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Semantic Memory for Food and Brain Correlates

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Abstract

Semantic memory stores knowledge about different types of objects: plants, animals, vehicles, utensils, conspecifics and food, among the others. Our ability to quickly recognize and categorize an object when we encounter it depends upon having experienced that object before and on semantic knowledge integrity. Semantic memory is one the most resilient cognitive abilities, it is less prone to interference than episodic memory and more declines slowly. The interest in how semantic memory is organized traces way back, however a great impulse was provided by the first systematic neuropsychological observations of patients with category specific recognition deficits. However, this debate is far from being resolved. In my dissertation, I will show how the study of food as a semantic category is extremely suitable to shed light on the organization of semantic knowledge.

The thesis is organized as follow. In Chapter 1, I will first define semantic memory, focusing on its characteristics, such as its relationship with experience, its resilience to cognitive decline and its neural correlates, and on how it has been studied by neuropsychologists. In addition, I will review the studies on the food category, focusing on some intrinsic dimensions such as the level of transformation. Chapter 2 includes Study 1, in which I have investigated the organization of semantic memory by using food (natural and transformed) and non-food (living and on-living things) in a group of patients suffering from temporal lobe atrophy (Alzheimer's disease, PPA and FTD) and healthy controls, using Voxel Based Morphometry and DTI. Results have shown that food breaks down in natural and transformed, and that this parsing mirrors that of living and non-living things, thus strongly supporting the Sensory-functional model of semantic knowledge. Chapter 3 contains Study 2, in which I have explored the relationship between semantic memory and experience. I collected information about life-long eating habits as a proxy of long-term experience with specific foods as well as information about semantic memory of

food in participants of different ages (36 – 108 years old). Results support the hypothesis that semantic memory is modulated by experience. In Chapter 4, the focus of Study 3 is on episodic memory. Here I investigated whether the difference between semantic memory for natural and transformed food highlighted in Study 2 extends also to episodic memory, and whether the *animacy effect* - a facilitation to remember living exemplars - holds for food as well. Specifically, I administered a recognition memory task to the same participants of Study 2, to a group of young participants and to patients with Alzheimer's disease, PPA and FTD. I found that young adults had better recognition memory for transformed foods compared to natural foods. This difference disappeared in centenarians, consistently with Study 2, and in patients. The natural/transformed distinction appears susceptible to decay only in the presence of a high degree of episodic memory impairment. Finally, with Study 4, described in Chapter 5, my aim was more translational, that is, to test whether a deficit in semantic memory for food could lead to specific eating disorders. This study empirically establishes the behavioural and neural correlates of abnormal changes in eating habits in dementia and their relationship with semantic memory.

In this thesis, I have shown that natural and transformed food do have different neural correlates, and that they are differently represented in semantic memory. By drawing together evidence from my studies and from studies of others I was allowed to propose a comprehensive model of semantic knowledge. Additionally, in my thesis I showed how food can be employed to study the organization of semantic knowledge, the way in which semantic knowledge is shaped by learning and experience, and its effect on behaviour.

Chapter 1

What is semantic memory?

1.1 Introduction

Semantic memory can be defined as a store of conceptual knowledge about different types of objects, such as vehicles, manmade tools, conspecifics and animals, among others. This information stored in semantic memory allows us to recognize an object that we have previously encountered, without having to relearn the information about that object every time we see it (Murphy, 2002). Even in uncertain circumstances, we tend to assign a stimulus to a category (Harnad, 1987); for instance, even if we have never seen a French Bulldog, we might be able to guess that it belongs to the category of 'dogs'. Once the object is recognized, the conceptual representation, with its information content, may trigger a specific operation upon the object, when a proper motivation is present. For this reason, this cognitive ability is extremely adaptive and of crucial importance for our survival: if this ability is disrupted, speech production (e.g. Gainotti, Silveri, Daniele & Giustolisi, 1993) and comprehension (e.g. Lambon Ralph et al., 2001) are impaired.

