pivotal discovery was basically neglected by the scientific community while their intuitive work on brain localization was that to be later confirmed by clinical evidence and thus recognized as their greatest contribution to neuroscience (Simpson, 2005).

Three major and famous cases made the phrenology's point.

In 1861, the French physician Paul Broca (1824-1880), described a case of expressive aphasia, later called Broca's aphasia after damage in the inferior left frontal lobe, an observation then confirmed in 1871 when he himself drained an intracranial abscess correctly identified by that specific language impairment (Schiller, 1992).

The second case bringing fuel to the phrenology observations was that of the German neurologist Carl Wernicke (1848-1905), who, in 1874, observed a similar case as that of Broca's except that his patient, victim of a stroke, could speak fluently but couldn't understand either spoken or written language, a condition now called Wernicke's aphasia. Wernicke found the lesion at the conjunction between the left parietal and temporal lobe, an area now called Wernicke's area (Wernicke, 1874)

The third and most famous case strengthening the view of Gall and Spurzheim was that of Phineas Cage, an American workman who in 1848 after a gunpowder explosion, got a crowbar driven through his left temporal lobe. Cage didn't suffer any major neurological defect but suffered from a severe change in personality. It was though only after 12 years from his injury that Cage died from an epileptic seizure and his physician J. M. Harlow, examining his skull could describe his condition, correlate it to his personality change and publish his findings (Barker, 1995).

In short despite the fact that phrenology was a pseudo-science based on non-empirical evidence, it succeeded in bringing forth its localization convictions thanks

to the intriguing fascination its theory brought, but also thanks to the striking personality of its founders.

"The fascination of the founders of phrenology does not lie only in their scientific achievements; it also lies in their flamboyant lives as scientific adventurers. Gall was a near genius, but he was also a shady 18th century sage, with his collections of skull, and his strings of mistresses and wives, and his self promoting travelling circus. He has been compared to the Italian super-quack and charlatan who called himself Count Cagliostro. Spurzheim comes through as a more respectable figure, with his virtuous wife, and his religiosity, and his very public fondness for horses and dogs; it is no wonder that Spurzheim went over better than Gall in pre-Victorian England. But like his master, Spurzheim was an adventurer, and like Gall he was always on the take" (Simpson, 2005).

So due or not due to the catchy personality of his founders phrenology lived on in the work of several other scientists, this time using more and more refined explorative methods.

In 1870 the German born Gustav Fritsch and Edouard Hitzig, applying electrical currents to the motor cortex of a dog, showed how this controls specific movement of the body (Hitzig, 1904). 6 years later their findings were replicated in monkeys by a Scottish physician, David Ferrier, who also showed that the somatosensory cortex, like the adjacent motor cortex, is topographically organised (Ferrier, 1876).

2 years before Ferrier, on the other side of the Atlantic, the American physician Robert Bartholow succeeded in stimulating the cortex of a patient suffering from a comprehensive skull fracture showing how the position of the stimulating probe on the motor cortex produced a muscle movement in a specific part of the body (Valenstein, 1973).

The quest for the localization of brain functions continued then with German neuroanatomist Korbinian Brodmann (1868-1918), who used staining techniques to differentiate cell types in the brain. His study culminated in 1909 when he published his view of the brain as divided into 52 distinct areas named Brodmann areas, a cytoarchitectonic atlas still used today (Brodmann, 1909).

More than 50 years later, The American born Canadian neurosurgeon Wilder Penfield (1891-1976) finally left no doubt that the brain is composed of several specialised areas. His contribution to neuroscience came directly from clinical practice. Together with his colleague Herbert Jasper (1906-1999), he treated epilepsy patients by destroying the nerve cells from the area in which the seizure originated, a technique called the Montreal procedure. An important pre-operative part of the Montreal procedure was also to try to reduce possible side-effects. In order to do so Penfield stimulated the brain of the still conscious patients, then only under local anesthesia, with electrical probes, observing their responses. It was this technique who made him develop a map of both sensory and motor cortex, called the cortical homunculus. These maps, as Brodmann's atlas, are still in use today (Penfield and Jasper, 1954).

Penfield's clinical observations leading to an evidence-based localization theory were then confirmed by the Russian neuropsychologist Alexander Luria (1902-1977), who derived his observations from studies on brain damaged soldiers during World War II. Luria postulated that all behaviour is the product of an interaction of different brain areas working together in synchrony (Luria, 1973).

While many clinicians and researchers were trying to unravel the secrets of the brain using clinical observations, at the same time, others were trying to reach the core of the brain working on the structure of the neuron. Two of the pioneers in this field were Santiago Ramon y Cajal (1852-1934) and Camillo Golgi (1843-1926), both awarded the Nobel Prize in Physiology or Medicine in 1906, despite being in disagreement with each other. While Golgi developed a staining method giving him the possibility to visualize several cells in a given area and making him believe that they were all connected through a common cytoplasm, Cajal found this theory not to be exact. In fact Cajal, studying less myelinated brain areas found out neurons to be separated cells. In short, his "neuron theory", considered the standing point of modern neuroscience, claimed the relationship between nerve cells to be based on contiguity, rather than on continuity, this last being instead Golgi's standpoint (Shepherd, 1991).

Nevertheless, despite countless studies and evidence, the debate about the location of the mind went on for centuries. And it would probably come as a shock that the first one to claim the mind emerges from the brain was Leonardo da Vinci (1452-1519), who, as a matter of fact shocked his peers too, but would now be acclaimed by most neuroscientists, and above all by Sir Francis Crick . Sir Francis Crick (1916-2004), awarded the Nobel Prize in Physiology or Medicine in 1962, and a molecular biologist turned neuroscientists, claimed the mind to be only a way to talk about the brain's functions (Crick, 1966). Leonardo couldn't have said it better.

So for thousands of years, experiments in molecular biology, electrophysiology, neuropathology, neurosurgery, and computational neuroscience, have tried to disentangle the secrets of the brain and gave rise to neuroscience, as it is called today. We had though to wait until 1971 for neuroscience to be considered a scientific field. That was the date of the first annual meeting of the Society for Neuroscience (established in 1969, and now with more than 40.000 members), held in Washington, D.C. and attended by 1.396 scientists.

Parallel to the rise of neuroscience, cognitive science too started to put together all the pieces of knowledge gathered during the 1950s and 1960s. What gave a new boost to the field was even here, a meeting of scientists, taking place on September 11th at the Massachussetts Institute of Technology. It's here where George Miller presented his famous article "The Magical Number Seven, Plus or Minus Two" (Neisser, 1967), the same George Miller who only 4 years later shared a cab with Michael Gazzaniga and gave a label to what came to become a never-ending interaction between neuroscience and cognitive science.

Since then cognitive neuroscience has tried to provide an explanation on how the mind emerges from the brain through the study on how neural substrates are

responsible for mental functions and behaviour. But despite the increasing advance in technologies and in particular of neuroimaging techniques, there is still much of controversy around such a complex research subject as the human brain. Nevertheless, there is no controversy at all about what Aristotle once wrote: “For the brain, or in creatures without a brain that which corresponds to it, is of all parts of the body the coolest”. I guess every cognitive neuroscientist would agree on that.

2.2 Emerging memory: bringing our first kiss to mind

It is said that the brain houses our personality. What we are is the product of our life’s experiences, knowledge, and memories. It’s the same experiences, knowledge, and memories that can be brought to mind as a conscious recollection, as everything that can potentially be declared, as declarative memory.
So how can we consciously recollect our first kiss? Cause isn’t that so that you never forget your first kiss?
In order to remember the sweetness of our first kiss, this information has to enter long-term memory first and subsequently be successfully retrieved from storage. In psychological terms what we do when we prepare a piece of information to enter our memory is to convert it into a code, or to encode it, meaning that the information gets processed before entering storage.
We can then consider the experience of our first kiss as an engram, also referred as the sum of the changes in the brain that constitutes a particular experience. So in short, the details about where we had our first kiss, its taste, the person we kissed, if it was in daylight or under a night sky, all this information, either as episodic (source or autobiographical memory) or semantic memory (encyclopedic or conceptual memory) is processed, and distributed in different brain regions, each specialized in a specific kind of information.
Luckily most of us can not only encode, but also store, and retrieve this information successfully and can still enjoy the memory of that first kiss. But it is important to bear in mind that an error can happen at any time, leading to the disruption of our memory.
In order to understand how memory can easily be formed but as easily disrupted, we are going to undertake a travel into the human brain, together with our memories.
A basic feature of memory is that it is divided into short-term and long-term memory.
Short-term memory retains information only for a limited period of time. After that period this information is lost unless continuously rehearsed or entered into long-term memory. Short-term memory can further be divided into immediate memory and working memory. Immediate memory has two basic features: it is limited and “persecuted by an integer” as George Miller wrote on his seminal paper “The

Magical number seven, plus or minus two: some limits on our capacity for processing information" (1956). What Miller found out and which came to be a measure of immediate memory is that when a subject is given an increasing number of stimuli to discriminate, it is possible to discern the point in which confusion starts, even called one's "channel capacity". This point is then proposed to be somewhere near seven, and called "the span of absolute judgment" (Miller, 1956). In sum, immediate memory has limited capacity of more or less seven items and it persists for less than 30 seconds. For those memories to be retained they have to be sustained in working memory, considered an extension of immediate memory. Finally those memories can be stored in long-term memory. While working memory is dependent of the sustained attention given by the top-down action of the frontal lobes, long-term memory is very much dependent on the medial temporal lobe system, which is both needed at the time of exposure and during a period of reorganization until the long-term representations are finally stored in the neocortex. In other words, if the consolidation of long-term memory is very much dependent on the medial temporal lobe, the final site of those memories (with some exception we will discussed later) is in the same areas of neocortex which perceive and process what is to be stored in memory, i.e. in their corresponding motor and sensory systems (for a review see Martin A, 2007).
The medial temporal lobe includes the amygdala, the hippocampus, and its adjacent areas such as the entorhinal cortex, the perirhinal cortex, and the parahippocampal cortex. The hippocampus, and its surrounding cortex are the areas crucial for the formation of declarative memory. The amygdala, on the other hand, is not essential for declarative memory, but has a crucial role in regulation of emotions and is important for emotional memory.
The hippocampus receives mainly information from the entorhinal cortex which in turns receives most of information from the perirhinal and parahippocampal cortex. All those areas receive and send information to a broad extent of other areas, the same ones that are responsible for the perception of what has to be stored and that finally keeps it in storage.
In sum, the saying: "what goes around comes around" fits perfectly as a definition of long-term memory.
Here the medial temporal lobe acts like a funnel in the transition between perception and memory. In other words, and to get back to our first kiss: the information is first processed and coded by areas of the neocortex specialized in the recognition of certain features (e.g. taste, movement, touch, and so on). This means that neural activity has to occur in those areas together with the sustained attention given by the frontal lobes. At the same time, the information processed by those different cortical areas projects into the parahippocampal, perirhinal, and entorhinal cortex, and enters the hippocampus by way of the dentate gyrus, the areas CA3 and CA1, and eventually exits by the subiculum and through the entorhinal cortex reaches the original areas of the neocortex for storage.

So, the memory of our first kiss takes several steps to get fixed in our memory, and it's during any of those steps that memory is still considered vulnerable and can be disrupted. It is now widely known from studies of brain injured patients that a lesion in the medial temporal lobe can impair all declarative memory even if perception is spared. In particular, a damage to the hippocampal formation disrupts the formation of new memories but can even affect memories acquired before the damage. In particular it seems that a damage to the CA1 region of the hippocampus disrupts any contribution of the hippocampus to the formation to long-term memory. Even more interestingly, a damage to the cortex surrounding the hippocampus, such as the perirhinal and parahippocampal cortex seems to affect memory even more than a direct damage of the hippocampus itself (for further reading see Squire and Kandel, 1999). So much for the memory of that one first kiss.

2.3 Independently dependent: semantic and episodic memory

It was the neuropsychologist Endel Tulving who not only introduced the notion of semantic memory but who also defined it as "the memory necessary for the use of language", in contrast to episodic memory defined as the memory for "temporally dates episodes or events, and the temporal-spatial relations among them" (Tulving, 1972). So when while in New York City we remember that we have been there on vacation one year ago, we rely on episodic memory, while knowing that New York is called the Big Apple is a knowledge coming from semantic memory, even denominated the memory for encyclopedic information or general knowledge about the world. Both types of memories are declarative, meaning that they are retrieved as conscious recollections but if episodic memory requires the recollection of a prior experience storing spatial and temporal landmarks identifying when and where the event occurred, semantic memory does not (Tulving, 1985). After Tulving's distinction between the two kinds of memory much of neuropsychological research has focused on finding neuropsychological and neuroanatomical proof for his theory. Among other things semantic knowledge was found to accumulate in cortical sites under the support of the medial temporal lobe. In contrast episodic memory was found to require the same cortical sites together with the medial temporal lobes, under the supervision of the frontal lobes. So the frontal lobes are crucial for maintaining the coherence of an episodic memory, as they function as a "top-down" controller making sure to bias neuronal activity in sensory cortex towards the right sensory information. It's this action of the frontal lobes that virtually define the uniqueness of the event to be remembered (for a review see Squire and Kandel, 1999).

Moreover several studies have pointed out how episodic memory (once established) is much more dependent on the intactness of the medial temporal lobes while semantic memory is not.
For example it has been shown that patients with damage in the medial temporal lobes suffer from severe impairment of episodic memory, affecting both anterograde and retrograde memories. Moreover they seem to have no ability to create new memories and show impaired premorbid episodic memory ranging from several years (Bayley et al, 2006) to the whole lifespan (Rosenbaum et al 2008). On the other hand the same group of amnesics has its premorbid semantic memory mainly intact apart for the knowledge acquired during the immediate premorbid period (Manns et al, 2003). This notion supports then the initial idea postulated by Tulving that semantic and episodic memory are two distinct entities and in particular that if episodic memory relies on the intactness of the medial temporal lobes, semantic memory relies on a healthy neocortex. Nevertheless while many researchers have tried to confirm Tulving's theories, others have focused on the interedependence of the two memory types. To tell the whole truth even Tulving already in 1972 observed that the formation of episodic memory is affected by information found in semantic memory. This view is also shared by the SPI model (Serial encoding, Parallel storage and Independent retrieval). The SPI model claims that the information is processed serially, starting from the perceptual system, passing through semantic memory, to eventually become episodic memory and thus can be stored in parallel and retrieved independently (Greenberg and Verfaeille, 2010). Similarly other researchers have claimed that the formation of semantic memories is dependent on the context in which they are generated (Reder et al, 2009; Mayes and Roberts, 2001). Nevertheless Tulving (1983) claimed that this interdependence is not always present but it is possible to discern situations at encoding and retrieval, in which it is present and others in which it is not. Several studies have shown that in normal controls episodic memory facilitates the formation of semantic memory together with the consolidation of those memories in the neocortex, while other studies claim that semantic memory facilitates the formation of episodic memories (Greenberg and Verfaeille, 2010). This latter view seems in particular confirmed by research on dyslexia, SD and aphasia which have shown that impaired semantic scaffold, at least in the verbal modality, impairs the acquisition of new episodic memories (Graham et al, 2000; Kinsbourne et al, 1991; Ween et al, 1996). In another study Greenberg et al (2009) studying autobiographical memory, showed that in normal subjects episodic memory helps to successfully retrieve semantic memories by providing a more organized access route. Similarly Westmancott et al (2004) showed that in patients suffering from medial temporal lobe amnesia episodic memory was impaired and this reduced successful semantic retrieval. Moreover a longitudinal study on autobiographical memories has shown that impaired autobiographical recollection reflects the worsening of semantic memory (Maguire et al, 2010).

In short episodic and semantic memory seems to be interdependent at the time of acquisition as well as episodic memory helps retrieve semantic information and semantic information constitutes the base of complex episodic memories.
So what do we measure when we create a cognitive task? Are we sure we are targeting the right memory storage? And if semantic and episodic memory are actually interdependent, how can we disentangle the one from the other? This is also one of the challenges of brain research.

2.4 "Our mental thesaurus": semantic memory

With the risk to seem obsessed with the object of my quest, I dare to repeat that semantic memory is the site of our conceptual knowledge, the storage site for objects, word meaning, facts and people, without the need for landmarks for time and place (theoretically). In other words, and to give an example, when we encounter a Bipedal Dragon we know that it belongs to the order of the Scales Dragons who in their turn belong to the subclass of the Lizard Dragons.
That's semantic memory. Nevertheless and although we now know what semantic memory is, "the search for the neuroanatomical locus of semantic memory has simultaneously led us nowhere and everywhere" (Thompson-Schill, 2003). Traditionally, and as we have discussed briefly previously, semantic memory is retained to reside in those regions overlapping or even corresponding to the regions for perceiving and acting, and thus distributed in neocortical sites. So, following this theory, our memory of the Bipedal dragon will be stored in proximity of brain areas that analyze visual stimuli concerning its visual features, close to brain areas involved in analyzing movement as for its manner of moving and flying, its description near language brain regions like for example the perysilvian areas, and so on. This view has led many investigators to put forward different theories, like for example the Sensory/Functional Theory (SFT) (Warrington and Shallice, 1984; Warrington and Mc Carthy, 1987), the Hierarchical Interference Theory (HIT) (Humphreys and Forde, 2001), the Organized Unitary Content Hypothesis (OUCH) (Caramazza et al, 1990; Hillis et al, 1990), the Domain-Specific Knowledge Hypothesis (DSKH) (Caramazza and Shelton, 1998; Mahon and Caramazza, 2003), the Sensory-Motor Model of Semantic Knowledge (SMMSK) (Gainotti, 2000), and finally the Conceptual Structure Account (CSA) (Tyler et al, 2000; Tyler and Moss, 2001; Moss et al, 2002). The SFT claims that our categorical organization in the brain derives from sensory and functional attribute channels, meaning that visual (sensory) and verbal (functional) semantic attributes are the main channels by which we acquire and store semantic memory. In particular this theory points out that deficits in accessing semantic memory are due to an impaired neuromodulatory system, while deficits in storage are caused by damage to neurons encoding semantic cues (Gotts and Plaut, 2002). The HIT, instead focuses mainly on visual encoding and it states

that visually alike items are encoded and positioned in anatomical proximity, thus encoded as a group. It's from this organization that categories emerge. A similar theory, the OUCH states that highly correlated items are represented in the brain in contiguous regions leading to a categorical organization. A fourth hypothesis, the DSKH, claims that categories which are evolutionarily important are selectively encoded in different brain regions. All the four theories abovementioned are all cognitive derived models even though with neural constraints, i. e. with non specified anatomic correlates. The SMMSK and the CSA are instead theories whose cognitive models are derived together with neuroanatomical correlates. The SMMSK's main focus is on sensorimotor information stating that this information is stored in dedicated brain regions. This theory claims that action and action names are represented in the left prefrontal and frontal lobes, artefacts in the left frontoparietal lobes, and biological entities in the anteromesial and inferior temporal lobes. Finally, the CSA model suggests that objects are represented by overlapping patterns of activation across features that constitute the object. Moreover, feature representations have two main characteristics: correlation, or how features are shared across items and thus indicating their membership to a certain category, and distinctiveness, or the degree of discrimination a feature has for the unique identification of the concept. Neuroanatomically speaking this theory relies mainly on the left hemisphere (Tyler et al, 2003). Last but not least the CSA hypothesis claims an involvement of the perirhinal and entorhinal cortices in the integration of features into objects. Those hypotheses, while focusing on different features, all sustain an idea of semantic memory as distributed in neuronal networks, even called by Patterson et al (2007), the distributed-only view. The same group contrasts this view to the proposal of a distributed-plus-hub-view. Their main claim for the existence of a semantic hub is the nature and central role of semantic memory, i.e. to generalize across concepts with similar semantic meaning but not necessarily similar attributes. Thanks to this feature of semantic memory, we can generalize across concepts with different attributes. Taken this into consideration, Patterson et al (2007) claim that semantic memory, in order to yield the ability to reach higher order generalization, must rely on something more than a network of modalities. They propose then the idea of a semantic hub.

This idea is though not entirely new as already Damasio's group (Damasio, 1989; Damasio et al, 1996; Tranel et al, 1997; Damasio et al, 2004) proposed the presence of a convergence zone associating different concepts. The hypothesis postulated by Damasio and co-workers is then the existence of multiple specialized convergence zones, each being important for representing different semantic category. Nevertheless Patterson's idea, in contrast with Damasio's theory, proposes a single semantic hub supporting the activation of a concept in all modalities and for all semantic categories. Following this assumption then damage to the hub should produce a semantic deficit independent on the modality of input and output while implicitly claiming that such a generalized impairment could

never be caused by a focal brain injury. The authors place this hub in the anterior temporal lobe (ATL) bilaterally, and base their theory on studies on SD, a clinical condition characterized by a selective impairment of semantic memory only affecting all modalities of reception and expression for all kinds of items, and by atrophy of both ATLs, especially at the temporal pole (I will discuss SD more in depth later on) In conclusion we can't do anything but agree with the assumption that the quest for the locus of semantic memory has led researchers everywhere and nowhere. Much has to be enquired and yet understood. We start with making a picture of semantic memory.

2.5 Imaging semantic memory

The search for the locus of semantic memory has taken great advantage from functional neuroimaging techniques such as Positron Emission Tomography (PET) and functional MRI, used to monitor cerebral activation while asking the participants and/or patients to perform different semantic tasks. First of all it has been shown that object properties are thought to be stored throughout the brain in their corresponding sensory and motor systems, and that one well known category-specific brain area is the lateral/medial fusiform gyrus, now widely considered the area for the distinction animal/tool (Martin, 2007). Another study focusing on the contrast between motor-based knowledge and abstract properties (function or context of use) of objects and using a visual functional MRI (fMRI) paradigm showed activation in the left frontoparietal network, this including the intraparietal sulcus, the inferior parietal lobule, and the dorsal premotor cortex, while the reverse contrast showed activation in the retrospinal and in the lateral anterior inferotemporal cortex (Canessa et al, 2008). Several other studies have investigated the locus of action conceptual knowledge, even finding that the mere mental representation of the interaction with certain objects shared the same activation of premotor regions as in a condition in which the subjects moved an arm or a foot for real (Esopenko et al, 2008). This result was also confirmed by a prime study in which words (prime) referring or not to an action were presented briefly before a congruent sound or a sound not related to the prime, showing an activation of the left inferior frontal and left middle temporal gyrus when a congruent condition was presented (Galati et al, 2008). Other studies have taken a computational approach. In one study, Grossman et al (2007) contrasted complex nouns, i.e. concepts defined by many features, with nominal entities, i.e. concepts directly defined by diagnostic features. Greater bilateral superior temporal and left prefrontal activation was found for complex nouns while bilateral medial parietal and right inferior parietal regions showed greater activation for nominal nouns. Another well enquired area of the semantic memory system is the contrast between concrete and abstract words. One study by Goldberg et al (2007) enquired the

different patterns of brain activation between perceptual and abstract properties about animals and found an increased engagement of prefrontal areas for abstract properties. Interestingly another study (Zahn et al, 2007) compared social concepts with abstract animal properties and found activation of the orbitofrontal cortex and medial frontal cortex, both areas thought to be involved in social cognition, and of the anterior temporal area, considered as a possible hub for high-order semantic processing as suggested by Patterson et al (2007) who find confirmation to their theory above all from PET studies. As a matter of fact, functional PET scans have showed ATL activation during different semantic tasks such as category fluency (Mummery et al, 1996), object naming (Price et al, 2005), category verification (Rogers et al, 2006), and finally word recognition (Bright et al, 2004). Moreover the left temporal pole seems to be engaged in deciphering real speech versus meaningless speech and in reading coherent text versus meaningless visual conditions, those results confirmed by both PET (Crinion et al, 2003; Scott et al, 2000) and fMRI scans (Lindenberg and Scheef, 2007). So, the function of the ATL in supporting semantic memory is no longer questionable, nevertheless there is no general consensus on its specific role in sustaining semantic memory. Other theories see the ATL as the site for the knowledge of specific entities like for example familiar faces and places (Damasio et al, 2004; Tranel, 2006), or as a store for general information (Frith, 2007; Olson et al, 2007; Zahn et al, 2007; 2009). Nevertheless other findings seem to point in other directions. First, lesion studies done using a 10 minute repetitive Transcranial Magnetic Simulation (rTMS) on the ATLs don't necessarily indicate to produce a neuropsychological "virtual lesion" specific for the ATLs (Simmons and Martin, 2009). Secondly most of the evidence of the ATLs pivotal role in semantic memory is based on studies on SD, a condition in which pathology is not restricted to the ATLs but often extends to the amygdala (Noppeney et al, 2007), and the frontal lobes (Brambati et al, 2009). Moreover it has been shown that semantic memory impairment equally correlates to pathology in the ATLs but also in the posterior regions of the fusiform gyrus (Williams et al, 2005). Thirdly it has been shown that when an anterioral temporal resection is needed to treat epilepsy, this seldom leads to generalized semantic impairment (Drane et al, 2008) but mostly to specialized semantic deficit such as person-specific information, and impaired name and familiar landmarks recognition (Fukatsu et al, 1999; Glosser et al, 2003; Tsukiura et al, 2003; Drane et al, 2008; Tranel, 2006). In any case, whether the ATL is the site of generalized conceptual knowledge or of more specific one, it seems that it has to be bilaterally damaged to generate "significant, clinically notable" disruption to semantic memory (Lambon Ralph et al, 2010).