While episodic memory allows us to remember that, when we were in high school, we have read Moby Dick by Herman Melville and we forgot to return it to the city library, semantic memory allows us to know that Herman Melville is an author, that an author writes novels, that a novel is a written narration, and that Moby Dick is a masterpiece of the *American Renaissance*. We owe the theoretical distinction between semantic memory and episodic memory to Endel Tulving in 1972. He proposed that episodic memory encodes new perceptual events only on the basis of their perceptual attributes and only when previously encoded contents are present. The retrieval of these temporally codified events is strongly autobiographical and more susceptible to modification when accessed, from time to time. On the other hand, semantic memory stores information about words, symbols, concepts and their relations, and is less sensitive to interference. Indeed, according to Tulving, by storing a cognitive signal (i.e. the object concept), rather than the encounter with the signal itself (i.e. the situation in which the object concept was encountered), semantic memory is more reliable than episodic. Semantic memory is argued to be dependent on experience (Warrington & Shallice, 1984; Martin, 2016). This implies that we can recognize things and access to the associated information about them that we have experienced before in our lives. The relationship between semantic memory and experience has been extensively investigated with the focus being primarily on an extreme and prolonged form of experience, that is *expertise*. Expertise can be defined as an exceptional skill at specific domains of knowledge, with respect to novices and to other domains (Ericsonn & Lehmann, 1996). This ability has been studied by systematically manipulating the participants' level of expertise of the object category at study (Rosch et al., 1976). Expertise has been found to affect the ability to list features for exemplars at the subordinate level (e.g. 'robin' rather than 'bird'), to categorize and name exemplars of one's domain of expertise (e.g., Tanaka & Taylor, 1991), and to recognize complex (Murphy, 1993) or and novel objects (Op de Beeck et al., 2006).

Moreover, semantic memory and episodic memory also seem to decline at a different pace in aging. It is commonly assumed that the various components of long-term memory follow different trajectories across the adult years, with semantic memory and non-declarative memory being more resilient to aging than episodic memory (for a review, see Nyberg et al., 2012). This pattern mirrors the two-component model of intelligence (Baltes et al., 1999), according to which intelligence is both fluid and crystallized: while the former component is more mechanic and reflects age-related variance in general intelligence, the latter is considered more pragmatic and dependent on experience and cultural knowledge (Lövden, Ghisletta, & Lindberg, 2004).

To date the evidence as to whether semantic memory is impaired in aging and, if so, to which extent, is controversial and seems to vary depending on the task administered. For instance, naming performance, widely used to test semantic memory, is normally found to be progressively reduced with the increase of age (Verhaeghen & Salthouse, 1997; Albert et al., 1988; Ardila & Rosselli, 1989; Au et al., 1993; Bowles et al., 1983; Goodglass, 1980; LaBarge et al., 1986; Le-Dorze & Durocher, 1992; Nicholas et al., 1983; Poon & Fozard, 1978; Rosselli, et al., 1990; Thomas et al., 1977; Welch et al., 1996), although not consistently (Farmer, 1990; Flicker et al., 1987; Mitchell, 1989; Poon & Fozard, 1978; Villardita et al., 1983). In contrast, the degradation of performance on knowledge-based tests (e.g., Vocabulary and General knowledge) is less linear, with a first sign of decline occurring at the age of 60, then at 90 (Salthouse, 2014), and possibly at 100 (for a review, see Gondo & Poon, 2007). Lastly, performance on the semantic category fluency has shown a tendency to decrease significantly in old-old age (Rönnlund et al., 2003; Nyberg et al., 2003).

As shown by the abovementioned studies about cognitive aging, the distinction between semantic memory and episodic memory is relevant not only theoretically, but also clinically. The observation of a dissociation between semantic and episodic memory has led to the investigation on how semantic knowledge is organized in the brain. In fact, the best way to study cognitive function consists in investigating its selective impairment derived from brain damage. The understanding of semantic knowledge has received great impulse from neuropsychological studies. In the following section I am going to review them in order to define the selectivity of the deficit to semantic memory, depending on the disorder or the lesion site.