2.6 Semantic memory made unconscious: semantic priming

Semantic priming is defined as an improvement in the ability to identify items or concepts after a previous experience with semantically related ones, or as a behavioural change as the result of a repeated presentation of a stimulus. For instance, after hearing the word "chair" in an experimental setting, we will react faster to the word "sofa" than to the word "dog". According to the network model of semantic memory described by Collins and Loftus (1975) words or lexical entries are represented by nodes and these nodes are connected to each other by many different relationships. When a stimulus item is presented to a subject, the corresponding node is activated and this activation spreads automatically to related nodes, causing these nodes to be activated (and therefore making corresponding words more easily recalled) for a limited period of time. For example, in a semantic network, the word "PhD student" will be semantically related (and therefore connected) to the words "mean editor", "congress", "researcher", and so on, but semantically unrelated to the words "mental health", "rest", and "normal life".

Priming's main feature is that it is unconscious. In one of their first pivotal studies on priming, Mitchell and Brown (1988) presented young subjects drawings of common objects twice, the second time mixed with new drawings. When asked to name the drawings as fast as possible the subjects implied 0,9 seconds to name new drawings but 0,8 to name drawings already encountered, showing a priming effect that could be labelled as perceptual. Nevertheless the automatic nature of semantic priming had already been proved 7 years before by Milberg and Blumstein (1981) who showed that semantic priming is intact and automatically activated even in patients with severe language impairment such as Wernicke's and Broca's aphasics.

Another key feature of priming is that it seems to persist for a very long time, as long as 7 days and even in amnestic subjects, as showed by Cave and Squire (1992), this confirming the theory that priming relies on its own brain system, independent on declarative memory. As a matter of fact the study of amnestic subjects has given researchers the opportunity to disentangle priming from declarative memory. In the description of their famous and profoundly amnesic patient E.P., Hamann and Squire (1997) reported fully intact priming in the presence of at-chance recognition memory, pointing out once again the independence of priming from conscious recollection. The fact that semantic memory would rely on both a conscious and an unconscious system doesn't seem very adaptive but according to Squire and Kandel (1999), it is actually the contrary. According to their theory priming evolved to improve the speed and the efficiency of an organism when interacting with a familiar environment and it's probably useful as we were born in world in which stimuli encountered once will be encountered again and again. So if we go back to what described before we can assume that a priming effect will affect the priming network creating a group of

silent neurons while others are activated, and that less neuronal activity will be required, as a consequence of the previous encounter with an item of similar semantic meaning.
Let's have a look.
One of the most common findings in neuroimaging studies of priming is a reduced hemodynamic response for primed stimuli in comparison to unprimed ones (see Schacter and Buckner, 1998 for a review), a phenomenon historically called "repetition suppression". From these findings we can hence infer some generalisations. First brain regions showing repetition suppression are in general restricted to the stimulus type, and here lower hemodynamic response is thought to be due to faster processing of primed stimuli, even called "hot tubes". Secondly repetition suppression can be detected in different brain regions suggesting the presence of a facilitated pathway between stimulus and response. Nevertheless a third generalisation states that not all regions associated with a particular stimulus or/and task are facilitated, for example it is now known that decreased hemodynamic response is not seen in early visual regions and late motor regions in visual-motor tasks, this suggesting that not the all pathways are facilitated (Henson, 2003). Priming can be of different kinds but for the purpose of this thesis we will focus on semantic priming. Semantic priming can be explained with two models: the automatic spreading of activation described by Collins and Loftus (1975), and the strategical/attentional effects by Posner and Snyder (1975). In particular strategic effects are thought to increase as the proportion of primed task pairs increase (Neely, 1991). Strategic effects were enquired by Mummery et al (1999) using PET in a lexical decision task in which the prime in related and unrelated conditions was presented for 50 ms. The brain regions in which hemodynamic response decreased with the proportion of related pairs presented were the left anterior temporal lobe and the anterior cingulate. Nevertheless it is hard to disentangle strategic effects from automatic ones even if as a rule of thumb it is now widely accepted that priming tasks using stimulus onset asynchrony (SOA) shorter than 250 ms unfold automatic spread of activation while those at longer SOA reflect strategic effects (Neely, 1991). In order to investigate the nature of semantic priming processing at long and short SOA, Rossell et al (2003) used an event-related fMRI paradigm in which SOA of 200 ms and of 1000 ms were compared in a lexical decision task. The results showed repetition suppression in the left anterior temporal cortex for both SOAs and thus no effect difference. This contrary to an ERP experiment performed under the same conditions which did show a SOA effect, where priming effect were found to onset 60 ms earlier for the long SOA, this probably showing how strategic effects affect the latency of neural activity rather than the magnitude. So how can we disentangle one effect from the other using different paradigms? It is important to bear in mind that enquiring semantic priming at such short SOAs through the recording of hemodynamic response is not optimal as the recorded response will be the aggregate of the prime and the target and not merely a semantic priming

effect. A way to avoid this problem in temporal response is to make use of EEG ERP paradigms. The EEG, which we will describe more in depth later on, is a non invasive measure of cortical and subcortical brain activity recording synchronic neural activity through electrodes placed on the scalp. ERP, in its turn, is defined as the sum of positive and negative deflections at a particular point in time and with a particular strength, reflecting the processing of a particular stimulus (Gunter et al, 1998). In this sense ERP EEG paradigms are much well suited to study automatic spread of activation. A well known component of ERP EEG is the N400, a negative going deflection peaking around 400 ms post-stimulus onset and at its max over centro-parietal areas, now even widely considered as the brain response to meaningful stimuli, like for example words (Kutas and Fadermeier, 2009). Bentin et al (1985) was one of the first investigating priming during an ERP paradigm. In their ERP priming paradigm with semantically related and unrelated pairs, they could show a larger (in amplitude) N400 effect for words preceded by an unrelated word. Despite the well studied and defined N400 effect, the literature is still in disagreement about its role as indicating automatic (Boddy, 1986; Anderson and Holcomb, 1995) or controlled processing (Besson et al, 1993; Neville et al, 1989; Brown and Hagoord, 1993; Chwilla et al, 1995). Although much has to be studied and proved the NP400 effect remain the perfect candidate for the study of semantic processing using ERP EEG, and thus it has been our method of choice in order to study automatic semantic processing.

3. STUDYING THE BRAIN: A CHALLENGING NIGHTMARE

"Compared with the elegant simplicity of the structure of the DNA, the tangled wiring of the brain is a nightmare" (Quartz and Sejnowski, 2002).
We tend to believe that all brains are alike but it is, unfortunately for a brain researcher, a false belief. As each human being is the product of his/her genetic make-up, is brought up in a specific environment and is moulded by different experiences, the architecture of each person's brain is unique. So, we do dance to our DNA's music and we are under the influence of the Genetic Despot but the brain is a democracy and the world gets a vote, as elegantly expressed by Quartz and Sejnowski in their book "lovers, liars and heroes" (2002). Through the study of monozygote (nearly genetically identical) and heterozygote (sharing some 50 % of their genes) twins, those assumptions have been confirmed. MRI studies have shown that 81% of our intracranial volume is hereditary (Baaré et al, 2001; Carmelli et al, 1998; Pfefferbaum et al, 2000) as well as 66 to 97 % of the total brain volume (Baaré et al, 2001; Bartley et al, 1997; Pennington et al, 2000; Wright et al, 2002). More specifically it seems our genes are responsible for 82 % of our brain's grey matter and 88 % of its white matter (Baaré et al, 2001), as well

as for 65% of the volume of each hemisphere (Geschwind et al, 2002). The same applies to 88% of cerebellar volume (Posthuma et al, 2000), and 79 to 94% of the corpus callosum (Pfefferbaum et al, 2000; Scamvougeras et al, 2003). On the other hand the environment too holds its shares. The same twin studies have shown that our unique interaction with the outside world accounts for both the overall gyral patterning of the cortex (Bartley et al, 1997; Eckert et al, 2002) and for the volume of the lateral ventricles as well as for vaste grey matter and white matter areas in their surroundings (Baaré et al, 2001; Wright et al, 2002, Hulshoff Pol et al, 2006). Moreover, and very interestingly, it seems that only 40% of the hippocampus is under the control of our DNA (Sullivan et al, 2001). And not only that, the hippocampus, and in particular the dentate gyrus were the first two areas of the brain discovered to undergo a life-long neurogenesis (Eriksson et al, 1998). This knowledge is of course very intriguing as, as we discussed previously, the hippocampus and its adjacent areas are of outmost importance for the formation of long-term memories. In sum we now know that our overall brain volume is under the control of our genes but also that unlike them, medial regions are largely influenced by the environment we interact with. And it's not even the whole story. Because the brain is not only the product of nature and nurture, it is also plastic, meaning that it can be cortically remapped during a whole life. Differently from the old knowledge that cortical areas are unchangeable after development with the only exception of the hippocampus and the dentate gyrus, we now know that the entire brain undergo plastic changes during childhood, adulthood, and even in old age (Boyke et al, 2008). Nevertheless it has taken science 60 years to prove fully what already formulated in the late 40's by the Polish neuroscientist Jerzy Konorsky (1948) and one year later by the Canadian neuropsychologist Donald Hebb (1949). In particular, what we now it is widely known as Hebbian learning states that "when an axon of cell A is near enough to excite cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased". More simply we can say that "neurons that fire together, wire together", a statement known as Hebb's Law. Although many studies have confirmed not only that neural networks change their firing patterns dependently on experience but also that experience change their organization (Jenkins et al, 1990; Merzenich et al, 1990; Nudo et al, 1990; Nudo and Milliken, 1996; Rauschecker, 2002; Nudo, 2006). The more striking evidence of brain plasticity comes from imaging studies on subjects with a particular expertise, like for example, musicians.

The study of professional musicians is a very powerful tool when it comes to explore how the brain can be modified by long-lasting and hard training. Let's for a minute think about which huge amount of training would be necessary for a pianist to be able to perform the Rach 3, Sergei Rachmaninoff's Third Piano Concerto, considered by many as the most difficult piano piece in the world. The Rach 3 running for about 45 minutes and requiring a full orchestra, is the piano

piece that contains more notes per second than any other musical piece. Moreover, its solo core, called the Ossia Cadenza, comprises the astonishing number of 70 notes per measure. Evolution doesn't make virtuosos so in order to achieve such amazing finger speed it is no wonder that the brain has to be re-shaped. The first seminal study in this direction was that by Elbert et al (1995) who investigated somatosensory evoked magnetic fields in string players finding that their cortical representation of the fingering hand (left hand) was larger than in non-musicians. Other studies in this direction have focused on the re-shaping of the auditory system. On the assumption that tones become music only when they are structured, researchers presented professional musicians and controls a series of 1.200-Hz tones occasionally interrupted by a 1.500-Hz tone in order to see if the tone mismatch leads to an ERP mismatch negativity (MMN), a marker of the pre-attentive detection of irregular sequences in auditory stimuli. Musicians showed a MMN in absence of any attention for tones mistimed by only 20 ms in a sequence of regular tones and even for impure chords presented among perfect major chords, this indicating a re-shaping of the auditory cortex to enable for automatic fine tuning (Münte et al, 2002). Thanks to advances in neuroimaging techniques it is now known that all those musical skills translate into different structure and size in brain areas such as the planum temporal, the anterior corpus callosum, the primary hand motor area, and the cerebellum, in short involving an increase in grey matter in areas involving both motor and auditory processes (Münte et al, 2002).

In sum we know from decades of brain research that all brains are not exactly the same, or, as David Eagleman rightfully wrote "Brains are more like fingerprints: we all have them, but they are not exactly alike" (Eagleman D, Sydney Morning Herald).

This lasting statement expresses perfectly what is the most dangerous curse and yet the most gifted blessing of studying the brain.

4. IMAGING THE BRAIN

4.1 Magnetic Resonance Imaging

The discovery and clinical applications of MRI have led to two different Nobel Prizes. The first one, a Nobel Prize in Physics was given to Bloch and Purcell in 1958, for their first successful nuclear magnetic resonance experiment in condensed matter. The second Nobel Prize, and this one in Medicine or Physiology, was awarded in 2003 to Lauterbur and Mansfield, for their discovery on how to make the Nuclear Magnetic Resonance to create an image. It is thanks to this later application that we can know look into the mystery of the brain *in vivo*.

In his first seminal paper Paul Lauterbur mentioned the potential applications of the newly discovered technique, from the study of various inhomogenous objects to the generation of pictures from the distribution of stable isotopes, and finally to the generation of field gradients that large to be able to create images of soft tissues using water resonance, this leading to the possibility to study malignant tumours in vivo (Lauterbur P, 1973).
Nowadays what can be done with an MR scanner and its applications, from specific sequences, to imaging processing, is much more complicated and exciting than what was feasible at its very birth.

4.1.1 The basics of ever-present magnetic attraction

Despite the fact that the MR system can seem to be an intricate labyrinth made of complex physics laws, its core is one and only one: the superconductive magnet, ranging in strength from 1.5 Tesla to up to 7 Tesla for clinical and research purposes on humans. The superconductive magnet is always on but it also requires to be constantly cooled down by liquid helium, in this case used as a crycogenic cooling system. In theory, the stronger the magnetic field, the better the signal-to noise-ratio (SNR). SNR, as we will later discussed, a very important parameter for image quality, is a measure of the contamination of the signal, by noise, like for example artifacts, or inhomogenities problems, like differences between the magnetic properties of different tissues or air-filled cavities. Thus, even if the SNR gets theoretically better with greater field strength, other factors contributes to its offset.
But the superconductive magnet can't make it all alone.
As the music produced by an orchestra is the coordinated sum of different stems, so it is an MR examination, where the diagnostic information about the scanned patient is the result of a priori determined inputs and outputs working as a unity. First the magnetic field (z) which is aligned with the Earth's magnetic field is knocked out of alignment by a specific pulse sequence, a combination of radiofrequency pulses (RP), and gradient pulses (GP). Different sequences are used for different purposes, but they all have in common two modifiable parameters: repetition time (TR), and echo time (TE). TR is considered as the time between two successive pulse sequences applied to the same slice. TR is not only an important factor in scan time, but its variation has also an important effect on image contrast. TE is the time in millisecond between the application of a pulse and the peak of the returning signal: the echo signal. The information about the patient's tissue thus consists of its response to RF pulses generated by a transmitter coil, and the produced MR signal detected by a receiver coil. Nevertheless in order to produce images of a particular area, the MR signal has to be localized exactly in that area. This is attained through the use of gradients, whose scope is to generate a

variation in magnetic field strength throughout the body. Those fields are produced by specific electrical pulse applied through three gradient coils, one for each direction (x, y, or z).
When it comes to enquiring the brain, there are three basic examinations: Proton Density (PD), sagittal T_1-weighted, and axial T_2-weighted images. Those different contrast images can be obtained using specific sequences in which both TR and TE are controlled. More specifically, after the first RF pulse is initiated, the magnetization gets back to its starting position through two different relaxation processes: spin lattice, or T_1, and spin-spin, or T_2 relaxation time. The detected signal is then captured either as a Spin Echo (SE) or Gradient Echo (GE). SE sequences start with a 90^0 pulse, in which TR is then the repetition time between two 90^0 pulses and TE the time between from the pulse to the echo. SE which can produce T_1, T_2, or PD-weighted images gives good image quality but requires long time to be acquired. In order to speed up the scanning time, Fast Spin Echo (FSE), even called Turbo Spin Echo can be used. GE sequences too produce both T_1, T_2^* (the combined T_2 and field inhomogenity), and PD-weighted images, but unlike SE sequences, they start with an angle which is previously chosen but always less than 90^0 , even called a flip angle α. GE sequences are faster than SE ones but they are more influenced by inhomogenities and timing parameters. The more used and basic contrasts images in brain examination are T_1 and T_2. T_1 images, even known as anatomical scans have a short TR and a short TE. As a consequence of the proton density of different tissues, in T_1 images fluids are very dark (long spin lattice relaxation), water-based tissues are grey (midrange spin lattice relaxation), and fat-based tissues are very bright (short spin lattice relaxation time). The contrary applies to T_2 (or T_2^*) images, even called pathology scans, which controls the decay of the signal in the transverse plan, and require long TR and long TE. Here fluids have the longest spin lattice time, water-based tissues, midrange, and fat-based tissues, the shortest time. In T_2 images abnormal tissue is bright and normal tissue, dark.
As previously mentioned, the quality of the image produced is very much dependent on a good SNR. Considering the SNR of an MR image, the signal is then the pixel or voxel brightness in the image while the noise is the sum of the random differences in pixel values. More specifically: an MR image consists of a finite amount of signal as the result of the tissue of interest and the sequence of choice. When the signal from the patient's tissue is recorded, it has to be divided amongst the voxels (each with a different number of protons!) the image consists of. The noise seen in the image, is then the product of random fluctuations in electrical currents within human tissues, like for example in nerve conduction. In sum, in an MR image, the individual voxel will contain a mixture of both signal and noise. Size parameters affecting the signal are slice width and Field of View (FOV), increasing them, increases the signal and thus the SNR. In short: doubling the slice width, doubles the SNR, while halving the FOV while keeping the same image matrix will quarter SNR. In its turn averaging parameters such as number of

signal averages, phase-encode and frequency-encode matrix size, affects noise with an inverse square root relationship. So, to sum up, how is an MR image acquired? Firstly the magnetic field is knocked out of alignment and 2D slices are produced by a combination of RF pulses (with a priori chosen TR and TE) and simultaneous slice-select gradient. Secondly, the in-plane signal is encoded using both phase-encoding and frequency-encoding gradients. Here every possible spatial frequency is collected before the data, known as k-space, is Fourier transformed in order to produce an image. K-space is then the temporary image space (a matrix) in which the raw data from the MR signal is stored and a Fourier transform is the mathematical form applied to process the data in order to reconstruct an image (for further reading see McRobbie et al, 2003).
So now that we have unraveled the basic tunes of the MRI orchestra we can go further to examine how MRI can take us to a journey in the intricate machinery of the brain.

4.1.2 The shape of the brain: Voxel-Based Morphometry

Morphometry is defined as the measurement of an external form, in this case the shape of a brain. Morphometric methods are then a way to statistically identify structural differences among different populations or to find correlations between brain shapes. There are broadly speaking two different approaches to brain morphometry: one which deals with differences in brain shape and the other which deals with differences in the composition of brain tissue after macroscopic differences in shape have been discarded. While the former method uses deformation fields as a result of spatial normalisation, the latter compares images in a voxel fashion after the deformation fields have been used to normalise the images. Two methods to study the brain using deformation fields are deformation-based morphometry (DBM) and tensor-based morphometry (TBM). In comparing groups while DBM uses deformation fields to identify differences in the relative positions of structures within the subjects' brains, TBM identifies differences in the local shape of brain structures. The second class of methods applied to a normalised image is called VBM, now widely considered the best approach to address small-scale differences like for example comparing patient groups whose condition is rare.
VBM implies those following steps: 1. spatial normalisation of all the images to the same template, 2. extracting grey matter, white matter, and cerebrospinal fluid from the normalised images, 3. smoothing, 4. perform statistical analysis to find group differences whose output is in the form of a statistical parametric map.
Spatial normalisation implies that all the data is transformed into the same stereotactic space through the registration of each image to a template. There are two important issues to take into account when applying spatial normalisation: the

first is that normalisation doesn't aim to match exactly every cortical feature but to correct for brain differences and the second is that spatially normalised images should be of relatively high resolution so that the extraction method to be performed to separate grey (GM) and white matter (WM) is not made less accurate by voxels containing a mixture of tissue types.
After spatial normalisation the images are segmented into GM, WM and cerebrospinal fluid (CSF).
Thirdly, the segmented data is smoothed. This makes each voxel as containing the average concentration of, for example GM, from around the voxel, a region in its turn defined by the smoothing kernel. Smoothing has also the effect of making the data more normally distributed and thus better suited for parametric statistical brain mapping.
The next step in VBM analysis is to statistically compare the studied groups. Statistical analysis can include either general linear model (GLM), in order to identify regions of particular interest, or standard parametric tests like t tests or F tests in order to test a hypothesis. As for the outcome of the statistical analysis it is important to bear in mind that as a large number of statistical analyses is performed they have to be corrected for multiple comparisons. One approach is to use the multiple comparison correction implemented in the Statistical Parametric Mapping (SPM) software, that is to say a modification of the Bonferroni correction, controlling the chance of false positives or familywise error rates. Another, more tolerant approach, is to control the expected proportion of false positives using the false discovery rate.
Nevertheless for VBM to be efficient in finding differences between groups or test a hypothesis a certain number of requirements have to be fulfilled. First and foremost in order to measure the amount of GM or WM the segmentation needs to be performed correctly. Secondly the images to be analysed must have been all acquired on the same scanner and with the same MRI sequence. Thirdly, and as for other kind of data, one must make sure the data to be processed is normally distributed before applying any kind of parametric test otherwise the use of non-parametric tests is advisable.
Proper segmentation is also an important issue in VBM. One problem is that many central GM structures don't show good contrasts and thus in those white matter and gray matter are almost indistinguishable which in turns makes the segmentation difficult. Another issue is the correct modelling of vowels containing a mixture of white and gray matter as the model assumes that the segmentation has successfully separated them.
In other words VBM can be considered as an improved segmentation method with the possibility to correct for image non-uniformity through the use of smoothing kernels in all three directions.
Moreover it is considered as an automated method analysing the whole brain and not implying any a prior assumptions, and thus unbiased, if compared to region-of-interest (ROI) methods. There are several ways to optimise VBM analysis. One

approach is to customise the used templates as it is important to remember that the Montreal Neurologic Institute (MNI) template, the most used template, was created for the brains of young control subjects and could create problems in analysing brains of elderly controls. The solution here is then to create a customised template made of age-matched controls. Those customised templates are also useful when having a group or more groups of patients, as this should minimise normalisation bias. Another approach is to mask every image with a previously segmented brain region to avoid segmentation errors, a method which is though time-consuming. A third method is GM optimisation. In this case spatial normalisation of each volume is based on matching the initial segmentation with the GM prior using a non linear normalisation instead of using the volume proper. The parameters from this normalisation are then applied to the whole brain. A fourth strategy is the use of modulation. Modulation is used to correct for volume change as consequence of spatial normalisation. Modulation is in particular useful when analysing pathological brains as volume differences may be lost when an atrophic brain is matched onto a non atrophic template. In this case the different intensities within an image are divided by the Jacobian values taken from the registration. Using this method, regions most affected by expansion will show less intensity as a consequence of reduction in tissue density (for a review see Ashburner and Friston, 2000; Whitwell and Clifford, 2005).
One of the first VBM studies and even one of the most cited in the media was that on the hippocampus of London taxi drivers. In this paper they showed that taxi drivers had on average a larger back part of the hippocampus compared to controls while the anterior part was smaller. This is in line with previous assumptions on the role of the hippocampus in spatial navigational skills, something taxi drivers train in as it is a skill needed for their work (Maguire et al, 2000). Another one of the first VBM papers analysed the effect of age on both GM and WM on a large cohort of normal adults. This study showed that while GM decreased linearly with age, WM remained stable (Good et al, 2001).
So in sum, VBM, which allows the analysis of the whole brain and thus it is better suited for the analysis of small groups has then been our method of choice for the examination of not only GM but even WM in both healthy controls as well as in patient groups.

4.2 The perfusion of the brain: Arterial Spin Labeling

Traditionally measurements of brain perfusion and cerebral blood flow (CBF) have been carried out with different techniques all having a common feature: the utilization of tracers. Ranging from PET using H_2O_{15}, or glucose metabolism, to SPECT with among others Tc-HMPAO, to inhaled stable Xenon in X-ray Computed Tomography (CT), and finally intravascular tracers in CT and

Gladolinium in MRI, all the available techniques have required an external agent (Alsop, 2006).
Because of this, measuring blood perfusion have not been feasible for all clinical populations, among others for patients with chronic renal failure, or young children, the former due to fears for nephrogenic system fibrosis, and the latter because of problems in intravenous access (Pollock et al, 2009).
Those problems came though to an end with advanced technologies in MRI and the birth, some 20 years ago, of Arterial Spin Labelling (ASL) techniques.
ASL doesn't imply the use of any contrast agent but utilises water as endogenous tracer, thus using spatially selective inversion of inflowing arterial blood. More specifically the MR signal from inverted blood is made negative in respect to uninverted blood, here used as a control condition, and perfusion calculated by means of subtraction of the two recorded images (Alsop, 2006).
In other words, ASL "labels" protons in the blood of the supplying vessels outside the imaging plane. The labeled protons then wait a certain period of time, called the post labeling delay (PLD), before reaching the parenchyma (neurons and glia cells), and finally the signal from the labeled and control (unlabeled) state is recorded as an image (Pollock et al, 2009).
In this case what the subtraction of the two images does is to eliminate the static tissue signal from the parenchyma. So the remaining signal, usually a fraction (1-2%) of the tissue signal, is proportional to the local CBF (Detre et al,1994; Buxton et al, 1998). This signal depends then on different parameters such as flow rate, T1 of the blood and tissue, and transit time (from tagging region to imaging plane).
Both the labelled and the control acquisitions are then converted into DICOM (Digital Imaging and Communication in Medicine) images, and then reconstructed into CBF maps using the appropriate algorithm for the sequence of choice (Monet et al, 2009).
Taking it from another angle, ASL technique requires two different components, a preparation component and an acquisition component. The preparation component labels the inflowing blood (note that the labelling area is to be proximal to the acquisition area) for both the control and label images while the acquisition component acquires the data. This is usually done with a fast acquisition method, either Spiral or Echo Planar Imaging (EPI) (Pollock et al, 2009).
It is also important to bear in mind that ASL's general principle of tag, delay for tissue deposition, and imaging gives a significant importance to the amount of the PLD in the sequence which in turns impacts significantly the CBF perfusion map. Here the rule of thumb is that short PLD shortens the acquisition time but the obtained image may not accurately represent CBF as there has not been enough time for slower flow tissue exchange. Long PDL, on the other hand, allows more time for tag deposition creating more homogenous images but it requires longer imaging time leading to less available signal at time imaging because of T_1 relaxation (Pollock et al, 2009).

As already mentioned, ASL technique has several advantages in comparison to other imaging techniques. Firstly it doesn't require the use of contrast either through injection or inhalation. Secondly it can be performed as one of the MRI sequences in a single run, this providing co-registration of anatomic and perfusion data at the same time. Thirdly ASL can be repeated several times. Moreover it can be acquired with good SNR, it gives a measure of absolute quantification, and can be acquired with robust sequences such as FSE without at the same time suffering from susceptibility signal loss. The use of water, which is largely free diffusible, is also an advantage (Alsop, 2006)

Further development in ASL technique has led to improvements in spatial and temporal resolution thanks to phased-array surface coils combined with parallel imaging. This latter enables shorter RF pulses with not only improved spatial discrimination, but also with correction for field inhomogenities (Wolf and Detre, 2007; Talagala et al, 2004).

Nevertheless the use of ASL doesn't leave a neuroscientist without troubles. Firstly even if the ideal situation would be to have all the protons deposited in the tissue by the time the image is generated, there is often residual tagged signal in the vasculature, which in turns creates problems when trying to quantify perfusion. This problem can be overcome by applying bipolar (crush) gradients prior to image recording, in order to suppress the undesired moving signal. Moreover ASL is very sensitive to even small head or respiratory motions, even if both pulse and respiration movements can be subtracted off-line if acquired. Another issue when using ASL is its susceptibility. As already mentioned ASL, which needs rapid acquisition, uses EPI images, but not without a cost, as EPI can lead to artefacts in particular around surgical hardware, craniotomy sites, hemorrhages, calcification and the paranasal sinuses. This last in particular makes it hard to measure perfusion in the medial temporal lobes and skull base (Pollock et al, 2009). Not really ideal for someone who wants to study the anatomical correlates of semantic memory!

Since its birth ASL has then developed into more and more sophisticated techniques, each one which its novel advantage but yet with its downsides. Those are: pulsed ASL (PALS), continuous ASL (CASL), pulsed (or pseudo) continuous ASL (PCALS), and velocity-selective ASL (VS-ASL).

PALS uses short RF pulses (5-20ms) to invert spins in the tagging plane while CASL use long and continuous RF pulses (1-2sec) together with a constant gradient field in order to induce a flow-driven adiabatic inversion close to the imaging plane. Continuous labelling then leads the signal to reach equilibrium in the slice of interest (Pollock et al, 2009; Monet et al, 2009). PALS has higher inversion efficiency and lower RF power deposition in comparison to CASL, but it lacks in distal edge of the tagging plane, which in its turn bias the CBF quantification. Nevertheless CASL requires extra equipment in the form of RF transmit hardware. Another drawback are magnetization transfer (MT) effects which require a second inversion in order to reach the control state even if this

problem can be overcome using a separate RF surface coil for blood labelling (Pollock et al, 2008; Wu et al, 2007; Petersen et al, 2006). Moreover CASL has lower inversion efficiency (80-95%) than PASL (95%) (Wu et al, 2007; Petersen et al, 2006) but this is compensated by its closer inversion to the imaging plane which holds to a minimum the loss of signal due to T_1 relaxation (Pollock et al, 2009).
PCASL, first developed by Garcia et al (2005) makes use of a repeated train of short RF pulses. PCALS then combines CASL and PASL techniques leading to a reduction of both MT and transit times' sensitivity and still preserving good SNR because of the prolonged period of labelling without the need of special hardware. Yet PCASL is susceptible to both B_0 inhomogeneity and eddy currents (Wu et al, 2007) but despite its drawbacks, it has been demonstrated that when combined with high field strength, parallel imaging, and 3D imaging with background noise suppression, the signal improves 10-fold (Wolf and Detre, 2007)
Finally VS-ASL implies the saturation of the blood moving faster than the chosen cut-off value in order to achieve perfusion contrast leading to a smaller and more uniform transfer delay. The problem with this technique is not only lower SNR but also and above all the choice of the appropriate cut-off velocity, as an inappropriate value results in incorrect perfusion value and can produce artifacts (Pollock et al, 2009).
In conclusion the introduction of ASL-MRI has opened new frontiers in the field of neuroscience but its great advantage relies very much on the choice of the right technique for the right purpose, thus balancing benefits and drawbacks.
In short: this machine is powerful but has no brain, use your own! We used this machine and our own brain to enquire blood perfusion in automatic semantic processing.

4.3 The diffusion in the brain: Diffusion Tensor Imaging

DTI applied to MRI is based on the principle of water diffusivity in the brain. The concept is that during their random displacement, water molecules give a measure of tissue structure at a macroscopic level. In other words the observed effect reflects the distribution of water molecules present in a voxel of several mm^3 and provides clues about the structure and geometric organisation of the studied tissue (Le Bihan et al, 2001). More specifically DTI provides a tool to investigate the brain's WM (Pierpaoli et al, 1996; Le Bihan et al, 2001), standing on the principle that water diffuses differently along than across axons (Taber et al, 2002).
DTI technique implies the acquisition of seven images for each brain part, and while one image is a standard T_2-weighted, the others are modified images in order to make them sensitive to water movement in different directions. When the full set of seven images is completed, a matrix is calculated. This matrix, called the

diffusion tensor, describes the speed of diffusion in each direction for every voxel in a given image (Taber et al, 2002).
It is now known that in WM the speed of water is greater along than across axons, and as such is directional. This principle, based on the difference between parallel and perpendicular motion is called anisotropic diffusion.
The most common measure in DTI is called fractional anisotropy (FA) and it gives information about the structural integrity of WM (Taber et al, 2002)
Conventionally higher FA values are interpreted as a sign of structural integrity as high structured WM fibers put more constraints on the directionality of diffusion (Pierpaoli et al, 1996).
Other sources of information are the components of the diffusion tensor eigen vectors: axial diffusivity (DA), radial diffusivity (DR), and mean diffusivity (MD). While MD is a computed overall diffusivity, DA and DR provide information about parallel respectively perpendicular diffusion (Taber et al, 2002; Li and Wahlund, 2010).
More specifically high DA values are considered to be an indicator of axonal pathology, while high DR values are linked to myelin pathology (Song et al, 2002; Sullivan et al, 2010; Vernooij et al, 2008). Finally high MD values sre considered to reflect a loss of barriers restricting water diffusion (Basser et al, 1994).
DTI has been our method of choice to study tract connectivity disruption in the brain due to different pathologies.

4.3.1 The analysis of diffusion: Tract-Based Spatial Statistics

Tract-Based Spatial Statistics (TBSS) is a technique allowing the automated analysis of WM integrity (Smith et al, 2006; Smith e al, 2007). More specifically TBSS applied to DTI data gives the possibility to investigate the whole brain of a group or several groups without prespecification of the tracts of interest through the estimation of a "group mean FA skeleteon" representing the centres of all fiber bundles common to all study participants. Each subject's FA data is then projected onto the mean FA skeleton. The basics steps are as following:

1. Identify a common registration target and align all FA images from all subjects to this target using nonlinear registration.
2. Create the mean of all aligned FA images and apply non-maximum-suppression to the local tract structure in order to create a skeletonised mean. It is important to apply a threshold here in order to avoid areas of low mean FA and/or high variability among subjects.
3. Project each subjects aligned FA image onto the skeleton, by filling the skeleton with FA values from the closest relevant tract.
4. Apply voxelwise statistics across subjects on FA data from the skeleton-space

(for a more detailed descripion see Smith et al, 2006)
Finally TBSS can also be used to analyse DR, DA and MD data using the data from the skeletonization stages, the nonlinear warps and the estimation of the projection vectors from FA images.

4.4 The perfusion of the brain: Single-Photon Emission Computed Tomography

SPECT is a nuclear imaging technique which, through the use of gamma rays detected by a gamma camera, is able to provide 3D information about regional cerebral blood flow (rCBF). SPECT technique requires the injection of a tracer. The tracer enters the cells because of its lipophilic characteristic, and remain inside the cell thanks to the conversion into a hydrophilic compound. Most of those tracers enter the brain during the first pass and their incorporation is proportional to CBF in the fist minutes. Importantly a modification of CBF after injection doesn't change the initial distribution of the tracer (Saha et al, 1994). Several tracers and isotopes are used in SPECT but the most commonly used are nowadays are technetium-Tc99m-labeled heamethylpropileneamine oxime (Tc99m-HMPAO) and Tc99m-ethylcysteinate dimmer (ECD) (Accorsi, 2008). In short SPECT provides a 2D view of a 3D distribution of a radionucleide. The gamma camera then acquires images (called projections) from multiple angles.
In order to obtain SPECT images the gamma camera is rotated around the patient. Projections are then acquired commonly every $3\text{-}6^0$ and in most of the cases a 360^0 rotation is applied. Each projection takes usually 15-20 seconds to acquire, giving a total scan of circa 15-20 minutes. Faster scan acquisition can be provided by a dual-headed camera, allowing the registration of 2 projections simultaneously, and by triple-headed camera. In general the number of the acquired projections is approximately equal to the width of the image obtained.
After the image acquisition, a tomographic reconstruction algorithm is applied to produce a 3D dataset.
The typical resolution of a constructed SPECT image is of 64x64 or 128x128 pixels, 3-6 mm in size. Artifacts in SPECT can be due to patient movement but also to an uneven distribution of the tracer, which can cause for example the obscuration of neighboring areas of activity, which can though be corrected using an iterative reconstruction algorithm. Another issue in SPECT is that attenuation of gamma rays within the patient's body can lead to understimate activity in deep tissues if compared to superficial ones. To correct for this miscalculation, approximate correction is possible, or an even better correction can be calculated with attenuation values. Moreover modern SPECT is nowadays equipped with an integrated X-ray CT scanner which can provide attenuation maps of the tissues. Those maps can be incorporated into the SPECT data to correct for attenuation.

As for the use of SPECT in brain imaging, the most used tracer is 99mTc-HMPAO. When 99mTc is attached to HMPAO, it can be taken up by brain tissue in a way which is proportional to the blood flow, which in turn can be detected by the gamma camera. As rCBF is coupled to local brain metabolism, 99mTc-HMPAO is used to study brain metabolisms, in particular in the study of dementia (for a review see Frankle et al, 2005; Herman et al, 2009).
Several studies have reported that SPECT is circa 74% sensitive in diagnosing AD. Other recent studies have reported the accuracy of SPECT in diagnosing AD to be up to 88% (Bonte et al, 2006). Finally a meta analysis has found SPECT to be superior to clinical exam (91%) and clinical criteria (70%) in differentiating AD from Vascular dementia (Dougall et al, 2004).
SPECT has been our method of choice to study brain perfusion in correlation to effortful semantic retrieval.

5. THE BRAIN'S VOLTAGE: ELECTROENCEPHALOGRAPHY

In order to maintain their resting state or to communicate with each other, neurons are constantly exchanging ions with the extracellular environment and when several ions are pushed outside their neurons, all at the same time, they can, in their turn, push neighbouring neurons in a wave-like process, even known as conduction (Tatum et al, 2008). This wave of movement can be measured with EEG. EEG is a neurophysiologic method which records electrical activity in the brain through the use of electrodes placed on the scalp. What is measured is the difference in voltage caused by the neuron's ionic currents as a result of brain activity. This difference in voltage between two different locations is then plotted over time. This is though not a direct measurement, but the EEG signal is the result of the recorded currents, together with the modification given by the conductive properties of the cerebral tissue, the conductive properties of the electrode itself and even the orientation of the cortical generator to the recording electrode. A known methodological issue in EEG is the so called inverse problem, that is to say the fact that the EEG reports a two-dimensional projection of a three-dimensional reality, meaning that in theory it is impossible to find the EEG generator only with the information given by the electrode placed on the scalp. What is measured with EEG is synaptic activity, as it is the only cerebral activity that fulfils EEG recording prerequisite both concerning duration and strength of the signal. What is recorded is both inhibitory pre-synaptic (IPSP) activity and excitatory post-synaptic (EPSP) one of the pyramidal neurons located in cortical layers III, IV, and VI, while dendrites deeper in the cortex such for example in the hippocampus, or producing tangential currents, are contributing much less to the EEG signal.

It is noteworthy that even nonsynaptic intracellular communication can potentially contribute to the EEG signal (Buszaski et al, 2003).
The EEG source is then mainly derived from the cerebral cortex where it takes the synchronised activity of approximate 180 neurons in an area of minimum 6 cm^2 to create a clear and visible signal. The signal for a given electrode is maximal when the voltage field is radial and the electrode placed face-on the source.
In the field of neurology EEG is used for a great variety of clinical applications, from epilepsy diagnosis, to the diagnosis of coma, encephalopathies and brain death, and despite the fact that its poor spatial resolution has been replaced by for example MRI, it is a very valuable tool in research and clinical settings above all when a temporal resolution of milliseconds is required. The advantages of EEG over MRI are the following: 1) its hardware is cheaper, 2) it can be placed basically everywhere, 3) it has a higher temporal resolution, in milliseconds instead of seconds, 4) it is more tolerant to movement, 5) it is a "silent" technique then much better suited for the study of brain response to auditory stimuli. On the other hand EEG has a lower spatial resolution than MRI and it is not well suited for the study of very complex cognitive tasks.
There are two different ways of measuring the EEG signal, either with conventional EEG in which a certain number of electrodes are placed on the scalp with a conductive mean (a gel or a paste) after the scalp is prepared by light abrasion in order to reduce impedance, or with a more modern approach in which the EEG systems make use of nets of electrodes in a cap-like fashion. This is usually the norm when a large number of electrodes are needed.
When recorded the EEG signal is stored digitally and filtered with a high-pass and a low-pass filter, the former usually set at 0.5-1 Hz and 35-70 Hz respectively. Those filters are necessary to filter artefacts such as electro galvanic signals and movement (high-pass filter), and electromyographic signals (low-pass filter). Additionally a notch filter is used to remove the artefacts caused by electrical power.
The EEG, as we remember, plots the difference in voltage between two electrodes, and in order to be displayed, the read-out of the signal has to be set in a specific montage. The most used montage is the referential one, in which each channel represents the difference between a particular electrode and an a priori designated referential electrode, usually placed in a midline position in order not to amplify the signal from one hemisphere in respect to the other.
Finally, the obtained EEG activity is divided into rhythmic and transient activity. Rhythmic activity is then divided into bands of frequency: Delta, Theta, Alpha, Beta, Gamma, and Mu (for a review see Olejniczak P, 2006; Niedermeyer and da Silva, 2004).

5.1 Event-Related Potential and the N400

ERP measured with EEG is considered as a measure of the electrophysiological response of the brain to a specific stimulus, either a cognitive, sensory, or motor event (Stevens, 2005). In this sense ERP applied to EEG are a powerful tool for the study of the brain synaptic function (Olichney et al, 2011).
More specifically ERPs reflects the sum of postsynaptic excitatory and inhibitory activity in the pyramidal cells of the neocortex (Nunez and Sirinivasan, 2006). What it is important to bare in mind is that one single stimulus or event is not visible in the EEG but the event has to be repeated up to 100 trials or more in order to average the results together in order to get a relevant waveform (the ERP) as the consequence of the random brain activity being averaged out (Coles and Rugg, 1996). As the ERPs have a so called, temporal immediacy, they are particular suitable to study memory encoding and retrieval especially when this process occurs very fast, like for example with priming. Moreover, as ERPs reflects the timing and neural pattern of the neural activity they aim to measure, they are very useful in quantify the sequence and timing of the different stages of the underlying cognitive processes (Olicheney et al, 2011). More specifically, it has been shown that early brain response reflects the stimulus characteristics while later responses mostly reflect the mental operation performed on the stimuli. It's those later components that have been proven to be sensitive to, for example AD, which, as widely know, is a condition in which the medial temporal lobe and neocortical association regions are more affected by pathology (Braak and Braak, 1991; Katada et al, 2004).
One of those components is the N400.
The N400 is a negative deflection peaking at circa 400 milliseconds post-stimulus onset (and observed between about 250 and 550 ms) in young adults and it is typically more intense around parietal electrodes sites. This deflection is normally a part of the brain response to words and other meaningful stimuli: visually and auditory words, signs, picture, faces, and even smells (Kutas and Federmeier, 2000). Even if the N400 has been found as a response of a great variety of paradigms, there are several kinds of experimental paradigms that are used to elicit its effect such as priming paradigms (Kutas and Federmeier, 2009). In priming paradigms the investigated N400 effect is on the target as a function of its relationship to the prime. In particular the N400 amplitudes to a target are reduced (meaning that they become more positive) when a prime has already activated some of the target's features, like for example if the prime and the target are semantically related. N400 priming effects have been recorded for overlapping features such as physical, functional, and affective shared characteristics (Bentin et al, 1985; Kellenbach et al, 2000; Zhang et al, 2006), and their magnitude of strength is graded by typicality and associative closeness (Harbin et al, 1984; Stuss et al, 1998). Moreover, the effect of the N400, seems to cross modality and stimulus type, so the N400 response to a target picture can be facilitated by its

semantic relationship to another picture (McPherson and Holcomb, 1999), by another visually presented word (Ganis et al, 1996), by an auditory word (Pratarelli, 1994) or by a smell (Grigor et al, 1999; Sarfarazi et al, 1999).
The study of N400 effects in language comprehension has provided evidence that language processing is immediate, incremental and graded. Evidence in this direction comes from the fact that, in a sentence context, the N400 can be detected within 200 milliseconds of the onset of a word that is semantically unexpected. This implies that the N400 is a direct brain response to the immediacy of language comprehension during both reading and listening, and even singing (Kutas and Federmeier, 2009). Moreover it now known that the N400 response is sensitive to healthy ageing and that N400 latency increases at ~2 ms/year and N400 amplitude decreases at 0.07 V/year across a lifespan (King and Kutas, 1995; Kutas and Iragui, 1998).
The N400 effect has been used in particular to study the integrity of semantic memory in dementia, especially in AD and quantitative measure of N400 latency have been found to be a useful tool in monitoring dementia stage and progression (Olichney et al, 2011). ERP EEG and in particular the study of he N400 effect have been our methods of choice in studying the brain response in automatic semantic processing in both healthy ageing and dementia.

5.1.1 The analysis of ERP EGG: electrical field topography, global field power, topographic consistency test and microstate analysis

When measuring one or two conditions at a given point in time, the aim is to test if those two conditions differ in active scalp source, something that can be estimated without knowing the location of the different sources. This is due to the fact that scalp fields are additive: if two sources are active at the same time, the data obtained is the scalp field produced by both. This means that it is possible to interpret the difference in scalp source given by two different conditions (note that identical sources from two conditions are cancelled out when the difference is computed). In other words, if we want to test if two conditions differ in their active source we have to prove that there are scalp source differences between these two conditions and they haven't occurred by chance. In order to avoid bias it is important to quantify the overall strength of scalp field differences, and when this is done, it can be used to test the result obtained against the null hypothesis. A well known measure of overall scalp field strength is the Global Field Power (GFP). When recording scalp activity with a multichannel approach, scalp maps are displayed as a change in potential distribution over time showing both epochs with little activity and others with high peaks. What GFP does is to quantify the amount of simultaneous activity at each time point, describing potential field without the need of an independent reference. GFP is then plotted over time and its highest

values are used to determine latencies in the evoked potential components of interest. Said in another way GFP delivers a measure of the standard deviation across all sensors (Skrandes, 1990).
The global measure of scalp field difference depends on the amplitudes of the mean differences among groups and/or conditions and on random variance, and in order to assess a particular effect it is important to rule out this randomness in favor of possible effect consistency across measurements. This can be tested by randomly shuffling the condition or group of conditions in each subject and recompute the global measure of scalp difference. In this case the result obtained will depend only on the random variance across subjects and conditions, with any value obtained being
a measure given by noise alone. Repeating a sequence of shuffling and computation it is then possible to obtain an estimation of the distribution of the global measure of scalp difference according to the null hypothesis and to contrast it against empirical data. A significant effect is then given by the percent of random scalp difference which is larger or equal to the values obtained with empirical data. This procedure is called topographic analysis of data (TANOVA). In short TANOVA is a method to analyse event-related scalp field data, which takes into account the physical basis of electromagnetic data but is model independent, or, in other words, is a way of determining the time period of significant topographic effects when all task conditions are included (for a review see Koenig et al, 2011).
A way to further (post-hoc) analyze ERP data is to perform a topographic consistency test in order to define the start and the end of the epoch. This test, also based on randomization, compares the GFP of the null hypothesis with the GFP of the ERP of interest, indicating the time frame in which a particular scalp field potential was recorded which can not be caused by noise. More specifically this method shuffles the electrodes, at each time point, for every single subject and condition (Koenig et al, 2011). Another used post-hoc test is the so called microstate anaysis. Microstates analysis is based on the fact that brain states changes in a non-continuous manner, from small variance in brain activity to quasi-stability, and major and rapid changes. If we take for example human conscious interact with the environment, brain neural activity can go from microstates of quasi-stable spatial distribution to fast changes, suggesting different brain function. Microstate analysis has then been developed as a way to interpret the functions of those sub-second states of the brain (Lehmann et al, 2009). In this thesis microstate analysis was used to assess ERP modulation in a given time domain.
Finally topographic component recognition (TCR) can be used to assess if a given map explains more of the variance in one particular condition, if it is more present in one condition or even if it covers a different time segment or peaks in one condition more than another (Brandeis et al, 1992)

6. A DUCK WITH FOUR LEGS: SEMANTIC DEMENTIA

If I would ask you to draw me a duck, do you think you would ever draw me a duck with four legs? Probably not. But for some other people it would be quite a natural choice.

So let me introduce to you Mr M.

"…Mr M driving through the countryside with his wife, retrieving the several-years-old-memory that they will have to turn left ahead. His view from the car window includes not just the cues to this preserved route knowledge (knowledge that many people with normal brains would find difficult to retrieve), but one of the most familiar scenes in the British countryside: a flock of sheep. The sheep are a puzzle to Mr M: not only does he not know what to call them, he no longer knows what they are. He wears a wool jacket when it's cold and eats roast lamb for Sunday lunch, but would not be able to say that "those things" out there are the source of these products. He would succeed in matching a photograph of a sheep taken from the side to one taken from the front ….. If asked whether the photograph of a sheep is an animal, he would probably say yes, but if asked what other animal is similar to it, he would look blank" (Patterson et al, 2007).

And Mrs P P.

"P.P., a 68-yr-old, right-handed ex-clerical officer and secretary presented in 1990 with a 2 yr history of progressive loss of memory for names of people, places and things, together with impaired comprehension of nominal terms. She has also complained from the onset of problems recognizing even very familiar people from sight, voice or description. Her fund of general knowledge was radically impoverished. When asked, "Have you ever been to America?, she replied "what's America?", or asked, "What's your favourite food?" she replied "food, food, I wish I knew what that was". Despite this profound deficit in semantic memory her day-to-day memory remained fairly good. She could remember appointments and keep track of family events. Sadly, she retained insight into her deficit and at times became severely depressed. There has been no deterioration in self-care. Spontaneous speech was well articulated with normal prosody. She was able to produce fluent and grammatically correct sentences, but conversation was punctuated by severe word-finding difficulty and frequent semantic paraphasias . Phonemic errors were never observed. The degree of anomia is such that she has never correctly named a single item, either on informal testing or on a number of formal naming tests. Comprehension of simple questions about personal events was maintained but there was a profound deficit in understanding of all but very common nominal terms, to such an extent that she was unable to point to very

common objects. Repetition of single words and even of grammatically complex sentences was normal. Reading was severely disrupted with letter-by-letter alexia, but she could identify, from oral spelling, words with regular spelling-to-sound correspondence. Similarly, she managed to write to dictation some regular words. She was able to do simple mental arithmetic. In contrast to her profound language impairment, her visuospatial abilities were remarkably well preserved; copies of complex geometric shapes were executed flawlessly. Computerized tomography and magnetic resonance imaging scans revealed a moderate degree of cerebral atrophy, more marked in the left hemisphere, particularly around the sylvian fissure. A positron emission tomography study, performed at the Hammersmith Hospital, revealed hypometabolism in the left inferior frontal and temporo-parietal areas. On follow-up over the subsequent 12 mths there has been only moderate change in her general abilities. She is still self-caring and is able to do very simple housework but when shopping she no longer knows which items to choose, and similar her cooking ability deteriorated because of a lack of understanding of the fundamental processes and utensils involved. She enjoys seeing family members and her visits to Cambridge. Language has deteriorated further. Her spontaneous speech now contains virtually no nouns and few verbs other than general ones like "come" and "do", and she tends to produce grammatically correct and fluent stereotyped phrases such as "Oh dear; I wish I could think what I wanted to say". Insight into her predicament is maintained. Eating habits, table manners, grooming and toileting are all normal and she has not exhibited any unusual or anti-social behavior." (Hodges et al, 1992)

Those two patients described by Patterson et al (2007) and by Hodges et al (1992) clearly present two persons suffering from a condition showing an intriguing combination of preserved and impaired cognitive abilities which has been documented in several hospitals all over the world and it is widely known under the name of SD).