1.2 *Semantic memory deficits*

First, I will discuss the semantic deficits and associated brain regions. Deficits affecting semantic memory may arise as a consequence of lesions involving the temporal lobes, as observed in different pathologies: Alzheimer’s disease (AD, Hodges & Patterson, 1993), vascular events (Chertkow, Bub, Deaudon & Whitehead, 1997), head injuries (Bub, Black, Hampson & Kertesz, 1998), herpes simplex encephalitis (HSE) (Warrington & Shallice, 1984; Kapur et al., 1994) and semantic dementia (Hodges, 2000; Snowden, Neary & Mann, 1996). These disorders will be described in detail in the following section. In the current section, I will focus on the tools that are commonly used to investigate the presence of a semantic deficit.

Indeed, several tasks have been employed to measure semantic deficit. The different tasks tap different levels of semantic knowledge: a perceptual, pre-semantic level, that deals with perceptual aspects of input, and a semantic level, that concerns different types of information related to the object (e.g. how to use the object, the prototypical user, the context in which it can be found etc.).

The most common and effective tool to assess the integrity of semantic memory is *picture naming*. In fact, noun production has been proposed to depend upon the information concerning the object depicted by that noun, triggered by, for instance, the vision of the object (Morton, 1983). Another frequently used task is the *word-picture matching task*, requiring the patient to identify the right picture target, named by the experimenter, among distractors. While naming to be performed required lexical integrity, word-picture matching taps on the central level of processing and allows to assess the performance also of patients with aphasia. The fact that both tasks are successful in assess semantics has been excellently shown in a study by Lambon-Ralph et al. (2001). In a longitudinal study on 16 patients, the authors distinguished two broad patterns of impairment: i) the decline in naming ability is linked to deterioration in comprehension, as shown by the low scores on the word to picture matching task, with the most common error type consisting in naming an exemplar by the noun of an exemplar of the same semantic category; ii) the decline in naming is due to anomia, with partially spared comprehension until the latter stage of the cognitive decline, when word-picture matching scores reach floor level. According to these results, naming requires both semantic and phonological integrity of the representation of the nouns. Also the pattern of atrophy supports this explanation. Indeed, patients with a primarily left atrophy of the anterior temporal lobe (ATL), that is the most common in semantic dementia (for a review on neural correlates of semantic deficits see next section), perform worse on naming tasks, and show a less impaired word-picture matching performance, whereas patients whose pattern of atrophy is more severe in the right ATL tend to be impaired at both naming and comprehension tasks. In addition, when the disease progresses, the pattern of atrophy becomes similar in both ATLs (e.g. Brambati et al., 2009; Thompson et al., 2003, Lambon-Ralph et al., 2001), as well as in the performance of patients with either atrophy side, as discussed above.

A category-specific impairment may be present also at presemantic levels of processing. For instance, this may be observed for object decision tasks, such as those requiring to *categorize* the object as real or unreal, or to say whether it belongs to the correct semantic category (see for instance Mahon and Caramazza, 2009). In these cases, the accuracy depends upon "the integrity of the visual structural description system" (Mahon and Caramazza, 2009, p.29). This system has been defined as a presemantic stage of object recognition (see Mahon and Caramazza, 2009; Humphreys et al., 1988). For instance, patients EW and KC, showing category-specific deficits in tasks such as picture naming performed differently on this type of task. Specifically, EW (Caramazza & Shelton, 1998) could not judge whether the pictures shown depicted real or unreal animals, whereas KC could even correctly categorize whether the object shown was a living thing, even if KC was strongly impaired at naming the same category (see also Mahon and Caramazza, 2009). Given this multi-level organization of semantic knowledge, in my dissertation I implied several tasks using the same set of stimuli in order to test, without confounds, the detrimental processes affecting semantic memory for specific categories at both the presemantic and the lexical-semantic levels of processing.

1.2.2 *Disorders entailing semantic deficits*

As mentioned above, damage leading to semantic memory impairment has been shown to be more pronounced in the anterior, inferior and lateral aspects of the TL (Mummery, Patterson, Wise, Price & Hodges, 1999; Mummery et al., 2000).