It's those patients that, if asked to draw a duck, would definitely draw one with four legs.

It's quite a typical tendency of those patients to include incorrect features on concepts belonging to the living domain, especially animals. A reason for this could be that living things such animals share more visually properties and that's why patients tend to add features to a concept or "over-extend" characteristics of a domain to a particular object which though doesn't share them (like drawing a duck with two more legs for example). Probably this happens as our visual representations are very much dependent on their corresponding semantic representations and thus the ability to picture a visual concept suffers from an impaired semantic memory system (Bozeat et al, 2003).

SD, as the name suggests, is very much a disease of the semantic memory system. The first reports on SD came already in the 1970's first by Warrington (1975). He described three patients with cerebral atrophy showing a loss of receptive and expressive vocabulary together with impaired conceptual knowledge in particular

for living things and inanimate objects at their subordinate/attributional level, while syntax and phonology were found to be intact. Shortly after Warrington's seminal paper (1975), his findings were confirmed by Schwartz et al (1979) but we have to wait until 1989 (Snowden et al, 1989) for the term semantic dementia to be introduced, and 1992 (Hodges et al) to get the first diagnostic criteria.
Hodges et al (1992) describe SD as: "a clinically recognizable syndrome with the following characteristics: (i) selective impairment of semantic memory causing severe anomia, impaired spoken and written single-word comprehension, reduced generation of exemplars on category fluency tests and an impoverished fund of general knowledge; (ii) relative sparing of other components of language output and comprehension, notably syntax and phonology; (iii) normal perceptual skills and non-verbal problem-solving abilities; (iv) relatively preserved autobiographical and day-to-day (episodic) memory; (v) a reading disorder with the pattern of surface dyslexia".
After 6 years from the first clinical description of SD, Neary et al (1998) agreed on the first clinical diagnostic criteria, divided into core diagnostic features and supportive diagnostic features (see List 1). Those diagnostic criteria have recently been revised (Gorno-Tempini et al, 2011) (see List 2)

List 1

1. Core diagnostic features
    a. Insidious onset and gradual progression
    b. Language disorder characterized by
        i. Progressive, fluent, empty spontaneous speech
        ii. Loss of word meaning, manifest by impaired naming and comprehension
        iii. Semantic paraphasias and/or
    c. Perceptual disorder characterized by
        i. Prosopagnosia: impaired recognition of identity of familiar faces and/or
        ii. Associative agnosia: impaired recognition of object identity
    d. Preserved perceptual matching and drawing reproduction
    e. Preserved ability to read aloud and write to dictation orthographically regular words
2. Supportive diagnostic features
    a. Speech and language
        i. Press of speech
        ii. Idiosyncratic word usage
        iii. Absence of phonemic paraphasias
        iv. Surface dyslexia and dysgraphia
        v. Preserved calculation
    b. Behavior
        i. Loss of sympathy and empathy
        ii. Narrowed preoccupations
        iii. Parsimony
    c. Physical signs

i. Absent or late primitive reflexes
ii. Akinesia, rigidity, and tremor

d. Neuropsychology
    i. Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
    ii. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing
e. Electroencephalography: normal
f. Brain imaging (structural and/or functional): predominant anterior temporal abnormality (symmetric or asymmetric)

List 2

1. Clinical diagnosis
   Both of the following core features must be present
    a. Impaired confrontation naming
    b. Impaired single-word comprehension

   At least 3 of the following other diagnostic features must be present
    a. Impaired object knowledge, particularly for low-frequency or low-familiar items
    b. Surface dyslexia or dysgraphia
    c. Spared repetition
    d. Spared speech production (grammar and motor speech)
2. Imaging-supported diagnosis
   Both of the following must be present
    a. Clinical diagnosis as in 1
    b. Imaging must show one or more of the following:
        i. Predominant anterior temporal lobe atrophy
        ii. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET
3. Pathology
   Clinical diagnosis as in 1 and either criterion 2 or 3 must be present
    a. Clinical diagnosis as in 1
    b. Histopathological evidence of a specific neurodegenerative pathology
    c. Presence of a known pathogenic mutation

In short, the main characteristic of SD is the dramatic reduction of expressive vocabulary, even called “anomia” (Pijnenburg et al, 2004; Thompson et al, 2003). Nonetheless receptive vocabulary results to be impaired as well. As the disease progresses the patients appear as being “word deaf”. Moreover, and despite suffering from anomia those patients show relatively normal phonology and grammar (Adlam et al, 2006; Ash et al, 2006). They also show a deficit in person knowledge ranging from the inability to name people, to generating information about their faces or names, to finally not being able to process if someone is familiar

or famous (Snowden et al, 2004; Thompson et al, 2004). In addition, and differently from AD patients, patients suffering from SD show well preserved time orientation, calculation and drawing skills (Hodges et al, 1992; Hodges et al, 1999; Perry and Hodges, 2000). Interestingly it seems that SD patients unlike healthy controls and even AD patients suffer from a "reversal of the concreteness effect", meaning that they show a worse performance with concrete than abstract words (Breedin et al, 1995; Yi et al, 2007; Warrington, 1975).

Behavioural changes in those patients are not primary signs early in the course of the disease but are present as the disease progresses, among them: degraded social functioning, emotional withdrawal, depression, apathy, irritability, and even change of food intake, from restricted diet to bizarre food choice (Bozeat et al, 2000; Seeley et al, 2005). Other behavioral abnormalities are repeated clockwatching and rigidity, and some patients even develop special intense interests like in jigsaw puzzles or word search puzzles (Snowden et al, 2001). Neuropsychologically one of the main findings is that all patients suffering from SD, apart from those in the very early stages, score very poorly on naming tests, a pattern that progresses over time. Category fluency is particularly impaired while letter fluency relatively spared (Hodges et al, 1995). More specifically those patients show impaired comprehension for content words, like nouns, verbs and adjectives, the more difficulties the less familiar the word is. In sum SD patients show a striking multimodal semantic impairment spanning from verbal as well as non verbal domains. Moreover what is the most striking characteristic of the impaired semantic system of those patients is the tendency to respond correctly only to objects and words typical for their class, making then so called "typicalisation" errors on atypical things especially if not familiar (Hodges and Patterson, 2007).

As a clinical condition SD is now widely considered as one of the main variant of Fronto-Temporal Dementia (FTD). It is also been estimated that between 1/4 and 1/3 of patients diagnosed with FTD do have SD (Chow et al, 2005).

Neuropathologically SD seems to have a predictable basis of ubiquitine-positive, tau-negative inclusion pathology (Snowden et al, 2007; Davies et al, 2005; Shi et al, 2005). Nevertheless a more recent study has found that its right variant could be related to TAR DNA-binding protein 43 (TDP-43) pathology (Josephs et al, 2009).

Neuroimaging findings indicate that patients with SD show bilateral, but typically asymmetrical atrophy of the anterior temporal lobe, which, with time, extends to the posterior temporal lobes or into the posterior, inferior frontal lobes, or both, as seen in coronal MRI (Hodges and Patterson, 2007). Nevertheless even if SD has been associated with bilateral atrophy of the anterior temporal lobes, most studies report mostly left shrinkage (Gorno-Tempini et al, 2004; Mummery et al, 2004; Mesulam et al, 2009; Galton et al, 2001; Rosen et al, 2002). These observations have been confirmed by quantitative and voxel-based MRI investigations, showing 50-80% of GM atrophy in the polar and perirhinal cortices and in the anterior fusiform gyri (Chan et al, 2002; Davies et al 2004; Du et al, 2007; Galton et al, 2001; Gorno-Tempini et al 2004; Rosen et al 2002). Besides volumetric studies, even metabolism

studies with Fludeoxiglucose-Positron Emission Tomography (FDG-PET) have confirmed anterior bilateral dysfunction in SD (Diehl et al, 2004; Nestor et al, 2006). Interestingly Nestor and al (2006) have demonstrated hypometabolism in the ATL, for all the SD patients investigated.

The first study using VBM on SD patients was the single-subject one by Mummery et al (2000), which found that significantly atrophied regions were predominantly in the left temporal lobe, and in particular in the temporal pole. Moreover they showed that the temporal lobe had greater GM loss in the anterior part, this suggesting that the disease starts anteriorly and spreads posteriorly. More GM loss was also found in the left insula and ventromedial frontal cortex in a left-greater-than-right fashion.

Later group studies on the same group of patients as the one by Good e al (2002) showed significant GM loss in the amygdala, fusiform gyrus, inferior and middle temporal gyrus, and temporal pole, more pronounced on the left side. Moreover they found atrophy in the hippocampus, entorhinal cortex and superior temporal gyrus. Hippocampal atrophy in SD has been confirmed by several other studies (Boxer et al, 2003; Rosen et al, 2002; Gorno-Tempini et al, 2004) whereas other studies have shown GM loss in ventromedial and superior frontal regions (Boxer et al, 2003; Rosen et al, 2002; Gorno-Tempini et al, 2004). Other studies have even shown atrophy in subcortical structures such as the left dorsomedial thalamus (Boxer et al, 2003) and the caudate nucleus (Gorno-Tempini et al, 2004). Last but not least several studies have enquired the degree of atrophy asymmetry in SD and while some have found a more pronounced left-sided shrinkage (Good et al, 2002; Grossman et al, 2004; Halpern et al, 2004), others found a more symmetrical pattern of atrophy (Boxer et al, 2003; Rosen et al, 2002; Gorno-Tempini et al, 2004).

Finally the study by Boxer et al (2003) compared AD and SD patients and found greater GM loss for the AD group, in the left parietal lobe and the posterior cingulated/precuneus bilaterally, in comparison to SD group. They also found the left parietal lobe to be the most atrophied. On the other hand the SD group showed greater shrinkage bilaterally in the amygdala, hippocampi, in the anterior temporal lobes, the right middle temporal gyrus, and the left temporal pole.

Very few studies have been conducted on SD patients using DTI in order to enquire WM pathology. Agosta et al (2010) found higher MD, DR and DA in the inferior longitudinal fasciculus, left uncinate and arcuate fascicule when SD patients were compared to controls, while lower FA was found in the genu of the corpus callosum. Moreover they found higher MD in the anterior part of the inferior longitudinal fasciculus and in the arcuate and uncinate fasciculus situated in the temporal pole. Another study by Withwell et al (2010) found MD increases in SD in the insula, frontal, parietal and occipital lobes, especially in the left hemisphere, while the greater changes in FA and DR could be identified in the left anterior and posterior inferior longitudinal fasciculus and left uncinate fasciculus.

In short, the peculiar clinical picture of SD and its circumscribed neuropathology makes it the perfect candidate to study the function and locus of semantic memory. Nevertheless the rarity of this condition makes it difficult for us researchers to gather a statistical reasonable group of patients in order to draw firm conclusions. As it is often said: not really like taking a duck to water even if this duck happens to have four legs.

7. LOSING YOUR MIND: ALZHEIMER'S DISEASE

Even if AD, as a clinicopathological condition was first described more than 100 years ago by the German psychiatrist and neuropathologist Aloïs Alzheimer (Alzheimer, 1911), it was at first seen as an uncommon condition and thus ignored for years. Nowadays AD is considered the most common cause of dementia in the elderly (Alzheimer's Association, 2010) and thus considered a great public health problem. AD, which is neuropathologically characterised by extracellular deposit of neuritic plaques mostly based of β-amyloid (Masters et al, 1985), and intracellular neurofibrillary tangles made by hyperphosphorilated tau (Goedert et al, 1991) (note that SD, instead is not a taupathy), is now estimated to affect 5.3 millions individuals only in the United States, 5.1 of whom, already over the age of 65 (Alzheimer's Association, 2010). Moreover the estimated prevalence in the United States will be 7.7 millions in 2030, and 14 millions in 2050, making AD the fifth most common cause of death for people older than 65 years of age (Heron et al, 2006). Over the years, longitudinal studies have shown how AD has an insidious onset accompanied by a gradual and progressive cognitive deterioration (Clifford and Jack, 2012).
The clinical diagnosis of AD has been based on several common criteria such as those from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA), the World Health Organization (WHO) International Classification of Diseases, Tenth Revision (ICD-10), and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (McKhann et al, 1984). Moreover in 2007, Dubois and collegues proposed criteria also including neuroimaging findings. Lately a task force charged by the National Institute of Aging and the Alzheimer's Association has extensively revised the first criteria from 1984 (McKhann et al, 2011), and defined clinical AD as following:

Probable AD

1. interference with the ability to function at work or at usual activities

2. represent a decline from previous levels of functioning and performing

3. is not explained by delirium or major psychiatric disorder

4. cognitive impairment is confirmed by a combination of history-taking from the patient or an informant and a mental status examination or neuropsychological testing

5. the cognitive or behavioral impairment involves a minimum of two of the following:

i) impaired ability to acquire and remember new information: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route;
ii) Impaired reasoning and handling of complex tasks, poor judgment symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities;
iii) impaired visuospatial abilities symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body;
iv) impaired language functions (speaking, reading, writing), symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors;
v) Changes in personality, behavior, or comportment, symptoms include: uncharacteristic mood fluctutions such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially
unacceptable behaviors.

6. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days

7. Clear-cut history of worsening of cognition by report or observation; and

8. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:

a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
b. Nonamnestic presentations:

- Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present
- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

9. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non- fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or

a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

So if AD is defined as a clinical condition characterized by cognitive dysfunction, one of its most prominent feature is the loss of word usage, causally dependent on the intactness of semantic memory, a condition defined as anomia. Semantic deficits in AD as been documented in depth through the use of several neuropsychological tests. Semantic disruption in AD affects subordinates more then superordinates (Chertkow & Bub,1990; Hodges et al 1992), biological entities more than non biological ones (Fung et al, 2001; Gonnerman et al, 1997; Whatmough et al, 2003), and impaired knowledge of famous people, when related to other kind of conceptual knowledge or to source (autobiographical) memory (Greene and Hodges, 1996; Thompson et al, 2002). All of those deficits abovementioned are considered impairments in effortful (conscious) semantic retrieval. In order to enquire automatic (unconscious) access to semantic knowledge several studies have enquired the magnitude of semantic priming in AD, finding both hypopriming (Ober and Shenaut, 1988), normal priming (Nebes et al, 1984; Rogers and Friedman, 2008), and hyperpriming (Chertkow et al, 1994). In sum the quest for semantic memory in AD, either acessed as effortful retrieval, or automatic spread of activation, is not over yet. ERP EEG studies using as a marker the presence or absence of amplitude of the N400 have tried to evaluate the integrity of the semantic network in AD. In most of the studies it is clear that the N400 is usually abnormal in AD, typically reduced in amplitude, and delayed in latency, in comparison to controls (Olichney et al, 2011). In particular reduced N400 in AD has been found with visual stimuli used as primes (Ford et al, 2001), targets (Auchterlonie, 2002), and as both prime and target (Castañeda et al, 1997)
Neuropathologically AD is characterised by progressive cerebral atrophy as it can be seen using MRI. This progression of atrophy can first be seen in the medial temporal lobe (Scahill et al, 2002), with the enthorinal cortex being the earliest site of atrophy, followed by the amygdala and the parahippocampus (Lehericy et al, 1994; Chan et al, 2001; Dickerson et al, 2001; Killiany et al, 2002). Moreoever other affeted structures are involve the limbic lobe, such as the posterior cingulate. This atrophy then spreads to th etemporal neocortex and to all the neocortical association areas (Johnson et al, 2012).
It is now well known that by the time an AD patient become symptomatic, atrophy is already widespread (Johnson et al, 2012). Even in patients with mild AD, the enthorinal volume is already reduced by 20-30 %, and the hippocampal volume by 15-25 % (Chan et al, 2001; Dickerson et al, 2001; Schuff et al, 2009). Several studies have then used VBM to study AD brains.
The first study in this direction was that of Rombouts et al (2000), who studied brain atrophy in a small group of mild and moderate AD patients compared to controls, and found the hippocampus to be the most affected structure. Since then studies performed with larger AD populations have showed a more widespread patterns of atrophy, like not only in the hippocampus, amygdala and entorhinal

cortex, but also in the posterior cingulate and precuneus, insula, temporoparietal association neocortex, prefrontal gyri, and moreover more central structures like the caudate, putamen, thalamus and hypothalamus (Baron et al, 2001).
Even if there is now a wide consensus over how hippocampal pathology is one of the first signs of incipient AD, several studies differ on the opinion about which other medial structures are affected. Some studies claim the implication of the amygdala (Baron et al, 2001; Kawachi et al, 2006; Ishii et al, 2005a; Ishii et al, 2005b), entorhinal cortex (Ohnishi et al, 2001), or the parahippocampal gyrus (Kawachi et al, 2006; Ohnishi et al, 2001).
Other studies have found both the thalamus (Boaokstein, 2001; Good et al, 2002), and the caudate nucleus (Good et al, 2002) to show significant atrophy in AD.
Moreover several studies, comparing voxels with higher significance or areas with larger atrophy, have found asymmetric atrophy in AD brain, especially on the right in the medial temporal lobe (Rombouts et al, 2000; Baron et al, 2001; Ishii et al, 2005a; Ishii et al, 2005b, Busatto et al, 2003; Frisoni et al, 2002), lateral temporal lobe (Busatto et al, 2003), and temporoparietal association cortex (Baron et al, 2001; Boxer et al, 2003; Zahn et al, 2005; Grossman et al, 2004). As for early sign of atrophy in AD brains, both the study by Frisoni et al (2002), and Busatto et al (2003), confirmed what already pointed out by Braak and Braak (1996), i.e. a pathological involvement of both the medial temporal lobes and inferior temporal sites.
Other studies have focused on brain perfusion using techniques such as SPECT or ASL MRI, giving a measure of relative respectively absolute CBF. The most striking findings using ASL to study perfusion in AD brains compared to healthy controls, is reduced CBF in the inferior parietal lobe, the posterior cingulated gyrus, the middle frontal gyrus, and the inferior temporal cortex (Johnson et al, 2005; Alsop et al, 2008), while hypermetabolism could be found in the hippocampus and other medial structures (Alsop et al, 2008; Dai et al, 2009; Fleisher et al, 2009), this suggested as a result of compensatory neural activity (Alsop et al, 2008). Brain SPECT reports reduced CBF in AD in the medial temporal, superior temporal, parietal, posterior cingulate cortex, and precuneus at the beginning, while reduced perfusion is found to affect the frontal cortex in advanced stages (Farid et al, 2011).
By way of MRI DTI, WM changes hasd been throughfully studied in AD brains. Areas of WM pathology have been found in the left inferior/middle temporal area, the left parahippocampal area, the left precuneus, and the left periventicular area (Salat et al, 2010). Other studies have described WM pathology in the cingulum, in the splenium of the corpus callosum, the right superior frontal gyrus, and the left parietal sub-gyral area (Zhang et al, 2007; Medina et al, 2006). Other WM tracts early affected by AD have been reported to be the cingulated and the inferior-frontal-occipital fasciculus bilaterally (Fallegiebel et al, 2008). Moreover Stricker et al (2009) reported WM pathology in the inferior longitudinal fasciculus and in

the superior longitudinal fasciculus. All those studies highlights the fact that WM pathology in AD targets areas responsible for higher order connectivity.

7.1 The good, the bad, and the things in between: Mild Cognitive Impairment

"A 70-year-old woman has been noticing increasing forgetfulness over the past 6 to 12 months. Although she has always had some difficulty recalling the names of acquaintances, she is now finding it difficult to keep track of appointments and recent telephone calls, but the process has been insidious. She lives independently in the community; she drives a car, pays her bills, and is normal in appearance. A mental status examination revealed slight difficulty on delayed recall of four words, but the results were otherwise normal. Does the patient have mild cognitive impairment? How should her case be managed? " (Petersen, 2011).
MCI is nowadays recognized as a prodormal state of AD. Nevertheless, while some eventually develop dementia, more often AD, some others undergo only a minor decline in their cognitive functions, while some few never worsen (Petersen et al, 1999). Nevertheless several studies have reported that patients suffering from MCI are at higher risk for developing dementia (Busse et al, 2006; Plassman et al, 2008; Manly et al, 2009; Lopez et al, 2003) and the prevalence of MCI is estimated to be between 10-20 % in persons older than 65 years of age (Busse et al, 2006; Di Carlo et al, 2007; Plassman et al, 2008; Manly et al, 2008; Lopez et al, 2003).
The original consensus criteria for MCI were those by Petersen et al (1999), then revised in 2004 by Winblad et al, according to three diagnostic features:

1. Not normal, non demented, the patient doesn't meet DSM-IV or ICD-10 criteria for dementia
2. Cognitve decline reported by the patient or/and by an informant and confirmed by cognitive testing
3. Preserved activities of daily living with some impairment in complex function

Those criteria were then revised by Petersen et al (2004) and the diagnosis of MCI subdivided into four different types: 1) amnestic MCI (aMCI), characterized by an isolated memory impairment, 2) single non memory MCI with an isolated impairment of a cognitive domain other than memory, 3) multiple domain aMCI, 4) multiple domain non amnestic MCI.
Recently new consensus criteria have been established for diagnosing MCI, including core clinical criteria to be used in clinical settings and research criteria. As a guideline for the clinicians those criteria include clinical and cognitive features as following:

1. the patient must suffer from a change in cognition in respect to her/his previous

level, either as reported from the patient, or an informant, or as observed by a clinician.
2. there should be evidence of lower performance in one or several cognitive domains taking into account the patient's age and years of education. Those domains can include memory, executive function, attention, language, visuospatial skills and/or episodic memory.
3. it is important to bare in mind that persons suffering from MCI do have mild problems in performing complex functional tasks that they used to do before: for instance shopping can take more time and be handled less efficiently.
4. it is important that the clinical diagnosis is accompanied with cognitive testing, in which usually patients with MCI perform 1 to 1.5 standard deviations below age and education matched controls. Those tests include measures of episodic memory, assessing both immediate and delayed recall of verbal and non-verbal material, executive function, language, and visuospatial skills
(for a more extensive lecture about MCI latest consensus criteria see Albert et al, 2011).

Neuropathologically MCI doesn't seems to have an own hallmark but to share some neuropathological features with AD, like for example medial temporal lobe atrophy (Petersen et al, 2006).
Neuroimaging findings have also confirmed MCI as pre-dementia, the more affected areas being the enthorinal cortex and the hippocampus, their volume loss being in a stage between healthy ageing and AD (Fennema-Notestine et al, 2009; Morra et al, 2009). Nevertheless MCI patients show GM loss spreading beyond the medial temporal lobe area to even neocortical areas, in particular in the lateral temporal cortex, posterior cingulate, inferior parietal, precuneus, and caudal middle frontal cortex (Fennema-Notestine et al, 2009).
Measures of brain perfusion done with SPECT on patients with subjective cognitive complaints, amnestic MCI (aMCI) and non amnestic MCI (nMCI) compared to controls have showed reduced perfusion in the left hippocampus and bilateral temporal cortex when comparing aMCI with controls, and in the left hippocampus and bilateral parietal cortex when comparing the same group with patients with subjective complaints. Moreover hypoperfusion could be detected in the nMCI group in the bilateral temporal cortex and right frontal cortex. Finally when comparing aMCI with nMCI, the former group showed decreased perfusion in the left parietal cortex and precuneus (Nobili et al, 2008).

8. SUBJECTS AND METHODS

Study I is a retrospective study in which patient data, neuropsychological data, and SPECT data were retrieved from the patients' medical journals. Study II, III, and IV are cross-sectional studies in collaboration with the University Hospital of Psychiatry at the University of Bern in Switzerland. In Study I all the participants were patients at the Memory Clinic at Karolinska University Hospital in Stockholm, Sweden. In study II, the participants were enrolled by advertisement.

In Study III and IV all the AD patients came from the Memory Clinic at Karolinska University Hospital, while SD patients were recruited all through Sweden.
In study I we used verb and animal fluency measures and correlated them to pattern of brain perfusion measured with SPECT. SPECT data was acquired at the Department of Radiology at Karolinska University Hospital with a single-headed rotating gamma camera (Siemens Diacam).
In study II, behavioural data, and a novel semantic priming paradigms together with ERP EEG. EEG data were acquired at the Memory Clinic at Karolinska University Hospital with an EEG cap with 32 sintered silver chloride ring electrodes mounted to the cap according to the international 10-20 system.
In study III and IV, behavioural data (not comprised in Study III) data from the semantic priming paradigm used in Study II together with ERP EEG were acquired at the Department of Linguistics at Stockholm University. Electrophysiological measurements were conducted with a high-impedance 128-channel HydroCel Geodesic Sensor Net connected to a Net Amps 300 amplifier (Electrical Geodesics Inc., Eugene, USA).

8.1 STUDY I

A total of 93 patients were included in the study: 30 with SCI, 30 with MCI and 33 with AD. The neuropsychological assessment comprised Mini-Mental State Examination (MMSE) (Table 1), Noun Fluency (NF), and Verb Fluency (VF) tasks.

	AGE	**EDUCATION**	**MMSE**
AD (33)	64.8 (9.4)	11.6 (4.0)	23.4 (3.9)
MCI (30)	60.5 (8.7)	12.5 (4.0)	27.6 (2.1)
SCI (30)	56.9 (7.4)	12.9 (2.7)	29.3 (0.8)

Table 1. Mean and standard deviation for age, years of education and MMSE scores for the three patient groups.

SCI was diagnosed in case of memory complaints without objective signs of cognitive decline. MCI patients were diagnosed according to the criteria by Wahlund et al (2003) while AD patients were diagnosed according to the International Classification of Diseases, tenth edition (ICD-10).
Each participant was injected with 1000 Mbq Tc-99m hexamethylpropylenamine oxime (HMPAO; Ceretec, Amersham Ltd). Data acquisition started 30 minutes after injection. 64 projections, evenly spread through 360^0 were acquired using a single-headed rotating gamma camera (Siemens Diacam). The total acquisition time was 32 minutes. Tomographic slices wee reconstructed using an iterative algorithm (Hosem, Nuclear Diagnostics AB, Sweden) with Chang attenuation

correction. The attenuation coefficient was 0.12. The data was formatted as a 3D dataset with 64x64x64 cubic voxels with 3.5 mm slides. The resolution in a tomographic slice was 10.2 mm full width at a half maximum. The data sets were pos-filtered with a Butterworth filter, cutoff was set at 1.0 cm-1.
Data registration and acquisition was done using the BRASS software (Radau et al, 2001). The data set was registered using 9 parameter linear registration to a normal template. The relative CBF was calculated as cerebra ratios. In sum the information from the SPECT scans consisted of measurements of relative CBF in 42 brain areas normalized to 4 regions of the cerebellum.
Moreover all the participants performed two fluency tasks: VF and NF. NF was measured asking the participants to name as many animals as they could recall in 1 minute. VF was measured by the verb or action fluency task by Piatt et al (1999a, 1999b) in which subjects were instructed to tell as many things as possible a person can do. Fluency scores were divided into 10-seconds intervals as in Fernaeus and Almkvist (1998).

8.2 STUDY II

A total of 15 elderly healthy controls (EC) and 14 young participants (YC) were included in the study (Table 2). All participants exhibited normal neuropsychological functioning measured by means of MMSE.

	AGE	**EDUCATION**
EC (15)	69.1 (6.2)	12.7 (3.3)
YC (14)	26.7 (4.5)	16.1 (2.9)

Table 2. Mean and standard deviation for age and years of education for the two groups.

The participants were neuropsychologically assessed with two explicit semantic tasks (NF and VF as described in Study I) and with an implicit novel semantic paradigm.

For the implicit semantic paradigm the stimulus material consisted of word and non-word pairs. The word pairs, in their turn were divided into concrete and abstract noun-noun combination that were either semantically related or unrelated. The combination of the 2 experimental factors (relatedness and concreteness) with 2 levels (Related; Unrelated; Concrete; Abstract) resulted in 4 experimental conditions In sum the stimulus material was made of 160 word pairs (60 per condition), 160 matched non-word pairs, and 60 filler word pairs. Each target word of the 4 experimental conditions occurred twice, once in the Unrelated and once in the Related condition, with different primes. The stimulus material was divided into 4 blocks, each block containing 20 concrete, 20 abstract, 40 non-word, and 15

filler word pairs. Only 2 blocks at the time contained the same target words either as an Unrelated or Related condition. The block sequences were then presented in balanced order across participants.
The paradigm was presented visually with a 150 ms SOA and each prime or non-word lasted on the screen for 100 ms and was preceded by a fixation cross lasting 450 ms. The inter-stimulus interval was set at 50 ms and the target or non-word displayed for 250 ms. The participant was then given 2250 ms to respond by pressing one of two different keyboard buttons to indicate if the pair prime-target contained two words or a non-word.

The experimental semantic task was conducted with a simultaneous ERP EEG recording. 32 sintered silver chloride ring electrodes were mounted on the EEG cap according to the international 10-20 system. One electrode was put underneath the subject's right eye in order to record the electroculogram (EOG). Electrode impedances were kept below 10 kΩ. Fz was the recording reference electrode. The electrodes were then connected to 16-bit BrainAmp Standard amplifier (Brain Products GmbH, Gilching, Germany). The EEG was band-pass filtered (0.1-1000 Hz) at a sampling rate of 5 kHz with an input range of 3.3 mV.

Before the experimental semantic task the participants performed both a computerized speed motoric task with the dominant hand, and a clinical resting EEG with periods of eyes closed (2 minutes) and eyes open (20 seconds) for a duration time of 6 minutes and 40 seconds.

8.3 STUDY III

A total of 38 participants were included in the study: 19 EC, 14 AD, and 5 SD (Table 3). They were all tested with a neuropsychological battery consisting of: MMSE, Boston Naming Test (BNT), AF, VF, Clock Task (CT, read and construct), and a computerized visuomotoric reaction time task. Additionally, AD and SD patients were tested with Global Deterioration Scale (GDS) and Cornell Depression Scale (CDS).

	AGE	EDUCATION
EC (19)	69.5 (3.1)	13.9 (3.0)
AD (14)	66.5 (9.6)	13.8 (4.2)
SD (5)	65.8 (3.8)	13.6 (2.9)

Table 3. Mean and standard deviation for age and years of education for the three groups.

They all underwent the semantic priming paradigm described in Study II.
The paradigm consisted of 160 word pairs (40 per condition), 160 matched non-word pair, and 32 filler word pairs (352 pairs altogether). The total number of word pairs differs slightly from Study II, in order to keep the task duration as short as

possible (approx. 21 min) while the SOA was prolonged (700 millisecond) and the maximum response time was kept at 1500 milliseconds.

The experimental semantic task was conducted with a simultaneous ERP EEG and a previous rest EEG recording as in Study II.

Electrophysiological measurements were conducted with a high-impedance 128-channel HydroCel Geodesic Sensor Net connected to a Net Amps 300 amplifier (Electrical Geodesics Inc., Eugene, USA). A potassium-chloride solution was applied to the electrodes in order to keep the impedances below 50 kΩ, checked before the rest-EEG and the ERP-EEG recordings. Recording reference was Cz and the ground electrode positioned between CPz and Pz. A fixed sampling rate of 20000 Hz was low-pass filtered at 4000 Hz, and further down sampled online to 250 Hz. Moreover, an offline band-pass filter was applied at 0.5 – 18 Hz (24 db/oct).

Moreover all participants underwent an MRI examination.

A 3T Siemens Magnetom Trio MR Scanner (Siemens, Erlangen, Germany) was used for MRI data acquisition. At first, a structural T1 weighted sequence was run. The parameters of this magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence were set as following: repletion time (TR)/ echo time (TE) 1900ms/2.57ms, 176 sagittal slices, slice thickness 1.0 mm, field of view (FOV) 230×230 mm, matrix size 256×256, leading to a voxel dimension of 0.9×0.9×1.0 mm. Second, a pseudo-continuous arterial spin labeling (PCASL) measurement was applied with these parameters: TE/TR/post label delay (ω)/tagging duration (τ) [ms] = 18/3500/1170/1600, 18 horizontal slices, FOV = 230×230, matrix size 64×64 and voxel size = 3.6×3.6×6.0 mm, slice acquisition time = 45 ms, TA = 8 min 22 s.

VBM analysis on GM and CBF quantification were subsequently applied to MRI data. Finally, for each ERP of interest (P1/N1/N400), a voxel-based linear regression was employed with GM masked CBF images.

8.4 STUDY IV

A total of 15 participants were included in the study: 18 EC, 15 AD, and 8 SD (Table 4)

	AGE	EDUCATION
EC (18)	69.4 (3,2)	14.1 (2.8)
AD (15)	66.7 (9)	12.7 (2.9)
SD (8)	63.8 (3)	14 (2.6)

Table 4. Mean and standard deviation for age and years of education for the three groups.

All participants underwent neuropsychological testing and an MRI structural examination as in Study III.
Moreover they all had a DTI MRI examination according to the following parameters: images were acquired in 30 directions using an echoplanar acquisition protocol as following: matrix= 116x116, TR=5300 ms, TE=91 ms, flip angle=90, field of view=232 mm, slice thickness=3mm, and voxel size=2x2x3mm, b-value 1 = 0 s/mm^2, b-value 2 = 1000 s/mm^2. The DTI sequence was acquired twice.

GM analysis was performed with the VBM method and DTI analysis with TBSS.

9. RESULTS AND DISCUSSION

As previously mentioned the aim of this thesis was to investigate explicit and implicit semantic memory in dementia using neuroimaging and neurophysiological techniques.

9.1 STUDY I

9.1.1 Results

Principal factor analysis on SPECT data showed seven significant factors in different anatomical regions (Table 5).

FACTORS	ANATOMICAL REGIONS
The Subcortical Factor (SBC)	left and right caudate nucleus, left and right thalamus, left and right insular cortex, left and right posterior cingulated gyrus, left and right anterior subcortical, and left and right posterior subcortical.
The Dosrsofrontal-Central Factor (DF-C)	left and right sensorimotor cortex, left and right anterior dorsal frontal cortex, and left and right posterior dorsal frontal cortex.
The Orbitofrontal Factor (OF)	left and right anterior orbital frontal cortex, and left and right posterior orbitofrontal cortex
The Temporal Lobe Factor (TL)	tleft and right medial temporal lobe, left and right posterior temporal lobe, left and right temporal pole.
The Parietotemporal-Occipital Factor (PTO)	left and right occipital cortex, left and right parietotemporal cortex, left and right superior parietal lobule.
The Brainstem Factor (BS)	pons, medulla and other subcortical areas
The Superioparietal-Central factor (SP-C)	left and right sensorimotor cortex, left and right superior parietal lobule

Table 5. Result of SPECT data divided by seven main factors and their corresponding anatomical regions

Further analysis of hypoperfusion factor scores revealed significant differences between AD on one hand and SCI and MCI on the other hand in factor scores overall $F(2, 89) = 11.92$, $p < .001$. Post-hoc analysis showed significant differences between SCI on one hand and MCI and AD on the other hand in the SBC Factor (AD vs SCI, $p < .001$; MCI vs SCI, $p < .02$), and significant differences between AD and SCI in the TL Factor ($p < .05$). In the PTO Factor there were significant differences between SCI and MCI ($p < .05$), and between AD and SCI ($p < .001$).

Taking 8 SPECT variables from the TL Factor of each hemisphere (temporal pole, medial temporal lobe, lateral temporal lobe, and posterior temporal lobe), an interaction was found [Rao $R(6, 176) = 2.47$; $p < .05$] indicating significant differences in the temporal pole and medial temporal lobe between SCI and MCI on one hand and AD on the other hand, with decreased perfusion in AD, and significant differences between MCI and SCI in the temporal pole, with decreased perfusion in MCI (LSD; $p < .01$).

Analysis of fluency data indicated a significant effect of type of test, $F(1,90) = 63.56$, $p < .001$, indicating higher performance in noun fluency than in verb

fluency.
Analysis of the interaction between type of fluency and diagnostic group, $F(2, 90) = 7.22$, $p < .01$ showed a greater difference between SCI and MCI on one hand and AD on the other hand, in noun fluency. Fisher LDS post-hoc analysis showed a significant difference in noun fluency between SCI and MCI on one hand, and AD ($p < .001$) (Figure 2).

Finally multiple regression analysis revealed that two variables predicted noun fluency: age, and the PTO factor ($R = .47$, $p < .001$), and two factors predicted verb fluency: years of education and the TL Factor ($R = .49$, $p < 001$).

9.1.2 Discussion

In this study performance in noun and verb fluency were associated with somehow different anatomical regions whose cerebral blood flow were measured with SPECT.
Decreased noun fluency was predicted by higher age and decreased perfusion in parieto-temporal occipital region as it was expected as those regions sustain object knowledge. Verb fluency, instead, was predicted by higher education and hypoperfusion in the temporal lobe. One reason for this result could be that higher educated people may be better prepared for the task by using a better grammatical frame. Nevertheless performance in verb fluency is usually not associated with pathology in the temporal lobe, but rather it is known to depend on frontal networks. We explain differences in performance in noun and verb fluency and their relatedness to hypoperfusion in parieto-temporal respective temporal regions with a linguistic approach, and a difference in test difficulty between the two tasks. So, as noun fluency performance relies on a given taxonomy, hierarchically structured and easily defined, verb fluency target a semantic network which is less coherent and requires a more effortful retrieval and thus should put an heavy load on the temporal lobe and in particular on the entorhinal cortex.
Last, perfusion data indicated hypoperfusion in the temporal lobes for both MCI and AD, with a significant decrease in the temporal lobes which could be seen already in MCI. Those regions, containing the anterior parahippocampal region, and including the perirhinal and entorhinal cortices confirm previous data indicating those areas as severely affected in AD.

9.2 STUDY II

9.2.1 Results

Results from the analysis of neuropsychological data can be seen in Table 6.

	EDUCATION	MMSE	AF	AF
YC	16.14 (2.93)	29.43 (0.65)	29.14 (6.21)	26 (3.82)
EC	12.73 (3.33)	28.73 (0.59)	22.73 (5.95)	19. 80 (4.81)

Table 6. Mean and standard deviation for education, MMSE, AF, and VF scores for the two groups.

Independent t-test analysis confirmed that the YC performed significantly better than the EC in both fluency tests ($p < .001$).

In the speed motoric task the EC reacted significantly slower than the YC as measured by Mann-Whitney test ($p < .001$).

Descriptive reaction time (RT) group means for all the semantic paradigm conditions and the 2x2x2 (relatedness x concreteness x age group) repeated measure ANOVA effects are listed in Table 7.

	F	df	p
Relatedness	20.037	27	< .001
Concreteness	7.909	27	< .01
Relatedness x age group	0.003	27	0.99
Concreteness x age group	0.064	27	0.80
Relatedness x concreteness	1.073	27	0.31
Relatedness x concreteness x age group	0.060	27	0.81
Age group	0.118	27	0.73

Table 7. Analysis result of the semantic paradigm RT (in milliseconds)

Both subject groups reacted significantly faster to the related than the unrelated condition. The effect of concreteness was also significant, with faster RT to concrete than abstract words. Age didn't show any significant effect, neither there were any interaction between factors. When a 2 x 2 x 2 x 2 ANOVA was applied (repetition x relatedness x concreteness x age group) the results showed no effect of repetition or interaction with the word condition or age group (repetition: $F(1,27) = 1.764$, $p = .195$; repetition x relatedness: $F(1,27) = 2.668$, $p = .114$; repetition x concreteness: $F(1,27) = 2.190$, $p < .150$; repetition x age group: $F(1,27) = .004$, $p = .949$.
Independent t-test on non-word RTs revealed no age difference ($p = .41$).

Both groups achieved high accuracy in the semantic paradigm and performed equally as measured by independent t-test of d-prime scores.

Topographic 2 x 2 x 2 (relatedness x concreteness x age group) TANOVA detected an N400-Late Positive Component (LPC) SP effect indicating significant topographic differences between related and unrelated target words. The investigation of age effects in the N400-LPC component revealed a significant age x relatedness interaction between 371 and 431 milliseconds.

Microstate analysis was set from 100 milliseconds to 700 milliseconds post target stimulus onset and showed that the N400-LPC occurred significantly earlier in the Related compared to the Unrelated condition and in the YC compared to the EC. The relatedness x age interaction was though not significant reflecting a comparable N400-LPC SP effect for both groups.

The 2 x 2 x 2 randomization test of the GFP values resulted in a main SP effect (relatedness effect) between 381 and 425, and between 455 and 603 milliseconds. A significant main effect of concreteness was also found between 39 and 90, and 429 and 525 milliseconds. Related words elicited a higher GFP effect than unrelated words ($p < .005$) and GFP was also higher for concrete words in comparison to abstract ones ($p < .05$). No age-related strength difference in the N400-LPC SP was found, and neither in the N400-LPC concreteness effect.

9.2.2 Discussion

In this study we investigated behavioral and biological correlates of automatic semantic retrieval in healthy young and healthy elderly.
We found that automatic word processing remain stable during a life span of an healthy adult. More specifically we found that both groups performed equally in the semantic priming task and activated comparable neural networks during semantic processing. Nevertheless the N400-LPC microstate was delayed in the elderly. This delay could be attributed to a general age slowing, as found in verbal fluency or to a compensating mechanism.
Both groups responded faster to related than unrelated word pairs. This semantic priming effect, given the short SOA implied in this study, could be attributed to an automatic spread of activation, in contrast to controlled processes. So, the automatic spread of activation in the elderly was equal to that seen in the young groups, this in agreement with previous studies. Further on, faster responses for concrete than abstract words confirmed the expected concreteness effect. Weaker word fluency scores for the EC group together with their equal result as the YC groups in the SP task further confirm the hypothesis that controlled processes are altered with older age while automatic spread of activation is not.
Electrophysiological analysis, through the analysis of GFP, showed lower electrical field strengths in the N400-LPC complex of the unrelated condition and thus a SP effect, as consistent with the literature. Moreover, GFP analysis showed significantly increased electrical field strength for concrete than abstract words,

which might reflect a higher connectivity for concrete words. Nevertheless our result showed no topographic difference between concrete and abstract words in the N400-LPC complex so that we made the assumption that comparable neural networks were activated in both conditions but to a higher extent in the concrete condition. In short both the EC and the YC group exhibited comparable N400-LPC topographic patterns and electrical filed strengths in all conditions. We postulated that this lack of significant age effect could be due to the short SOA used, where controlled processing was kept to a minimum, this is in its turn revealing how automatic spread of activation remain stable during healthy adulthood.

9.3 STUDY III

9.3.1 Results

Demographics, neuropsychological scores as well as statistics are listed in Table 8.

	EC Mean	EC StD	AD Mean	AD StD	SD Mean	SD StD	X^2	df	p
AGE	69.5	3.1	66.5	9.6	65.8	3.8	3.59	2	0.17
EDUCATION	13.9	3.0	13.8	4.2	13.6	2.9	0.19	2	0.91
MMSE	28.7	0.9	24.8	3.9	23	5.4	21.20	2	<0.001
BNT	54	3.9	46.3	6.1	9.4	7.4	22.73	2	<0.001
AF	23.8	6.3	14.9	2.2	5.6	4.3	23.41	2	<0.001
VF	21.6	5.8	12.4	4.3	9	6.6	19.34	2	<0.001
CT construct	3.8	1.4	3.6	0.8	3.3	2	1.25	2	0.54
CT read	4.6	0.9	4.3	1.2	4.8	0.4	1.07	2	0.59

Table 8. Demographics, neuropsychological scores and statistics for the three enquired groups.

Group-wise post-hoc Mann-Whitney test showed significant differences in MMSE, BNT, AF, and NF between EC and AD, EC and SD, and AD and SD ($p<0.01$), except for MMSE and VF in which the contrast between AD and SD didn't reach significance.

All groups showed SP, so shorter RT for related compared to unrelated word pairs. Post-hoc test revealed that SDs had longer RT than ADs and ECs.
The Scheffe' post-hoc test showed that the three groups differed significantly from each other in task performance, with the SD group having the poorest performance and the EC group performing best.

The TANOVA detected an early semantic priming effect between 94 and 302 milliseconds post target onset, as well as a late topographical semantic priming effect between 382 and 546 milliseconds.

Moreover Kruskal-Wallis test of TCR revealed significant difference between groups in the N400 component only. Scheffe' post-hoc test showed significant difference in the N400 between EC and AD, and EC and SD.

The participants didn't differ in GM volume as shown by the Kruskal-Wallis test. A voxel-wise t-test revealed GM differences between EC and AD in the hippocampus, parahippocampal region, amygdala and inferior temporal lobe.
The SD group showed reduced GM in the largest cluster extending from the left fusiform gyrus over the parahippocampal, hippocampal, inferior temporal gyri and the temporal pole to the insula.
Moreover the SD group showed greater GM volume in the left inferior parietal lobule compared to AD, and in the right middle occipital gyrus compared to the other groups. Finally significant differences in GM volume could be detected between AD and EC in the right middle frontal gyrus, the AD group having the lover GM volume.

AD had lower global GM CBF compared to EC as measured by the Scheffe' post-hoc test. The largest CBF cluster ranged from the temporal pole to the fusiform gyrus, the hippocampus, to reach the parahippocampal region. T-test applied on this cluster showed that both AD and AD had significant CBF decrease in comparison to EC. Both the AD and SD group showed reduced CBF in the left inferior temporal gyrus and left insula.

Linear regression between CBF and ERP resulted in seven clusters and only for the N400 complex. The clusters converged with those inferred by VBM analysis except for the left superior temporal gyrus. On the other hand, the left putamen and globus pallidus didn't show any significance between CBF and N400. The lowest values in both domains were found in the SD groups, while the EC group showed the opposite pattern, and the AD group can be considered as the intermediate group.

The calculation of the sensitivity and specificity of the correlation CBF-ERP showed a result of 0.79 each for all values between the confidence interval, between EC and AD, but no significant result between AD and SD.

9.3.2 Discussion

This study aimed to find an early marker for AD and SD using a semantic priming paradigm combined with EEG recording. Subsequently ERP EEG was obtained focusing on the P1 and the N400 complex, and those correlated with measure of CBF obtained by PCALS.
Firstly, the result obtained by VBM GM analysis showing volume differences

between AD and SD is mostly in line with previous studies.
Decreased CBF in the anterior temporal lobes in AD and SD, and in the temporal poles bilaterally for SD but only in the left for AD is in live with previous findings. Nevertheless CBF was not decreased in the medial temporal lobes in AD, this maybe due to the mild condition of the investigated group.
Despite the deviant behavioral results of those patients in both BNT, VF, and AF, they showed SP effect in the semantic priming paradigm, this indicating that automatic spread of activation is spared in mild dementia.
In particular the notion of preserved spread of activation was supported by comparable topographies in AD and SD in comparison to EC, although the patients' correlation were lower than in the EC group. Nevertheless the SD group showed no N400 effect indicating severe deficits in controlled semantic retrieval, so the current result support the notion that the N400 complex separates SD from AD and EC even if the sensitivity and specificity analysis doesn't really support this assumption. Nonetheless it was found the N400-correlation significantly separates EC from early dementia patients and thus it can be considered a marker for early dementia. Importantly, this study showed how the automatic spread of activation is preserved in both AD and SD.
Finally, in contrast with our hypothesis we found that neither P1 nor N1 topographies related to CBF changes. This could be due to the fact that the semantic network was not functionally changed in our cohort. On the other hand, preserved N400 topography was associated with higher CBF values in the left temporal pole and the lateral temporal lobe, as well as in the left insula and right lateral temporal lobe, indicating that controlled word retrieval relies on the anterior temporal lobe function.
In conclusion the present study demonstrates that altered N400 electrophysiology of dementia patients with semantic memory impairment is closely related to their structural and baseline blood flow degeneration, and this in particular, in regions involved in controlled semantic word processing.

9.4 STUDY IV

9.4.1 Results

Contrasting EC and AD, the largest clusters of GM loss were found in the right amygdala, left caudate head, and right parahippocampal gyrus. Other areas of interest were the left parahippocampal gyrus, the left uncus, and the left amygdala.

Comparison between EC and SD showed GM volume loss in both the limbic lobe and in the temporal lobe. The largest cluster was found in the left uncus, followed by the right superior temporal gyrus, the right uncus, and left parahippocampal gyrus.

Patterns of GM loss between AD and SD could be found in both the limbic lobe and temporal lobe. The involved areas were the left superior temporal gyrus, and right superior temporal gyrus, followed by the left uncus and the right uncus.

In comparison to EC, AD patients showed decreased FA in the temporal lobe and the left inferior longitudinal fasciculus. Relative to SD, AD patients showed significant decrease only in the frontal lobe, in the right superior corona radiata. Finally, contrasting SD with EC, FA was lower in SD patients in temporal lobe, in both the right and left inferior longitudinal fasciculus.

Global MD for AD in comparison to EC showed compromise of the frontal lobe, and in particular of the right inferior fronto-occipital fasciculus. The same comparison between AD and SD (AD<SD) showed also involvement of the forceps minor in the frontal lobe, while the reverse contrast (SD>AD) showed an increase in MD in the limbic lobe, in particular in the left and right inferior longitudinal fasciculus. The same pattern of MD increase was found contrasting SD with EC.