One of the disorders of the brain that most frequently entails semantic deficit is a specific variant of the frontotemporal lobar degeneration (FTD). This class of disorders has been parsed in several variants: (1) behavioral variant of FTD (bvFTD), (2) primary progressive aphasia, divided in semantic variant PPA (svPPA), nonfluent agrammatic variant PPA (nfPPA), and logopenic variant PPA (lvPPA), (4) corticobasal syndrome, (3) progressive supranuclear palsy, and (6) FTD associated with motor neuron disease. However, among this variants, we are going to explore in greater detail only those that are best known to entail semantic deficits, that is bvFTD and svPPA or semantic dementia (for a review see Finger, 2016). The common feature of these disorders is an initial sparing of episodic memory and other cognitive abilities and an extensive atrophy of frontoparietal structures.

svPPA or *semantic dementia* (SD) is characterized by a progressive degradation of semantic knowledge (Snowden et al., 1989), regardless of the input and output modality (Bozeat et al., 2000; Rogers et al., 2004). The semantic deficit produced by SD is selective. As mentioned above, at early stages of this illness, this impairment leaves other cognitive functions, such as episodic memory and visuospatial skills, almost intact. This pattern was first reported by Elizabeth Warrington (1973), who described three patients with the same neurodegeneration and with comparable symptoms. These symptoms, until very late stages of the disease, consist in anomia and in a comprehension impairment, with perceptual and spatial skills being relatively intact, as well as day-to-day memory. Semantic dementia has been shown to entail also some recognition memory deficits (Graham, Simons, Pratt, Patterson & Hodges, 2000), but the extent to which this cognitive ability is affected is very limited, due to the fact that nonsemantic processes that are not degraded are more relevant for performing these tasks, as long term memory in the case of recognition memory (for a discussion, see Lambon-Ralph et al., 2001). Concerning language, syntax and phonology (i.e. repetition) are generally spared. SD has been stably associated with semantic deficits and with a bilateral, atrophy in temporal lobe, but more pronounced in the inferior temporal left aspect (Noppeney et al., 2007), inferior/middle temporal and fusiform gyri, the amygdaloid complex and, in certain cases, the ventromedial frontal cortex (Levy et al., 2004; Mummery et al., 2000; Rosen et al., 2002). However, as the disease progresses, also the right temporal lobe becomes atrophic and contributes to semantic deficits. In fact, we know that the left hemisphere has a strong role in the language function and in lexical-semantic deficits (e.g., Vigneau et al., 2006, for a meta-analysis) and has been more frequently associated to SD, with respect to the right temporal lobe. Recently, several studies have shown that, indeed, SD patients have mostly left-lateralized atrophy in the temporal lobe but also that, with the progression of the disease, the lesion spreads to the other side of the brain as well (e.g., Brambati et al., 2009; Whitwell et al., 2004; Thompson et al., 2003, Lambon-Ralph et al., 2001); in addition, the behavioural pattern eventually converges with that of the logopenic and the nonfluent variants mentioned above.

This pattern of atrophy observed in patients with SD is mirrored by a worsened performance on tasks tapping semantic memory. In a longitudinal study, Hodges, Graham and Patterson (1993) showed that patient JL had impaired comprehension and a naming accuracy dropped from 36% to 1% over the course of 18 months, with error types suggesting that the deficit was at the level of semantic knowledge. In addition, Hodges (1992) and Graham, Patterson & Hodges (1993) studied the case of patient FM, who displayed a progressive pure anomia with spared comprehension and a pattern of atrophy in the left inferior temporal lobe. The authors proposed a reduced transmission of activation between semantic and phonological representations. Tyler, Moss, Patterson & Hodges (1997) performed a further assessment FM who then showed impaired comprehension as well, meeting the criteria for a blown semantic dementia.