Compared to EC, AD patients showed DA increase in the forceps minor of the frontal lobe. DA was increased in AD compared to SD in the forceps minor of genu of the corpus callosum, while the reverse contrast showed (SD>AD) DA increase in the limbic lobe, in both the right and left inferior longitudinal fasciculus. DA increase in the same areas was found also in SD relative to EC (SD>EC).

DR analysis between AD and EC showed a diffusivity increase in the right inferior longitudinal fasciculus of the temporal lobe. The same analysis between AD and SD showed DA increase in the frontal lobe, in the left superior corona radiata. The reverse contrast (SD>AD) showed again a diffusivity increase in the limbic lobe, in both the left inferior longitudinal fasciculus and right inferior longitudinal fasciculus. The same result was obtained in the comparison between SD and EC.

9.4.2 Discussion

This study investigated grey and white matter pathology in AD compared to SD patients and their degree of gray and white matter loss compared to a cohort of EC using a multimodal imaging approach.
VBM analysis of regional GM distribution showed that both SD and AD brains in comparison to those of ECs show GM loss in the limbic lobe. What distinguished AD from SD is that, in contrast to EC, AD showed GM shrinkage in subcortical structures, while shrinkage in SD was found in the temporal lobe.
Taken together the GM loss found in AD confirmed the results of previous studies, in particular concerning the involvement of the amygdala and of the parahippocampal gyrus, as well as the caudate nucleus.

Comparing AD with SD brains our data partially confirm earlier findings about a bilateral temporal lobe involvement. However, we did not find any significant GM decrease in either the amygdala, hippocampi, or anterior temporal lobes, as listed in the literature. The difference in our findings may be due to several factors, like methodological differences between the studies as in acquisition and analysis of the images, but also differences in population size.
As for the DTI results, the inferior longitudinal fasciculus seems to be the common denominator through all the contrasts.
In this study we could demonstrate clearly that both the left and right inferior longitudinal fasciculus tracts are involved in both AD and SD pathology in comparison to healthy aging. Whereas AD shows an involvement of the right inferior fronto-occipital fasciculus, SD is characterised by white matter pathology in the inferior longitudinal fasciculus only. This anatomical dissociation significantly separates AD from SD. Taken together, and recalling the circumscribed cognitive impairment in SD, these results make us speculate about the role of the inferior longitudinal fasciculus in semantic memory, connecting areas needed for the recall of facts and meaningful use of words.

10. CONCLUSIONS AND FUTURE PERSPECTIVES

The aim of this thesis was to unravel the neurobiological substrate of semantic memory through the study of language in healthy ageing and dementia. In particular we have focused on neurodegenerative dementia disorders such as MCI and AD, and in SD, of particular interest here as being a condition characterized by a selective impairment of semantic memory. To reach our goals we have combined different neuropsychological techniques ranging from measuring conscious semantic retrieval to automatic spread of activation by means of semantic priming. Moreover, and in order to chase the locus of semantic memory we have combined those neuropsychological tasks with different neurophysiological end neuroimaging methods, such as SPECT, ERP EEG, PCASL, and DTI.
We could show that controlled semantic retrieval is impaired in dementia, already in subjects with MCI, and that this in particular affects VF, whose performance most heavily rely on the intactness of the entorhinal cortex. Moreover relative measure of CBF as measured with SPECT have shown a significant decrease in the temporal lobes, already in patients with MCI, thus confirming this dementia diagnosis as a pre-stage of AD.
As we could show that controlled semantic processing is severely affected in neurodegenerative dementias and its disruption significantly correlates with particular anatomical regions, we have turned our interest on automatic semantic processing using a semantic priming paradigm. Our first goal has been to study automatic semantic retrieval in healthy adulthood where our hypothesis has been

confirmed. We have been able to show that automatic semantic spread of activation is stable during a life span. More specifically we could prove that both healthy young and healthy elderly performed equally in the semantic priming task and activated comparable neural networks (as measured by ERP EEG) during semantic processing, while this was not the case in controlled semantic retrieval where the elderly population showed a general slowing in performance.
Now that the evidence had shown the robustness of automatic semantic processing, we used the same method to investigate healthy ageing, AD and SD patients, in their automatic semantic retrieval during ERP EEG, and correlated them to measures of blood perfusion obtained by PCALS. Here again we could show that automatic spread of activation is spared in mild dementia despite the deviant result in measures of controlled semantic processes. Interestingly, and finding an absence of the N400 component in the SD group we could show severe deficit in controlled semantic retrieval in this group, thus finding a possible significant marker able to separate SD from AD and EC. Preserved N400 topography was found to be associated with higher CBF values in the anterior temporal lobe, this indicating that altered N400 electrophysiology of patients with semantic memory impairment is closely related to their structural and baseline blood flow degeneration, in particular, in regions involved in controlled semantic word processing.
Finally, and in the last attempt to chase the locus of semantic memory we investigated GM and WM pathology in the same groups by means of structural MRI and DTI MRI. We could detect GM loss in both SD and AD in the limbic lobe, in particular greater GM shrinkage in AD patients was found in subcortical structures, while SD patients showed GM loss in the temporal lobe. Interestingly DTI data pointed to
both the left and right inferior longitudinal fasciculus tracts as involved in both AD and SD pathology in comparison to healthy aging. Moreover whereas the AD group showed an involvement of the right inferior fronto-occipital fasciculus, SD is characterised by white matter pathology in the inferior longitudinal fasciculus only. These results make us speculate about the role of the inferior longitudinal fasciculus in semantic memory, connecting areas needed for the recall of facts and meaningful use of words.
So in conclusion we could demonstrate that semantic controlled processes are not only disrupted in dementia but are also impaired in healthy ageing while automatic semantic processes remain stable under a life spam. This has made us speculate how the combination of these two different kinds of semantic access can be a useful marker in the detection of early dementia. Moreover we could show that the two different routes of semantic retrieval are associated with different anatomical regions as demonstrated with neuroimaging and neurophysiological methods. Finally, and focusing the study of SD, we have been able to individuate the inferior longitudinal fasciculus as an important player in the WM connectivity needed for semantic retrieval.

We suggest that future studies should focus on the dichotomy controlled/automatic semantic retrieval as an important clinical diagnostic marker for dementia.
In addition those measures should be supported by more refined neurophysiological and neuroimaging techniques, such for example a combination of ERP EEG and fMRI.
The study of SD has proved to be a powerful tool in studying semantic memory disruption. Unfortunately SD is a rare condition which doesn't allow the study of big populations and thus to infer robust statistical results. To this extent we suggest that future studies using a cohort of SD patients should be multicenter studies.

11. ACKNOWLEDGEMENTS

I remember being a student during the first week of my undergraduate education in speech pathology and therapy. I met **Per** back then. I didn't know it at that point but later on he would come to be my co-supervisor. "I am going to be a PhD" I told him. This thesis is my kept promise. My drive, my passion, my curiosity, my stubbornness, they all fit in this thesis. It has been a long journey, I have fallen many times and stand up the same amount of times. My relationship with science has been like a true marriage should probably be, I have loved it every single moment, even when it sucked. And I have sometimes felt very lonely but I have never been alone. **This is my eternal gratitude to my travel companions.**

My main supervisor **Professor Lars-Olof Wahlund** for opening the door for me, even if the sign stated "enter at your own risk". Thank you for having shared your knowledge with me, and above all for having taught me the very difficult art of clinical research, the art of describing reality the way it is and forgetting the beloved research dogma of total control of the enquired variables. You made me a sharper researcher. And thank you for your patience. I know I have not been a very easy person to handle, even if I want to believe I have always been your favourite student ☺

My co-supervisor **Professor Francisco Lacerda** for giving me such a hard time with intricate methodological discussions. And for teaching me that all directions are right directions as long as you can defend your motives and position. You know you have always been a role model for me and I have always looked up to you. In particular I admire your bravery and stubbornness in standing for what is right no matter the consequences. You are my number one Portuguese, yes, not even Mourinho can take your spot! ☺

My co-supervisor **Per Östberg, PhD,** for many years of intellectual stimulation. Per, I remember first meeting you in 2001 as my teacher, and fellow PhD student, and since then I have had the never-ending privilege of having you by my side. You have always been like the most exclusive library of knowledge, there is no reference which can escape your attention. And of course I have always cherished our informal moments with good food and a beer. Having you as a co-supervisor has brought the last missing piece to my work. I only resent I had to stop calling you "darling" then, it didn't seem that appropriate ☺

My mentor **Professor Elias Arnér** for being the calm during the most devastating storms. For your love for science which has affected every part of my brain and my heart. Elias, you are a real scientific poet, a true artist in biochemistry wonderland. When I grow up I want to be like you.

My mentor **Professor Lars Gustavsson** for being such a safe harbour, yet teaching me that even if a ship is safe at harbuor, it is not what ships are made for. Thank you

for always pushing me to the limit of my intellectual capacity and creative burst. But you know, if I was so confident in doing it, it is because I knew you were there to catch me if I fell.

My mentor **Professor Jan-Åke Gustavsson** for always encouraging me to stand on the edge, cause the one not standing on the edge is probably taking too much space. Despite the fact that most people feel a mix of respect, awe, and fear in front of you, I have always felt safe in your presence. Nothing and no one has ever been able to hurt me on your watch.

My guardian angels **Ángel, Katarina, Mariana** and **Nina**.

Ángel, I have waited long to write these words to you and now I am speechless. As your care and affection for me are not of this world, I can't find any good description for what you mean to me, cause that too, it's not of this world. How can I describe the indescribable? You, my top-researcher big brother, are my beauty mirror. Cause when I see my image reflected in your eyes, I feel perfect. Te quiero. Siempre.

Katarina, you are my precious sister. You have saved my life countless times and you have hold my life in your hands every day. You have swept my tears away, you have laughed with me, you have put your gentle hand on my forehead while I was lying in despair and your strength has made me overcome everything. You mean the world to me and I love you and our girls **Julia** and **Kyra** immensely. I am a Brusewitz!

Mariana, you are my fixed point in life. I don't know how you do it but you have the rare gift of being the most powerful shelter no matter what happens. You are a real chaos pilot. It is my privilege in life not only to have had the possibility to work with you, but above all to have you close to me every day. Your strength and determination have always given me the hope that I can achieve everything. Thousand "thank you" would never be enough.

Nina, with you I have always felt I could be as crazy as I wanted to be. You have always been able to handle me like an equilibrist. And yet, you have always been there to listen carefully to all this craziness and to try to put me back on track. You are a strong flower. And thank you for having given me the time and the possibility to be part of **Bella**'s life. She is amazing.

Associate Professor OLA HERMANSSON (yes I told you I would have written your name in capital letters ☺ for having written, produced, and performed my absolute favourite song Ups & Downs, and for having shared with me pick-nicks, football, and pancakes. And last but not least for knowing me so well and being the weirdo you are. In certain matters I think you are a male Ra, or maybe it's me being a female Ola. I have particularly enjoyed our never-ending discussions about who is the best, you or me ☺

Patti, as the talented MR researcher you are, you have always known how to align my wild protons. Your friendship has kept me going in good as bad whatever conditions. That's priceless. And thank you for having given me the opportunity to get to know **Steven** and the joy of two beautiful nieces **Chloe** and **Mira.**

Liss-Eric, for being the best girlfriend ever. With you I have not only shared the office but even a tacit mutual understanding of being there for each other. I have said and been told "I care for you" with everything but words. You sitting right behind me has given me many times the opportunity to lean on you without the need to explain why. You have always taken me with the mood of the day. Thanks.

Silvia, thank you for always being there for me. Take care of Liss-Eric, you made a very wise choice…unless he is dressed in pajamas at work…. ☺

Carolina not only for giving me your brain (to scan), but above all for giving me your heart and your courage.

Nat for being one of the most skilled neurologists I know, but above all for being my beloved sister, and for giving me a great inspiration: **Miro.**

Noel, for all the beauty you have shared with me even if you are a pain in the ass with short respite intervals. You have a 2 minutes rebound rate, and then you start doing your next pain in the ass thing ☺

Monica, Desi, and **Sofia**, my very very special girls. **Desi**, you are my favourite personal assistant.

Johan, Rikkard, and **David**. You are a standing source of inspiration for me cause you have always followed your dreams, no matter the obstacles and no matter what others thought. I am not only flattered but I always blush when I think that you started a company whose name is Raffaella AB. I wonder what I have done for good in life to deserve the three of you.

Cat, for being such a seductive researcher, but above all for being a true friend. I love your sharp brain, your warm heart, and your brave soul.

Cilla, thank you for always listening to me and sharing with me quite crazy experiences. It has been a long way to Pasadena…but here we are now and I wouldn't have made it without you. Thank you my wonderful Toast Mistress!

Simon, the circumstances that led me to you were ugly but you are beautiful. And if I had to go through all over again to have the privilege of your friendship, I would. You rock, man! And sometimes you roll…☺

I miei amici in Italia: **Alessia, Luca, Vale, Maury, Simo, Isa, Feli, Calo, Katia**, **Dani, Fra, Andri, Mati, Andy, Miky, Samy, Mary, Dutch, Paolo, Mile** e **Zuf** e i miei amati cugini **Sergio, Andrea**, e **Mauro.** Siete le luci piu' potenti quando tutte le luci si spengono.
Fra, sempre io e te tu ed io: SPEED DEMON per sempre!
Mauro, sei talmente unico che quando sei nato hanno buttato lo stampino, anzi no, aspetta, qualcuno deve averlo salvato, perche' esattamente 10 anni dopo sono nata io! Grazie per la forza che mi dai sempre.

Cinzia Casgrande e tutto il **Neo Movement**: siete il tocco di pazza bellezza nella mia vita. Fotografarvi e' il mio privilegio, la vostra amicizia la mia fortuna.

Professor Zadrko Lazcovic, once in Bruxelles you told me: "I will talk you like a father. Remember that whatever you decide, I love you, and my love is unconditional". You are my scientific father.

To all the past and present previous researchers and PhD students at NVS Department, and to all the staff at Stockholm Medical Image Laboratory and Education (SMILE). I always brag I have the best collegues in the world. It's true. A very very special thank goes to **Gabi**, glue of the lab and MRI excellence, and to our secretaries **Marianne** and **Anette,** cause without you nothing works, and I mean NOTHING!

My collegues in Bern, Switzerland, for having shared their knowledge with me: **Thomas D, Thomas K, Andrea, Kay, Mara, Nadja, Claudia, Miranka, Caroline, Simon, Yvonne**, but above all **Matthias,** for having shared with me not only every problem, craziness and joy encountered developing the Madrugada and the Ramones projects (and yes, I particularly appreciate you agreed it was a great idea to give our projects band names!) but also beautiful music and breathtaking football matches (I remember you told me that half of the fun was to watch me watching and commenting the match!)

Bettina, Caro, and **Natalia**, for giving me the warmth of a family while I was in Bern.

The **Medical Students' Association (MSA)** crew for all the laughs, crisis, happiness, sorrow, and victories we have underwent together. In particular my deepest gratitude goes to my two vice presidents **Johan Karlsson** and **Kalle Kruse**, for having been such a great support and for having not only accepted all my peculiarities and insanities, but also for being that special "cavalry". A. Stevenson wrote "it is hard to lead a cavalry charge if you think you look funny on a horse". Well, the two of you have always looked amazing on that horse! Besides I am particularly grateful to those who were by my side during this special travel: **Nina Wolmer Solberg, Clara Brandkvist, Jens Andersson, Göran Örnhed, Maria Eriksson, Jonas Binnmyr, Zuzana Dubovanova, Wilhelm Engström, Hans Hjelmqvist,**

And last but not least my skilled employees: **Sanna Johansson, Kerstin Beckenius, Anna-Lena Lindgren,** and **Clara Cordemans.**

The **Graduate Students Association (GSA)** crew for always challenging KI to be a top-of-the-pop place for research education. In particular I would like to thank **Mohammed Homman, Tobias Berghrot, Johan Öckinger, Emma Lindhal, Jesper Ericsson, Michela Barbaro Jönulv, Pernilla Stridh, Louisa Cheung, Melanie Thiessen-Hedreul** and **Anestis Sofiadis**.

The **Sveriges Doktorander (SDok)** crew for years of very stimulating work. I am especially grateful to **Rio, Thomas**, and **Daniel.**

The **EURODOC** crew and in particular **Raquel, Dunja, Dejan, Harpreet, Wolfgan, Armando,** and **Tine Ejdrup** for having given me the opportunity to grow with you. The journey with you has been amazing. I am very proud you have given me the opportunity to lead our work, and I am very grateful you were always ready to fix my diplomatic outrageous missteps, but above all I am thankful you wanted to give me not only your trust but also your friendship. And **Raquel,** our trip to Seattle will always remain in my heart!

Petter Kallioinen, King of the EEG lab, and even the author of the beautiful drawing on the front page of this thesis. I also would like to thank **Linnea Engström**, who has helped us with the EEG measurements and neuropsychological assessments of the patients. A very bright fast learner!

Johan Bergqvist, Mårten Bengtsson, Tommy Wassgren and **Johan Sundin** or **The Genuine Fakes.** Thank you guys for drowning me in beautiful music and for sharing your path towards the stars with me. And thank you **Johan** and **Mårten** for sharing with me a very poetic moment: the Posies' concert! It was magic.

I also would like to thank **Torsten Kindström** and **María Marrero.**
The rest of my Stockholm entourage: Mirre (Örnen), Jonas, Tobbe, Marisol, and **Emelie.** You rock my world!

To **Lisa, Barbro, Kjell,** and **Erik Tullus.** We are done now, we have made it. You are holding in your hand Carl's and mine thesis.

The Twitter researchers' community for having given me not only a lot of articles but above all a lot of inspiration.

To **all my friends** who gladly and voluntarily have been my exclusive guinea pigs (did you realize then, that I had done an EEG only once before and that I had just got my MR driving license? ☺ and to **all the healthy controls and patients** who have made this thesis possible.

To **all my grant givers** who have given me a very luxurious position: to be supported by many but dominated by none. **Nationella Forskarskolan i Vård och Omsorg, Palle Ferbs Minnesfond, Alzheimerfonden, Stohnes Stiftelse, Demensfonden, Lions Forskningsfond för åldersrelaterade sjukdomar** thanks for believing in me.

Jan Anders Näslund, thank you for showing me that hell can be quite a safe place to be in. I will always be your darlingbud, your sister forever.

Mark, thank you for being so nice to my girls and thank you for checking on my written English with such a short notice!

Alla mia **famiglia allargata** che ha tirato fuori il meglio della mia testardaggine. E in particolare a **mio fratello**…
…avrei mille cose da dirti e da raccontarti che non so da dove cominciare, **Gianlu**, il mare se ne frega ci sente appena e vive il mondo alla sua maniera. E´un po' che non parliamo come facevamo, gli sbagli ci hanno allontanato piu' degli anni e quante volte ho pensato che non mi capissi, ti chiedevo di abbracciarmi in tutti i miei strilli, ma il male viene fuori in tutti i modi e l' amore e' un' arma, tanto cuce tanto taglia, e mettici pure che ho preso un caratteraccio senza eta', arrivo dove posso, e sette passi piu' in la', quando ho fatto la valigia e sbattuto la porta ho pensato che sarebbe stata l' ultima volta, in cui mi avresti detto che mi avevi perso, ora mi chiedo se stanotte mi cerchi, perche' io ti cerco.
Vorrei vestire la tua calma, **Gianlu**, ma il sangue preme dentro le vene piene e balla, ho una tua foto da ragazzo in questa stanza, bello che a dire bello, non e' mai abbastanza, il mondo mi vuole forte, veloce e in gamba, il mare se ne frega se non resto a galla, e quindi nuoto e corro, il resto viene dopo, e poi mi importa poco, basta che mi muovo, e se prima mi vergognavo per quanto ci assomigliamo adesso amo i lati nei quail siamo uguali. Stessi occhi, stessse labbra, il mare non ci cambia, e' lui che ci tocca appena, torno presto **Gianlu**.

Liwia, grazie di amare (ma questo e' facile!) e di prenderti cura di mio fratello, miglior paladina della giustizia su tacco 12 non potevo trovare!

Simo, sei la rivincita di mille cuori infranti. La mia scelta cosciente. Il mio sogno ricorrente.

And if during those years I have done something weird or inappropriate, this is my disclaimer: **det kan ha varit jag, det kan ha varit nån annan, det får vi aldrig veta.**

LOVE YA!

12. REFERENCES

Accorsi, R. (2008). Brain Single-Photon Emission CT Physics Principles. *American Journal of Neuroradiology* , *29*, 1247–1256.

Adlam, A-LR., Patterson K., Rogers T.T., Nestor, P.J., Salmond, C.H., Acosta-Cabronero, J., et al. (2006). Semantic dementia and fluent primary progressive aphasia: two sides of the same coin? *Brain, 129*, 3066-3080

Albert, M.S., DeKosky, S.T., Dicksond, D., Duboise, B., Feldmanf, H.H., Foxg, N.C., et al (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*, 270-279.

Alsop, D.C. (2006). *ASL Perfusion: Concepts and Applications.* Paper presented at the International Society for ISMRM Magnetic Resonance Imaging Annual Meeting.

Alsop, D.C., Casement, M., de Bazelaire, C., Fong, T., Press, D.Z. (2008). Hippocampal hyperperfusion in Alzheimer's disease. *Neuroimage, 42*,1267-1274.

Alzheimer, A. (1911).Uber eigenartige Krankheits- falle des spateren Alters. Zeitschrift für die Gesamte Neurologie und *Psychiatrie, 4*(1), 356–385.

Alzheimer's Association. (2010). Alzheimer's disease facts and figures. *Alzheimer and Dementia, 6*(2), 158–194.

Anderson, J.E. & Holcomb, J.P. (1995). Auditory and visual semantic priming using different stimulus onset asynchronies. An event-related brain potential study. *Psychophysiology, 32*, 177-190.

Ash, S., Moore, P., Antani, S., McCawley, G., Work, M., Grossman, M. (2006). Trying to tell a tale: discourse impairments in progressive aphasia and frontotemporal dementia. *Neurology, 66*, 1405-1413.

Ashburner, J. & Friston, K. J. (2000). Voxel-Based Morphometry-The Methods. *Neuroimage 11*, 805-821.

Auchterlonie, S., Phillips, P.A., Chertkow, H. (2002) Behavioral and electrical brain measures of semantic priming in patients with Alzheimer's disease: implications for access failure versus deterioration hypotheses. Brain and Cognition, *48*, 264-267.

Baaré, W.F., Hulshoff Pol, H.E., Boomsma, D.I., Posthuma, D., de Geus, E.J., Schnack, H.G. (2001). Quantitative genetic modeling of variation in human brain morphology. *Cerebral Cortex, 11*, 816-824.

Barker, F.G. (1995). Phineas among the phrenologists: the American crowbar case and nineteenth-century theories of cerebral localization. *Journal of Neurosurgery, 82*, 672-682.

Baron JC, Chételat G, Desgranges B, Perchey, G., Landeau, B., de la Sayette, V., et al. (2001). In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *Neuroimage, 14*, 298-309.

Bartley, A.J., Jones, D.W., Weinberger, D.R. (1997). Genetic variability of human brain size and cortical gyral patterns. *Brain, 120* (Part 2), 257-269.

Basser, P.J., Mattiello, J., Le Bihan, D. (1994). Estimation of the effective self-diffusion tensor from the NMR spin echo. *Journal of Magnetic Resonance Series B, 103*, 247-254.

Bayley, P.J., Hopkins, R.O., Squire, L.R. (2006). The fate of old memories after medial temporal lobe damage. *Journal of Neuroscience, 26* , 13311 –13317.

Bentin, S., McCarthy, G., Wood, C.C. (1985). Event-related potentials associated with semantic priming. *Electroencephalography and Clinical Neurophysiology, 60*, 343-355.

Besson, M., Fischler, I., Boaz, T., Raney, G. (1992). Effects of automatic associative activation on explicit and impliciti memory. *Journal of Experimental Psychology: Learning, Memory and Cognition, 18*, 89-105.

Boaokstein, F.L. (2001). "Voxel-based morphometry" should not be used with imperfectly registered images. *Neuroimage, 14*, 1454-1462.

Boddy, J. (1986). Event-related potentials in chronometric analysis and primed word recognition with different stimulus onset asynchronies. *Psychophysiology, 23*, 232-245.

Bonte, F.J., Harris, T.S., Hynan, L.S., Bigio, E.H., White, C.L. (2006). Tc-99m HMPAO SPECT in the differential diagnosis of the dementias with histopathologic confirmation. *Clinical Nuclear Medicine, 31* (7), 376–378.

Boxer, A.L., Rankin, K.P., Miller, B.L., Schuff, N., Weiner, M., Gorno-Tempini, M.L., et al. (2003). Cinguloparietal atrophy distinguishes Alzheimer's disease from semantic dementia. *Archives of Neurology, 60*, 949-956.

Boyke, J., Driemeyer, J., Gaser, C., Buchel, C., May, A. (2008). Training-induced brain structure changes in the elderly. *Journal of Neuroscience, 28*(28), 7031-7035.

Bozeat, S., Gregory, C.A., Lambon Ralph, M.A., Hodges, J.R. (2000). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology Neurosurgery and Psychiatry, 69*, 178-186.