Taken together these studies show that the semantic deficits entailed by SD depend upon the integrity of semantic memory. The main interpretations, given by these authors, of these results are the following: i) there are two variants of FTD, which are semantic dementia and progressive anomia, ii) the level between the semantic and the phonological domains is impaired, which would be the level of lemmas/abstract, word-specific representations (Levelt, 1992; Dell & O'Seaghdha, 1992), or iii) the two patterns of impairment show differences only at the early and middle stage of the disease, because at later stages both patients showed both speech production and comprehension deficits (e.g. see Lambon Ralph et al., 2001 for a broad discussion). This latter interpretation is the most likely and consistent with the one according to which SD is a *semantic variant of primary progressive aphasia* (e.g. Neary, Snowden, Gustafson et al., 1998; Gorno Tempini et al., 2011), distinguishing it from *nonfluent* and *logopenic PPA*.

Behavioural FTD (bvFTD), differently from SD, has been associated to behavioural symptoms such disinhibition and social inappropriateness, eating disturbances such as hyperphagia, which is associated to a lack of inhibition as well (Ismail et al., 2008; Whitwell et al., 2007; Woolley et al., 2007) whereas, except for executive functions, other cognitive abilities are relatively spared. Specifically, these patients, if compared to other variants of FTLD or to AD, perform reasonably well on recall, recognition and visual memory, verbal fluency tasks, while they fail when their ability to plan is tested (Kramer et al., 2003).

Concerning *Alzheimer's disease*, temporal lobe structures are known to be affected very early in the course of AD (Forbes et al., 2002; Pestell, Shanks, Warrington, & Venneri, 2000). Specifically, AD's pattern of atrophy starts with the development of the characteristic neurofibrillary tangles first in the transentorhinal region (stages I-II), disrupting connections to and from the hippocampal formation, therefore the impairment in encoding new memories (Braak and Braak, 1993). In later stages, the degeneration reaches the regions of the entorhinal cortex, the subiculum and the hippocampal zone CA 1 (Ill-IV). All cortical association areas are widely reached by the neurodegeneration in the final stages of the disease (V-VI). Due to the large involvement of the temporal lobe, AD patients perform poorly at recall, recognition and visual memory tests but, compared to FTD patients, their executive functions are initially preserved (e.g. Kramer et al., 2003). Moreover, patients with AD are known also to perform poorly on semantic memory tests from very early in the course of the disease, such category fluency, picture naming, naming to description, and answering semantic features questions (Hodges & Patterson, 1993).

Brain damage following Herpes simplex encephalitis (*HSE)* also entails semantic deficits. HSE is the most common encephalitis in humans (Kennedy & Chaudhuri, 2002), and is an infection of the human nervous system that affects 1 in 230,000–300,000 individuals (Baringer, 2008) causing cerebral oedema and haemorrhagic necrosis. The brain damage affects mostly the temporal, in a more medial aspect (Noppeney et al., 2007), frontal lobes and diencephalic regions; more specifically, the damage involves the amygdala, hippocampus, peririnal and enthorinal cortices, parahippocampal and orbitofrontal cortex, insula and cingulate gyri (Gitelman et al., 2001). The main symptoms are fever, headache, nausea, and vomiting, which may progress into seizures, confusion. In some cases, focal neurological deficits are observed as well (Sabah, Mulcahy, & Zeman, 2012). The most frequent cognitive symptom is anterograde amnesia and, to a lesser extent, impairments of semantic memory and of the executive functions (Kapur et al., 1994).

1.3 *Category-specific semantic impairments and Models of Semantic Memory*

Patient studies proved very useful to explain how semantic memory is organized in the brain. After repeatedly observing patients disproportionally impaired at recognizing different categories of objects with a partial sparing of knowledge relative to other categories, neuropsychologist proposed different models of semantic memory. Neilsen (1946) produced the first anecdotal report on category-specificity in which he described two patients selectively impaired at recognizing objects (e.g. utensils) and foods presented through the visual or tactile modality, but did not display the same deficit for animate entities (see also McCrae & Trolle, 1936). Subsequently, several cases of category-specific semantic deficits have been reported, starting with the seminal studies by Warrington, Shallice and McCarthy (Warrington & McCarthy, 1983; 1987; Warrington & Shallice, 1984), who observed clear-cut dissociations in recognizing different semantic categories, as it will be described in the next section (for reviews see Capitani et al. 2003, Hart et al. 2007, Humphreys & Forde 2001, Tyler & Moss 2001).