Bozeat, S., Lambon, Ralph M.A., Graham, K.S., Patterson, K., Wilkin, H., Rowland, J., et al. (2003). A duck with four legs: Investigating the structure of conceptual knowledge using picture drawing in semantic dementia. *Cognitive Neuropsychology, 20* (1), 27-47.

Braak, H., & Braak, E. (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*, 239-259.

Braak, H., & Braak, E. (1996). Evolution of the neuropathology of Alzheimer's disease. *Acta Neurologica Scandinavica Supplementum, 165*, 3-12.

Brambati, S.M., Rankin, K.P., Narvid, J., Seeley, W.W., Dean, D., Rosen, H.J., et al. (2009). Atrophy progression in semantic dementia with asymmetric temporal involvement: A tensor-based morphometry study. *Neurobiology of Aging, 30*, 103-111.

Brandeis, D., Naylor, H., Halliday, R., Callaway, E., Yano, L. (1992). Scopolamine effects on visual information processing, attention, and event-related potential map latencies. *Psychophysiology, 29*, 315-336.

Breedin, S.D., Saffran, E.M., Coslett, H.B. (1995). Reversal of a concreteness effect in a patient with semantic dementia. *Cognitive Neuropsychology, 11*, 617-660.

Bright, P., Moss, H., Tyler, L.K. (2004). Unitary vs multiple semantics: PET studies of word and picture processing. *Brain and Language, 89*, 417-432.

Brodmann, K. (1909). *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* Leipzig: Johann Ambrosius Barth Verlag.

Brown, C.M., and Hagoort, P. (1993). The processing nature of the N400: Evidence from masked priming. *Journal of Cognitive Neuroscience, 5*, 34-44.

Busatto GF, Garrido GE, Almeida OP, Castro, C.C., Camargo, C.H., Cid, C.G., et al. (2003). A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiology of Aging, 24*, 221-231.

Busse, A., Hensel, A., Gühne, U., Angermeyer, M.C., Riedel-Heller, S.G. (2006) Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology, 67*, 176-185.

Buxton, R.B., Frank, L.R., Wong, E.C., Siewert, B., Warach, S., Edelman, R.R. (1998). A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magnetic Resonance in Medicine, 40*, 383-396.

Buzsaki, G., Traub, R.D., Pedley, T.A. (2003). The cellular basis of EEG activity. (Eds.). *Current practice of clinical electroencephalography* (3rd ed., pp. 1-11). Philadelphia: Lippincott Williams and Wilkins.

Canessa, N., Borgo, F., Cappa, S.F., Perani, D., Falini, A., Buccino, G., et al. (2008). The different neural correlates of action and functional knowledge in semantic memory: an fMRI study. *Cerebral Cortex, 18*, 740-751.

Caramazza, A., Hillis, A., Rapp, B. (1990). The multiple semantic hypothesis: Multiple confusions? *Cognitive Neuropsychology, 7*, 161-189.

Caramazza, A., & Shelton, J.R. (1998). Domain-specific knowledge systems in the brain the animate-inanimate distinction. *Journal of Cognitive Neuroscience, 10*, 1-34.

Carmelli, D., DeCarli, C., Swan, G.E., Jack, L.M., Reed, T., Wolf, P.A., et al. (1998). Evidence for genetic variance in white matter hyperintensity volume in normal elderly male twins. *Stroke, 29,* 1177-1181.

Castañeda, M., Ostrosky-Solís, F., Pérez, M., Bobes, M.A., Rangel, L.E. (1997) Erp assessment of semantic memory in Alzheimer's disease. *International Journal of Psychophysiology, 27,* 201-214.

Cave, C.B., & Squire, L.R. (1992). Intact and long-lasting repetition priming in amnesia. *Journal of Experimental Psychology Learning Memory and Cognition, 18*(3), 509-520.

Chan, D., Fox, N.C., Scahill, R.I., Crum, W.R., Whitwell, J.L., Leschziner, G., et al. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Annals of Neurology, 49,* 433-442.

Chan, D., Fox, N., Rossor, M. (2002). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology, 58,* 838.

Chertkow, H., & Bub, D. (1990). Semantic memory loss in dementia of Alzheimer'stype. What do various measures measure? *Brain, 113*(Pt 2), 397–417.

Chertkow, H., Bub, D., Bergman, H., Bruemmer, A., Merling, A., Rothfleisch, J. (1994). Increased semantic priming in patients with dementia of the Alzheimer's type. *Journal of Clinical and Experimental Neuropsychology, 16*, 608-622.

Chow, T.W., Hodges, J.R., Dawson, K.E., Miller, B.L., Smith, V., Mendez, M.F., et al. (2005). Referral patterns for syndromes associated with frontotemporal lobe degeneration. *Alzheimer Disease Associated Disorders, 19*, 17-19.

Chwilla, D.J., Brown, C.M., Hagoort, P. (1995). The N400 as a function of levels of processing. *Psychophysiology, 32,* 274-285.

Clifford, R. & Jack Jr, M.D. (2012). Alzheimer Disease: New Concepts on its Neurobiology and the Clinical Role Imaging will play. *Radiology, 263*(2), 344-361.

Coles, M.G.H., & Rugg, M.D. (1996). Event-related brain potentials: an introduction". *Electrophysiology of Mind* (pp. 1-27). Oxford Scholarship Online Monographs.

Collins, A.M. & Loftus, E.F. (1975). A spreading activation theory of semantic processing. *Psychological Review, 82,* 407-428.

Crick, F. (1966). *Of molecules and men.* Seattle: University of Washington Press.

Crinion, J.T., Lambon-Ralph, M.A., Warburton, E.A., Howard, D., Wise, R.J.S. (2003). Temporal lobe regions engaged in normal speech comprehension. *Brain, 126,* 1193-1201.

Dai, W., Lopez, O.L., Carmichael, O.T., Becker, J.T., Kuller, L.H., Gach, H.M. (2009). Mild cognitive impairment and alzheimer disease: patterns of altered cerebral blood flow at MR imaging. *Radiology, 250,* 856-866.

Damasio, A.R. (1989). The brain binds entities and events by multiregional activation from convergence zones. *Neural Computation, 1*, 123-132.

Damasio, H., Grabowski, T.J., Tranel, D., Hichwa, R.D., Damasio, A.R. (1996). A neural basis for lexical retrieval. *Nature, 380,* 499-505.

Damasio, H., Tranel, D., Grabowski, T., Adolphs, R., Damasio, A.R. (2004). Neural systems behind word and concept retrieval. *Cognition, 92,* 179-229.

Davies, R., Graham, K.S., Xuereb, J.H., Williams, G.B., Hodges, J.R. (2004). The human perirhinal cortex and semantic memory. *European Journal of Neuroscience, 20*, 2441-2446.

Davies, R.R., Hodges, J.R., Kril, J., Patterson, K., Halliday, G., Xuereb, J. (2005). The pathological basis of semantic dementia. *Brain, 128,* 1984-1985.

Detre, J.A., Zhang, W., Roberts, D.A., Silva, A.C, Williams, D.S., Grandis, D.J., et al. (1994). Tissue specific perfusion imaging using arterial spin labeling. *NMR in Biomedicine, 7*, 75-82.

Di Carlo A, Lamassa M, Baldereschi M, Inzitari, E., Scafato, G., Farchi, D., et al. (2007). CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. *Neurology, 68*, 1909-1916.

Dickerson, B.C., Goncharova, I., Sullivan, M.P., Forchetti, C., Wilson, R.S., Bennett, D.A., et al. (2001). MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiology of Aging, 22,* 747–754.

Diehl, J., Grimmer, T., Drzezga, A., Riemenschnaider, M., Förstl, H., Kurz. (2004). Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiology of aging, 25*, 1051-1056.

Dougall, N.J., Bruggink, S., Ebmeier, K.P. (2004). "Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia". *American Journal of Geriatric Psychiatry, 12*(6), 554–70.

Drane, D.L., Ojemann, G.A., Aylward, E., Ojemann, J.G., Johnson, L.C., Silbergeld, D.L. et al. (2008). Category-specific naming and recognition deficits in temporal lobe epilepsy surgical patients. *Neuropsychologia, 46,* 1242-1255.

Du, A.T., Schuff, N., Kramer, J.H., Rosen, H.J, Gorno-Tempini, M.L., Rankin, K., et al. (2007). Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain, 130*, 1159-116.

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology 6*(8), 734–746.

Eagelman, D. (2011, April 7) One-sixe-fits-all approach ignores our varied biology. *Sidney Morning Herald.*

Eckert ,M.A, .Leonard, C.M., Molloy, E.A., Blumenthal, J., Zijdenbos, A., Giedd, J.N. (2002). The epigenesis of planum temporale asymmetry in twins. *Cerebral Cortex, 12*, 749-755.

Elbert, T. Pantev, C., Wienbruch, C., Rockstroh, B., Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. *Science, 270,* 305-307.

Eriksson, P.S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A.M. Nordborg, C., Peterson, D.A. et al. (1998). Neurogenesis in the adult human hippocampus. *Nature Medicine, 4*(11), 1313-1317.

Esopenko, C., Borowsky, R., Cummine, J., Sarty, G. (2008). Mapping the semantic homunculus: a functional and behavioural analysis of overt semantic generation. *Brain Topography, 20*, 89-96.

Farid, K., Caillat-Vigneron, N., Sibon, I. (2011). Is brain SPECT useful in degenerative dementia diagnosis? *Journal of Computed Assisted Tomography, 35*, 1-3.

Fellgiebel, A., Schermuly, I., Gerhard, A., Keller, I., Albrecht, J., Weibrich, C., et al. (2008). Functional relevant loss of long association fiber tracts integrity in early Alzheimer's disease. *Neuropsychologia, 46,* 1698-1706.

Fennema-Notestine, C., Hagler, D.J.J., McEvoy, L.K., Fleisher, A.S., Wu, E.H., Karow, D.S., et al. (2009). Structural MRI biomarkers for preclinical and mild Alzheimer's disease. *Human Brain Mapping, 30,* 3238-3253.

Fernaeus, S-E, & Almkvist, O. (1998). Word production: Dissociation of two retrieval modes of semantic memory across time. *Journal of Clinical and Experimental Neuropsychology, 20,* 137-143.

Ferrier,D. (1876). *The functions of the Brain*. Smith, Elder, & Co.

Fleisher AS, Podraza KM, Bangen KJ, Taylor C, Sherzai A, Sidhar K, et al. (2009). Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. *Neurobiology of Aging, 30,* 1737-1748.

Ford, J.M., Askari, N., Mathalon, D.H., Menon, V., Gabrieli, J.D., Tinklenberg, J.R., et al. (2001). Event-related brain potential evidence of spared knowledge in Alzheimer's disease. *Psychology and Aging, 16*, 161-176.

Frankle, W.G., Slifstein, M., Talbot, P.S., Laruelle, M. (2005). Neuroreceptor Imaging in Psychiatry: Theory and Applications. *International Review of Neurobiology, 67*, 385–440.

Frisoni, G.B., Testa, C., Zorzan, A., Sabattoli, F., Beltramello, A., Soininen, H., et al. (2002). Detection of gray matter loss in mild Alzheimer's disease with voxel-based morphometry. *Journal of Neurology Neurosurgery and Psychiatry, 73*, 657-664.

Frith, C.D. (2007). The social brain? *Philosophical transactions of the Royal Society London: Series B, Biological Sciences, 362,* 671-678.

Fukatsu, R., Fujii, T., Tsukiura, T., Yamadori, A., Otsuki, T. (1999). Proper name anomia after left temporal lobectomy: A patient study. *Neurology, 52,* 1096-1099.

Fung, T.D., Chertkow, H., Murtha, S., Whatmough, C., Peloquin, L., Whitehead,V., et al. (2001). The spectrum of category effects in object and action knowledge in dementia of the Alzheimer'stype. *Neuropsychology, 15*(3), 371–379.

Gainotti, G. (2000). What the locus of brain lesions tells us about the nature of the cognitive defect underlying category-specific disorders: A review. *Cortex, 36,* 539-559.

Galati, G., Committieri, G., Spitoni, G, Aprile, T., Di Russo, F., Pitzalis, S., et al. (2008). A selective representation of the meaning of actions in the auditory mirror system. *Neuroimage, 40*, 1274-1286.

Galton, C.J., Patterson, K., Graham, K., Lambon-Ralph, M.A., Williams, G., Antoun, N., et al. (2001). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology, 57*, 216-225.

Ganis, G., Kutas, M., & Sereno, M. I. (1996). The search for "common sense": An electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience, 8,* 89-106.

Garcia, D.M., Bazelaire, C.D., Alsop, D. (2005*). Pseudo-continuous Flow Driven Adiabatic Inversion for Arterial Spin Labeling*. Paper presented at ISMRM 5.

Geschwind, D.H., Miller, B.L., DeCarli, C., Carmelli, D. (2002). Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. *PNAS, 99*, 3176-3181.

Glosser, G., Salvucci, A.E., Chiaravalloti, N.D. (2003). Naming and recognizing famous faces in temporal lobe epilepsy. *Neurology, 61,* 81-86.

Goedert, M., Spillantini, M.G., Crowther, R.A. (1991). Tau proteins and neurofibrillary degeneration. *Brain Pathology, 1*(4), 279-286.

Goldberg, R.F., Perfetti, C.A., Fiez, J.A., Schneider, W. (2007). Selective retrieval of abstract semantic knowledge in left prefrontal cortex. *Journal of Neuroscience, 27,* 3790-3798.

Gonnerman, L.M., Andersen, E.S., Devlin, J.T., Kempler, D., Seidenberg, M.S. (1997).Double dissociation of semantic categories in Alzheimer's disease. *Brain and Language, 57*(2), 254–279.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N.A., Friston, K.J., Frackowiak, R.S.J. (2001). A Voxel-Based Morphometry Study of Ageing in 465 Normal Adult Human Brains. *Neuroimage, 14,* 21-36.

Good, C.D., Scahill, R.I., Fox, N.C., Ashburner, J., Friston, K.J, Chan, D., et al. (2002). Automatic differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. *Neuroimage, 17*, 29-46.

Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. (2011). Classification of primary progressive aphasia and its variants. *Neurology, 76,* 1006-1014.

Gorno-Tempini, M.L., Dronkers, N.F., Rankin, K.P., Ogar, J.M, Phengrasamy, L., Rosen, H.J, et al. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology, 55*, 335-346.

Gotts, S.J., & Plaut, D.C. (2002). The impact of synaptic depression following brain damage: A connectionist account of "access/refractory" and "degrade store" semantic impairments. Cognitive. *Affective & Behavioral Neuroscience, 2,* 187-213.

Graham , K.S. , Simons , J.S. , Pratt , K.H. , Patterson , K. , & Hodges , J.R.(2000). Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia* , *38,* 313-324.

Greene, J.D., & Hodges, J.R. (1996). The fractionation of remote memory. Evidence from a longitudinal study of dementia of Alzheimer type. *Brain, 119*(Pt 1), 129–142.

Greenberg , D.L. , Keane , M.M. , Ryan , L.R. & Verfaellie , M. (2009). Impaired category fluency in medial temporal lobe amnesia: The role of episodic memory. *Journal of Neuroscience* , *29* , 1900-1908.

Greenberg, D.L., & Verfaeille, M. (2010). Interdependence of semantic and episodic memory: evidence from neuropsychology. *Journal of the International Neuropsychological Society, 16,* 748-753.

Grigor, J., Van Toller, S., Behan, J., Richardson, A. (1999). The effect of odour priming on long latency visual evoked potentials of matching and mismatching objects. *Chemical Senses, 24*(2), 137-144.

Grossman, M., McMillian, C., Moore, P., Ding, L., Glosser, G., Work, M., et al. (2004). What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in

Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain, 127*, 628-649.

Grossman, M., Troiani, V., Koenig, P., Work, M., Moore, P. (2007). How neccesary are the stripes of a tiger? Diagnostic and characteristics features in an fMRI study of word meaning. *Neuropsychologia, 45*, 1055-1064.

Gunter, T.C., Jackson, J.L., Mulder ,G. (1998). Priming and Aging: An Electrophysiological Investigation of N400 and Recall. *Brain and Language, 65,* 333-355.

Halpern, C.H., Glosser, G., Clark, R., Gee, J., Moore, P., Dennis, K. (2004). Dissociation of numbers and objects in corticobasal degeneration and semantic dementia*. Neurology, 62*, 1163-1169.

Hamann, S.B., & Squire, L.R. (1997). Intact perceptual memory in the absence of conscious memory. *Behavioral Neuroscience, 111*(4), 850-854.

Harbin,T.J., Marsh, G.R., Harvey, M.T. (1984). Differences in the late components of the event-related potential due to age and to semantic and non-semantic tasks. *Electroencephalography and Clinical Neurophysiology, 59*(6), 489-496.

Hebb, D.O. (1949). *The organization of behavior*. New York: Wiley.

Henson, R.N.A. (2003). Neuroimaging studies of priming. *Progress in Neurobiology, 70,* 53-81.

Herman, G.T. (2009). *Fundamentals of Computerized Tomography: Image Reconstruction from Projections* (2nd ed.). Springer.

Heron, M., Hoyert, D.L., Murphy, S.L., Xu, J., Kochanek, K.D., Tejada-Vera, B. (2009). Deaths: final data for 2006. *National Vital Statistics Reports, 57*(14), 1–134.

Hillis, A.E., Rapp, B., Romani, C., Caramazza, A. (1990). Selective impairment of semantics in lexical processing. *Cognitive Neuropsychology, 7,* 191-243.

Hitzig, E. (1904). *Physiologische und klinische Untersuchungen über das Gehirn*. Berlin A. Hirschwald.

Hodges, J.R., Patterson, K., Oxbury, S., Funnell, E. (1992). Semantic Dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain, 115,* 1783-1806.

Hodges, J.R., Graham, N., Patterson, K. (1995). Charting the progression in semantic dementia: Implications for the organisation of semantic memory. *Memory, 3,* 463-495.

Hodges, J.R., Patterson, K., Ward, R., Garrard, P., Bak, T., Perry, R, et al. (1999). The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal

variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology, 13*, 31-40.

Hodges, J.R., & Patterson, K. (2007). Semantic dementia: a unique clinicopathological syndrome. *Lancet Neurology, 6,* 1004-1014.

Hulshoff Pol, H.E., Schnak, H.G., Posthuma, D., Mandl, R.C., Baare, W.F., van Oel, C., et al. (2006). Genetic contributions to human brain morphology and intelligence. Journal of *Neuroscience, 26,* 10235-10242.

Humphreys, G.W., & Forde, E.M.E. (2001). Hierarchies, similarity, and interactivity in object recognition: "Category-specific" neuropsychological deficits. *Behavioural and Brain Sciences, 24,* 453-509.

Ishii, K., Kawachi, T., Sasaki, H., Kono, A. K., Fukuda, T., Kojima, Y., et al. (2005a).Voxel-based morphometric comparison between early-and late-onset mild Alzheimer's disease and assessment of diagnostic performance of z score images. *American Journal of Neuroradiology, 26*, 333-340.

Ishii K, Sasaki H, Kono AK, Miyamoto, N., Fukuda, T., Mori, E., et al. (2005b). Comparison of gray matter and metabolic reduction in mild Alzheimer's disease using FDG-PET and voxel-based morphometric MR studies. *European Journal of Nuclear Medicine and Molecular Imaging, 32*, 959-963.

Jenkins, W.M., Merzenich, M.M., Recanzone, G. (1990). Neocortical representational dynamics in adult primates: implications for neuropsychology. *Neuropsychologia, 28*(6): 573-584.

Johnson, A.K., Fox, N.C., Sperling, R.A., Klunk, W.E. (2012). Brain imaging in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine, 2*(4), a006213.

Johnson, N.A., Jahng, G.H., Weiner, M.W., Miller, B.L., Chui, H.C., Jagust, W.J., et al. 2005. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology, 234*, 851-859.

Josephs, K.A., Whitwell, J.L., Knopman, D.S., Boeve, B.F., Vemuri, P., Senjem, M.L., et al. (2009). Two distinct subtypes of right temporal variant frontotemporal dementia. *Neurology, 73,* 1443-1450.

Juni JE, Waxman AD, Devous MD Sr, Tikofsky, R.S, Ichise, M., Van Heertum, R.L. (2009) Procedure guideline for brain perfusion SPECT using (99m)Tc radiopharmaceuticals 3.0. *Journal of Nuclear Medicine Technology, 37*, 191-195.

Kapucu OL, Nobili F, Varrone A, Booij, J., Vander Borght, T., Någren, K., et al. (2009). EANM procedure guideline for brain perfusion SPECT using (99m)Tc-labelled radiopharmaceuticals, version 2. European Journal of Nuclear Medicine and Molecular Imaging, 36, 2093-2102.

Katada, E., Sato, K., Ojika, K., Ueda, R. (2004) Cognitive event- related potentials: useful clinical information in Alzheimer's disease. *Current Alzheimer Research, 1*, 63-69.

Kawachi, T., Ishii, K., Sakamoto, S. Sasaki, M., Mori, T., Yamashita, F., et al. et al. (2006). Comparison of the diagnostic performance of FDG-PET and VBM-MRI in very mild Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging, 33*, 801-809.

Kellenbach, M. L., Wijers, A. A., Mulder, G. (2000). Visual semantic features are activated during the processing of concrete words: Event-related potential evidence for perceptual semantic priming. *Cognitive Brain Research, 10,* 67–75.

King, J., Kutas, M. (1995) Do the waves begin to waver? ERP studies of language processing in the elderly. (Eds.). *Advances in Psychology: Age Differences in Word and Language Processing* (pp. 314-334).Amsterdam: Elsevier.

Kinsbourne, M., Tocci Rufo, D., Gamzu E., Palmer, R.L., Berliner, A.K. (1991). Neuropsychological deficits in adults with dyslexia . *Developmental Medicine and Child Neurology* , *33* ,763 –775.

Killiany, R.J., Hyman, B.T., Gomez-Isla, T., Moss, M.B., Kikinis, R., Jolesz, F., et al. (2002). MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology, 58*, 1188 – 1196.

Koenig, T., Kottlow, M., Stein, M., Melie-Garcia, L. (2011). Ragu: A Free Tool for the Analysis of EEG and MEG Event-Related Scalp Field Data Using Global Randomization Statistics. Computational Intelligence and Neuroscience, 1-14.

Konorski, J. (1948). *Conditioned reflexes and neuron organization*. Cambridge, MA: Cambridge University Press.

Kutas, M., Iragui, V. (1998) The n400 in a semantic categorization task across 6 decades. *Electroencephalography and Clinical Neurophysiology, 108*, 456-471.

Kutas, M., & Federmeier, K.D. (2000). Electrophysiology reveal semantic memory use in language comprehension. *Trends in Cognitive Science 4*(12), 463-470.

Kutas, M. & Federmeier, K.D. (2009). N400. *Scholarpedia, 4*(10), 7790.

Lambon Ralph, M.A., Cipolotti, L., Manes, F., Patterson, K. (2010). Taking both sides: do unilateral anterior temporal lobe lesions disrupt semantic memory? *Brain, 133,* 3243-3255.

Lauterbur, P.C. (1973). Image formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance. *Nature, 242* (5394), 190-191.

Li, T-Q. , & Wahlund, L-O. (2010). The search for neuroimaging biomarkers of Alzheimer's disease with advanced MRI techniques. *Acta Radiologica 52*, 211-222.

Lindenberg, R., & Scheef, L. (2007). Supramodal language comprehension: role of the left temporal lobe for listening and reading. *Neuropsychologia, 45,* 2407-2415.

Le Bihan, D., Mangin, J-F., Poupon, C., Clark, C.A., Pappata, S., Molko, N., et al. (2001). Diffusion Tensor Imaging: Concepts and Applications. *Journal of Magnetic Resonance Imaging, 13*, 534 –546.

Lehericy, S., Baulac, M., Chiras, J., Pierot, L., Martin, N., Pillon, B., et al. (1994). Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. *American Journal of Neuroradiology, 15*, 929 -937.

Lehmann, D., Pascual-Marqui, R., Michel, C. (2009). *Scholarpedia 4*(3), 7632.

Lopez, O.L., Jagust, W.J., DeKosky, S.T., Becker, J.T., Fitzpatrick, A., Dulberg, C., et al. (2003) Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Archives of Neurology, 60*, 1385-1389.

Luria, A.R. (1973). *The Working Brain: An Introduction to Neuropsychology*. New York: Basic Books.

Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J.,Frackowiak, R.S.J., et al. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *PNAS, 97*(8), 4398-4403.

Maguire, E.A., Kumaran D., Hassabis, D., Kopelman, M.D. (2010). Autobiographical memory in semantic dementia: A longitudinal fMRI study. *Neuropsychologia, 48* ,123–136.

Mahon, B.Z., & Caramazza, A. (2003). Constraining questions about the organization and representation of conceptual knowledge. *Cognitive Neuropsychology, 20*, 433-450.

Manly, J.J., Tang, M.X., Schupf, N., Stern, Y., Vonsattel, J.P., Mayeux, R. (2008). Frequency and course of mild cognitive impairment in a multiethnic community. *Annals of Neurology, 63*, 494-506.

Manns, J.R. Hopkins, R.O. , Squire, L.R. (2003). Semantic memory and the human hippocampus . *Neuron*, *38*, 127 –133.

Martin, A. (2007). The representation of object concepts in the brain. *Annual Review of Psychology, 58*, 25-45.

Masters, C.L., Simms, G., Weinman, N.A., Multhaup, G., McDonald, B.L., Beyreuther, K. (1985). Amyloid plaque core protein in Alzheimer's disease and Down syndrome. *PNAS, 1*(4), 4245-4249.

Mayes, A.R., & Roberts, N.(2001). Theories of episodic memory. *Philosophical Transactions of the Royal Society of London*, *356,* 1395 –1408.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology 34*(7), 939–944.

McPherson, W. B., & Holcomb, P. J. (1999). An electrophysiological investigation of semantic priming with pictures of real objects. *Psychophysiology, 36*(1), 53-65.

McRobbie, D.W., Moore, E.A., Graves, M.J., Prince, M.R. (2003). *MRI: From Picture to Proton*. Cambridge University Press.

Medina, D.A., de Toledo-Morrell, F., Urresta, F., Gabrieli, J.D., Moseley, M., Fleischman, et al. (2006). White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. *Neurobiology of Aging, 27*, 663-672.

Milberg, W., & Blusmtein, S.E. (1981). Lexical decision and aphasia: Evidence for semantic processing. *Brain and Language, 14* (2), 371-385.

Miller, G. (1956). The Magical number seven, plus or minus two: some limits on our capacity for processing information. *The Psychological Review, 63*(2): 81-97.

Mitchell, D.B., & Brown, A.S. (1988). Persistent repetition priming in picture naming and its dissociation from recognition memory. Journal of Experimental Psychology Learning Memory and Cognition, 14(2), 213-222.

Merzenich, M.M., Recanzone, G.H., Jenkins, W.M., Grajski, K.A. (1990). Adaptive mechanisms in cortical network underlying cortical contributions to learning and nondeclarative memory. *Cold Spring Harbor Symposia on Quantitative Biology, 55*, 873-887.

Mesulam, M., Weineke, C., Rogalski, E., Cobia, D., Thompson, C., Weintraub, S. (2009). Quantitative templatefor subtyping primary progressive aphasia. *Archives of Neurology, 66*, 1545-1551.

Monet, P., Franc, J., Brasseur, A., Desblanche, J., Saliou, G., Deramond, H., Lehmann, P. (2009). Arterial Spin Labeling: state of the art. *Journal of Radiology, 90*, 1031-1037.

Morra, J.H., Tu, Z., Apostolova, L.G., Green, A.E., Avedissian, C., Madsen, S.K., Parikshak, N. et al. (2009). Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. *Human Brain Mapping, 30*, 2766-2788.

Moss, H.E., Tyler, L.K., Devlin, J. (2002). The emergence of category specific deficits in a distributed semantic system. (Eds.). *Category-specificity in brain and mind* (pp. 115-145). Hove, UK: Psychology Press.

Mummery, C.J., Patterson, K., Hodges, J.R., Wise, R.J.S. (1996). Generating "tiger" as an animal namenor a word beginning with T: differences in brain activation. *Proceedings of the Royal Society B: Biological Sciences, 263*, 989-995.

Mummery, C.J., Patterson, K., Price, C.J., Ashburner, J., Frackowiak, R.S., Hodges, J.R. (2004). A voxel-based morphometry study of semantic dementia. Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology, 47*, 36-45.

Münte, T.F., Altenmüller, E., Jäncke, L. (2002). The musician's brain as a model of neuroplasticity. *Nature Neuroscience Reviews, 3*, 473-478.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998). Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. *Neurology, 51*, 1546-1554.

Nebes, R.D., Martin, D.C., Horn, L.C. (1984). Sparing of semantic memory in Alzheimer's disease. *Journal of Abnormal Psychology, 93*, 321-330.

Neely, J.H. (1991). Semantic priming effects in visual word recognition: a selective review of current findings and theories. (Eds). *Basic Process in Reading: Visual Word Recognition*. Lawrence Erlbaum, Hillsdale, NJ.

Neisser, U. (1967). *Cognitive psychology*. New York, NY: Meredith.

Nestor, P.J., Fryer, T.D., Hodges, J.R. (2006). Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage, 30*, 1010-1020.

Neville, H.J., Pratarelli, M.E., Foster, K.I. (1989). *Distinct neural systems for lexical and episodic representations of words*. Paper published in Neuroscience Abstracts, 15, abstract No 10111.

Niedermeyer, E., & da Silva, F.L. (2004). *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. Lippincot Williams & Wilkins.

Nobili, F., Frisoni, G.B., Portet, F., Verhey, F., Rodriguez, G., Caroli, A., et al. (2008). Brain SPECT in subtypes of mild cognitive impairment. Findings from the DESCRIPA multicenter study. *Journal of Neurology, 255*, 1344-1353.

Noppeney, U., Patterson, K., Tyler, L.K., Moss, H., Stamatakis, E.A., Bright, P., et al. (2007). Temporal lobe lesions and semantic impairment: A comparison of herpes simplex virus encephalitis and semantic dementia. *Brain, 130*, 1138-1147.

Nudo, R.J., Jenkins, W.M., Merzenich, M.M. (1990). Repetitive microstimulation alters the cortical representation of movements in adult rats. *Somatosensensory and Motor Research, 7*(4), 463-483.

Nudo, R.J., & Milliken, G.W. (1996). Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *Journal of Neurophysiology, 75*(5), 2144-2149.

Nudo, R.J. (2006). Plasticity. *NeuroRx Research, 3*(4), 420-427.

Nunez, P.L., Srinivasan, R. (2006) *Oxford University Press, Electric fields of the brain: the neurophysics of EEG (2nd Ed.)*. New York, pp.

Ober, B.A., & Shenaut, G.K. (1988). Lexical decision and priming in Alzheimer's disease. *Neuropsychologia, 26*, 273-286.

Ohnishi, T., Matsuda, H., Tabira, T., Asada, T., Uno, M. (2001). Changes in brain morphology in Alzheimer disease and normal aging: is Alzheimer disease an exaggerated aging process? *American Journal of Neuroradiology, 22*, 1680-1685.

Olejniczak, P. (2006). Neurophysiologic basis of EEG. *Journal of Clinical Neurophysiology, 23*, 186–189.

Olichney, J.M., Yang, J-C., Taylor, J., Kutas, M. (2011). Cognitive Event-Related Potentials: Biomarkers of Synaptic Dysfunction Across the Stages of Alzheimer's Disease. *Journal of Alzheimer's Disease, 26*, 215-228.

Olson, I.R., Plotzker, A., Ezzyat, Y. (2007). The enigmatic temporal pole. A review of findings on social and emotional processing. *Brain, 130*, 1718-1731.

Patterson, K., Nestor, P.J., Rogers, T.T. (2007). Where do you know what do you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience, 8*, 976-987.

Piatt, A.L, Fields, J.A., Paolo, A.M., Koller, W.c, Tröster, A.I. (1999a). Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. *Journal of Clinical and Experimental Neuropsychology, 21,* 435-443.

Piatt, A.L., Fields, J.A, Paolo, A.M, Tröster, A.I. (199b). Action (verb naming) fluency as an executive function measure: Convergent and divergent evidence of validity. *Neuropsychologia, 37,* 1499-1503.

Pierpaoli C, Jezzard P, Basser PJ, Barnett, A., Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology, 201*, 637–648.

Pijnenburg, Y.A., Gillissen, F., Jonker, C., Scheltens, P. (2004). Initial compliants in frontotemporal lobe degeneration. *Dementia and Geriatric Cognitive Disorders, 17*, 302-306.

Penfield, W. & Jasper, H. (1954). *Epilepsy and the functional anatomy of the human brain*. Oxford: England: Litte, Brown, & Co.

Penfield, W. (1975). *The Mystery of the Mind*. Princeton, New Jersey: Princeton University Press.

Pennington, B.F., Filipek, P.A., Lefly, D., Chhabildas, N., Kennedy, D.N., Simon, J.H., et al. (2000). A twin MRI study of size variations in human brain. *Journal of Cognitive Neuroscience 12*, 223-232.

Perry, R.J., & Hodges, J.R. (2000). Differentating frontal and temporal variant frontotemporal dementia. *Neurology, 54*, 2277-2284.

Petersen, E.T., Zimine, I., Hoy, Y.C., Golay, X. (2006). Non-invasive measurement of perfusion: a critical review of arterial spin labeling techniques. British Journal of Radiology, 79, 688-701.

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

Petersen, R.C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183-194.

Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, et al. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Archives of Neurology, 63*, 665-672.

Petersen, R.C. (2011). Mild Cognitive Impairment. *New England Journal of Medicine, 364*, 2227-2234.

Pfefferbaum, A., Sullivan, E.V., Swan, G.E., Carmelli, D. (2000). Brain structure in men remains high heritable in the seventh and eight decades of life. *Neurobiology of Aging, 21*, 63-74.

Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weird, D.R., Ofstedal, M.B., et al. (2008). Prevalence of cognitive impairment without dementia in the United States. *Annals of Internal Medicine, 148*, 427-434

Pollock, J.M., Kraft, R.A., Tan, H., Maldjian, A. (2008). *Arterial Spin Labeled Perfusion Imaging of the Orbit: Initial Experience.* Paper presented at the American Society of Head and Neck Radiology 42th Annual Meeting; Toronto, Canada.

Pollock, M.J., Tan, H., Kraft, R.A., Whitlow, C.T., Burdette, J.H., Maldjian, J.A. (2009). Arterial Spin Labeled MRI Perfusio Imaging: Clinical Applications. *Magnetic Resonance Imaging Clinics of North America, 17*(2), 315-338.

Posner, M.I., & Snyder, C.R.R. (1975). Facilitation and inhibition in the processing of signals.(Eds). *Attention and performance, vol V*. New York: Academic Press.

Posthuma, D., & Boomsma, D.I. (2000). A note on the statistical power in extended twin designs. *Behavioral Genetics, 30*, 147-158.

Pratarelli, M.E. (1994). Semantic processing of pictures and spoken words: Evidence from event-related brain potentials. *Brain and Cognition, 24*, 137–157.

Price, C.J., Devlin, J.T., Moore, C.J., Morton, C., Laird, A. (2005). Meta-analyses of object naming: effect of baseline. *Human Brain Mapping, 25*, 70-82.

Quartz, S.R., & Sejnowski, T.J. (2002). liars, lovers, and heroes. New York: NY, HarperCollins Publishers.

Radau, P.E., Slomka, P.J., Julin, P., Svensson, L., Wahlund, L-O. (2001). Evaluation of linear registration algorithms for brain SPECT and the error due to hypoperfusion lesions. *Journal of Medical Physics, 28,* 1660-1668.

Rauschecker, J.P. (2002). Cortical map plasticity in animals and humans. *Progress in Brain Research, 138*, 73-88.

Reder, L.M., Park, H., Kieffaber, P.D. (2009). Memory systems do not divide on consciousness: Reinterpreting memory in terms of activation and binding . *Psychological Bulletin, 135* , 23 –49.

Rogers, S.L., & Friedman, R.B. (2008). The underlying mechanisms of semantic memory loss in Alzheimer's disease and semantic dementia. *Neuropsychologia, 46*, 12-21.

Rogers, T.T., Hocking, J., Noppeney, U., Mechelli, A., Gorno-Tempini, M.L., Patterson, K., et al. (2006). Anterior temporal cortex and semantic memory: reconciling findings from neuropsychology and functional imaging. *Cognitive Affective and Behavioral Neuroscience, 6*, 201-213.

Rombouts, S.A., Barkhof, F., Witter, M.P., Scheltens, P. (2000). Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. Neuroscience Letters, 285, 231-233.

Rosen, H.J., Kramer, J.H., Gorno-Tempini, M.L., Schuff, N., Weiner, M., Miller, B.L. (2002). Patterns of cerebral atrophy in primary progressive aphasia. *American Journal of Geriatric Psychiatry, 10*, 89-97.

Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry, R.J, Schuff, N., Weiner, M., et al. (2002). Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology, 58*, 198-208.

Rosenbaum, R.S. Moscovitch, M., Foster J.K., Schnyer, D.M., Gao F.Q., Kovacevic, N., et al. (2008). Patterns of autobiographical memory loss in medial temporal lobe amnesic patients. *Journal of Cognitive Neuroscience*, *20*, 1490 –1506.

Rossel, S., Price, C.J., Nobre, A.C. (2003). The anatomy and time course of semantic priming investigated by fMRI and ERPs. *Neuropsychologia, 41*, 550-564.

Saha, G.B., MacIntyre, W.J., Go, R.T. (1994). Radiopharmaceuticals for brain imaging. *Seminars in Nuclear Medicine, 24*, 324-349.

Salat, D.H., Tuch, D.S., van der Kowe, A.J.W., Greve, D.N., Pappu, V., Lee, S.Y., et al. (2010). White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiology of Aging, 31*(2), 244-256.

Sarfarazi, M., Cave, B., Richardson, A., Behan, J., Sedgwick, E.M. (1999). Visual event related potentials modulated by contextually relevant and irrelevant olfactory primes. *Chemical Senses, 24*, 145–154.

Scahill, R.I., Schott, J.M., Stevens, J.M., Rossor, M.N., Fox, N.C. (2002). Mapping the evolution of regional atrophy in Alzheimer's disease: Unbiased analysis of fluid-registered serial MRI. *PNAS, 99*, 4703-4707.

Simmons, W.K., & Martin, A. (2009). The anterior temporal lobes and the functional architecture of semantic memory. *Journal of the International Neuropsychological Society, 15*, 645-649.

Scamvougeras, A., Kigar, D.L., Jones, D., Weinberger, D.R., Witelson, S.F. (2003). Size of the human corpus callosum is genetically determined: An MRI study in mono and dizygotic twins. *Neuroscience Letters, 338*, 91-94.

Schacter, D.L., & Buckner, R.L. (1998). Priming in the brain. *Neuron, 20*, 185-195.

Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L.M., Trojanowski, J.Q., et al. (2009). MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain, 132*, 1067–1077.

Schwartz, M.F., Martin, O.S., Saffran, E.M. (1979). Dissociation of language function in dementia: a case study. *Brain and Language, 7*, 277-306.

Sciller, F. (1992). *Paul Broca, Founder of French Anthropology, Explorer of the Brain*. New York: Oxford University Press.

Scott, S.K., Blank, C.C., Rosen, S., Wise, R.J.S. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain, 123*, 2400-2406.

Seeley WW, Bauer AM, Miller BL, Gorno-Tempini, M.L., Kramer, J.H, Weiner, M., et al. (2005). The natural history of temporal variant frontotemporal dementia. *Neurology, 64*, 1384-1390.

Shepherd, G.M. (1991). *Foundations of the neuron doctrine*. Oxford University Press.

Shi, J., Shaw, C.L., Du Plessis, D, Richardson, A.M, Bailey, K.L., Julien, C., et al. (2005). Histopathological changes underlying frontotemporal lobe degeneration with clinicopathological correlation. *Acta Neuropathologica (Berl), 110*, 501-512.

Simpson, D. (2005). Phrenology and the neurosciences: contributions of F. J. Gall and J. G. Spurzheim. *ANZ Journal of Surgery, 75*, 475-482.

Skrandes, W. (1990). Global field power and topographic similarity. *Brain Topography, 3*, 137-141.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, et al. (2006). Tract- based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage 31*, 1487-1505.

Smith, S.M., Johansen-Berg, H., Jenkinson, M., Rueckert, D., Nichols, T.E., Miller, K.L., et al. (2007). Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nature Protocols, 2*, 499-503.

Snowden, J.S., Goulding, P.J., Neary, D. (1989). Semantic dementia: a form of circumscribed cerebral atrophy. *Behavioral Neurology, 2*, 111-138.

Snowden, J.S., Bathgate, D., Varma, A., Blackshaw, A., Gibbons, Z.C., Neary, D. (2001). Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of Neurology Neurosurgery and Psychiatry, 70*, 323-332.

Snowden, J.S., Thompson, J.C., Neary, D. (2004). Knowledge of famous faces and names in semantic dementia. *Brain, 127*, 860-872.

Snowden, J., Neary, D., Mann, D. (2007). Frontotemporal lobe degeneration: clinical and pathological relationships. *Acta Neuropathologica (Berl), 114*, 31-38.

Song, S.K., Sun, S.W., Ramsbottom, M.J., Chang, C., Russell, J., Cross, A.H. (2002). Dysmyelination revealed through MRI as increased radial (but un- changed axial) diffusion of water. *Neuroimage, 17*, 1429 –1436.

Spillane, J.D. (1981). *The doctrine of the nerves: chapters in the history of neurology*. Oxford and New York: Oxford University Press.

Spurzheim, G. (1826). *The Anatomy of the Brain, with a Generla View of the Nervous System*. Translated from the unpublished French MS by R. Willis. London, Highley, 1826. Reprinted in facsimile by the Classics of Neurology and Neurosurgery Library. Birmingham, Alabhama: Gryphon, 1989.

Squire, L.R., & Kandel, E.R. (1999). *Memory. From Minds to Molecules*. NY: Scientific American Library.

Steven, L.J. (2005). *An Introduction to the Event-Related Potential Technique*. The MIT Press

Stricker, N.H., Schweinsburg, B.C., Delano-Wood, L., Wierenga, C.E., Bangen, K.J., Haaland, K.Y., et al. (2009). Decreased white matter integrity in late-myelinating fiber pathways in Alheimer's disease supports retrogenesis. *Neuroimage, 45*, 10-16.

Sullivan, E.V., Pfefferbaum, A., Swan, G.E., Carmelli, D. (2001). Heritability of hippocampal size in elderly twin men: Equivalent influence from genes and environment. *Hippocampus, 11*, 754-762.

Sullivan, E.V., Rohlfing, T., Pfefferbaum, A. (2010). Quantitative fiber tracking of lateral and interhemispheric white matter system in normal aging: relations to timed performance. *Neurobiology of Aging, 31*(3), 464-481.

Stuss, D., Picton, T., Cerri, M. (1988). Electrophysiological manifestations of typicality judgment. *Brain and Language, 33*, 260–272.

Taber, K., Pierpaoli, C., Rose, S.E., Rugg-Gunn, F.J., Chalk, J.B., Jones, D.K., et al. (2002). The Future for Diffusion Tensor Imaging in Neuropsychiatry. *Journal of Neuropsychiatry and Clinical Neuroscience, 14*(1), 1-5.

Talagala, S.L., Ye, F.Q., Ledden, P.J., Chesnik, S. (2004). Whole-brain 3D perfusion MRI at 3.0 T using CASL with a separate labeling coil. *Magnetic Resonance in Medicine, 52*, 131-140.

Tatum, W.O., Husain, A.M., Benbadis, S. R. (2008). Handbook of EEG Interpretation. Demos Medical Publishing.

Thompson, S.A., Graham, K.S., Patterson, K., Sahakian, B.J., Hodges, J.R. (2002). Is knowledge of famous people disproportionately impaired in patients with early and questionable Alzheimer's disease? *Neuropsychology, 16*(3), 344–358.

Thompson, S.A., Patterson, K., Hodges, J.R. (2003). Left/right asymmetry of atrophy in semantic dementia: behavioural cognitive implications. *Neurology, 61*, 1196-1203.

Thompson, S.A., Graham, K.S., Williams, G., Patterson, K., Kapur, N., Hodges, J.R. (2004). Dissociating person-specific from general semantic knowledge: Roles of the left and right temporal lobes. *Neuropsychologia, 42*, 359-370.

Tranel, D., Damasio, H., Damasio, A.R. (1997). A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia, 35*, 1319-1327.

Tranel, D. (2006). Impaired naming of unique landmarks is associated with left temporal polar damage. *Neuropsychologia, 20*, 1-10.

Thompsom-Schill, S.L. (2003). Neuroimaging studies of semantic memory: inferring "how" from "where". *Neuropsychologia, 41*, 280-292.

Tsukiura, T., Toshikatsu, F., Fukatsu, R., Otsuki, T., Okuda, J., Umetsu, A., et al. (2003). Neural basis of the retrieval of people's names: Evidence from brain-damaged patients and fMRI. *Journal of Cognitive Neuroscience, 14*, 922-937.

Tulving, E. (1972). Episodic and semantic memory. (Eds). *Organization of memory* (pp 381-403). New York: Academic Press.

Tulving, E. (1985). Memory and consciousness . *Canadian Psychology, 26* , 1–12.

Tyler, L.K., Moss, H.E., Durrant-Peatfield, M.R., Levy, J.P. (2000). Conceptual structure and the structure of concepts: A distributed account of category-specific deficits. *Brain and Language, 75*, 195-231.

Tyler, L.K., & Moss, H.E. (2001). Towards a distribute account of conceptual knowledge. *Trends in Cognitive Science, 5*, 244-252.

Tyler, L.K., Stamatakis, E.A., Dick, E., Bright, P., Fletcher, P., Moss, H. (2003). Objects and their actions: Evidence for a neutrally distributed semantic system. *Neuroimage, 18*, 542-557.

Valenstein, E.S. (1973*). Brain stimulation and motivation: Research and commentary*. Glenview, Illinois: Scott, Foresman.

Vernooij, M.W., de Groot, M., van der Lugt, A., Ikram, M.A., Krestin, G.P., Hofman, A., et al. (2008). White matter atrophy and lesion formation explain the loss of structural integrity of white matter in aging. *Neuroimage, 43*, 470-477.

Wahlund, L-O., Pihlstrand, E., Eriksdotter-Jörnhagen, M. (2003). Mild cognitive impairment: Experience from a memory clinic. *Acta Neurologica Scandinavica, 179,* 21-24.

Warrington, E.K. (1975). The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology, 27*, 635-657.

Warrington, E.K., & McCarthy, R.A. (1987). Categories of knowledge: further fractionation and an attempted integration. Brain, 110, 1273-1296.

Warrington, E.K., & Shallice, T. (1984). Category specific semantic impairment. *Brain, 107*, 829-854.

Whatmough, C., Chertkow, H., Murtha, S., Templeman, D., Babins, L., Kelner, N. (2003). The semantic category effect increases with worsening anomia in Alzheimer's type dementia. *Brain and Language, 84*(1), 134–147.

Williams, G.B., Nestor, P.J., Hodges, J.R. (2005). Neural correlates of semantic and behavioural deficits in frontotemporal dementia. *Neuroimage, 24*, 1042-1051.

Ween, J.E., Verfaellie, M., Alexander, M.P. (1996).Verbal memory function in mild aphasia. *Neurology* , *47* , 795 –801.

Wernicke, C. (1874). *Der aphasische Symptomencomplex: Eine Psychologische Studie auf anatomischer Basis*. Breslau, Max Cohn & Weigert.

Westmacott, R., Black, S.E., Freedman, M., Moscovitch, M.(2004). The contribution of autobiographical significance to semantic memory: Evidence from Alzheimer's disease, semantic dementia, and amnesia. *Neuropsychologia , 42* , 25 –48.

Whitwell, J.L., & Clifford, R.J. Jr. (2005). Comparisons Between Alzheimer Disease and Frontotemporal Lobar Degeneration, and Normal Aging With Brain Mapping. *Topics in Magnetic Resonance Imaging, 16*, 409-425.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L, et al. (2004). Mild cognitive impairment-beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256*, 240-246.

Wolf, R.L., & Detre, J.A. (2007). Clinical neuroimaging using arterial spin-labeled perfusion magnetic resonance imaging. *Neurotherapeutics, 4*, 349-359.

Wright, I.C., Sham, P., Murray, R.M., Weinberger, D.R., Bullmore, E.T. (2002). Genetic contribution to regional variability in human brain structure: Methods and preliminary results. *Neuroimage, 17*, 256-271.

Wu, W.C., Fernandez-Seara, M., Detre, J.A., Wehri, F.W., Wang, J. (2007). A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magnetic Resonance in Medicine, 58*, 1020-1027.

Yi, H.A., Moore, P., Grossman, M. (2007). Reversal of the concreteness effects of verbs in patients with semantic dementia. *Neuropsychology, 21*, 9-19.

Zahn, R., Buechert, M., Overmans, J., Talazko, J, Specht, K., Ko, C.W., et al. (2005). Mapping of temporal and and parietal cortex in progressive nonfluent aphasia and Alzheimer's disease using chemical shift imaging, voxel-based morphometry and positron emission tomography. *Psychiatry Research, 140*, 115-131.

Zahn, R., Moll, J., Krueger, F., Huey, E.D., Garrido, G., Grafman, J. (2007). Social concepts are represented in the superior anterior temporal cortex. *PNAS, 104*, 6430-6435.

Zahn, R., Moll, J., Iyengar, V., Huey, E.D., Tierney, M., Krueger, F. et al. (2009). Social conceptual impairments in frontotemporal lobar degeneration with right anterior temporal hypometabolism. *Brain, 132*, 604-616.

Zhang, Q., Lawson, A., Guo, C., Jiang, Y. (2006). Electrophysiological correlates of visual affective priming. *Brain Research Bulletin, 71*, 316–323.

Zhang, Y., Schuff, N., Jahng, G.H., Bayne, W., Mori, S., Schad, L., et al. (2007). Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer's disease. *Neurology, 68*(1), 13-9.