For several decades' scholars have focused on defining the organizing principles of semantic knowledge in the brain. Different strands of research over the years have supported different models of semantic memory, focusing mainly on the distinction between living (e.g. plants, fruit and vegetables, animals) and nonliving things (e.g. vehicles, tools). Specifically, two main classes of models have been developed. The first class are the *neural structures principle* models according to which our brain is organized based on neurological constraints, with specific neural correlates being involved in the representation of semantic categories (e.g. Warrington & Shallice, 1984; Caramazza & Shelton, 1998). The second class contains models that adhere to the *correlated structure principle* according to which semantic memory is organized based on the co-occurrence of certain object properties (e.g. McClelland & Rogers 2003, Tyler & Moss, 2001). Theories within either class vary. In the following paragraphs, I will discuss the main theories belonging to the *neural structures principle* models, as Study 1 will largely focus on them and on the anatomical correlates of categories and I will use features as a tool to assess semantic knowledge, rather than measuring their intercorrelation.

1.3.1 *The Sensory-functional Hypothesis*

Warrington & Shallice (1984) described four patients with Herpes Simplex Encephalitis (HSE) as being disproportionately more impaired at recognizing living things than nonliving things in both the visual and the verbal modalities of stimulus presentation. This pattern was complementary to the one observed the year before in patient V.E.R. who was disproportionately impaired at recognizing nonliving things compared with living things (Warrington & McCarthy, 1983). This double dissociation led to propose the *Sensory-functional hypothesis* (SFH) according to which living things and nonliving things might be represented in different subsystems, one coding sensory properties and the other coding functional properties (Warrington & Shallice, 1984; Warrington & McCarthy, 1983). Specifically, damage to the sensory subsystem, better described by sensory/perceptual features, would lead to a deficit at recognizing living things. For instance, a plant is better recognized by relying on its colour, shape or texture. By contrast, damage to the functional subsystem should impair recognition of nonliving things that are more efficiently recognized by relying on functional features. For example, the concept of hammer is better captured by its prototypical use to stick nails in the wall.

Patients with HSE displayed an impairment at selectively recognizing living things (e.g., Gainotti et al., 1993; Capitani et al., 2003; Warrington and Shallice, 1984; Laiacona et al., 2003); since the ATLs are damaged in these patients, these regions have been proposed as being the site of (sensory) semantic knowledge. In contrast, patients with a disproportionate deficit at naming nonliving things, such as V.E.R (for a review see Capitani et al., 2003), have lesions entailing the parietal cortex that traditionally has been associated with functional semantic knowledge.

A computational model by Farah and McClelland (1991) also provided evidence in support of Warrington and Shallice's SFT. The authors found that visual features where those that more efficiently described living things, whereas the opposite was observed for non-living things, with features relative to function being significantly associated.

Further evidence in support of the sensory-functional model of semantic memory will be discussed in the following. The fMRI study by Chao and Martin (1999) showed that knowledge about tool use is represented in the posterior parietal cortex, whereas knowledge of sensory properties, such as colour and form, are represented in the ATL. Brambati et al. (2006), explored the neural correlates of semantic knowledge for living things and non-living things in a large sample of patients. Specifically, they correlated the scores at a picture naming task with structural T1 MRI images from 132 patients with PPA (comprehending SD and non-semantic PPA), patients with neurodegenerative disorders different from PPA and control subjects. The authors found that semantic memory for living things correlated with grey matter concentration in the right ATL, specifically in the parahippocampal gyrus, whereas naming nonliving things correlated with the left posterior middle temporal gyrus. Similar findings, showing that retrieval of sensory properties is coded in the ATLs, have emerged from other fMRI studies (see for instance Xiao et al., 2016. Mummery et al., 1998).

However, single-case reports have also provided conflicting evidence, showing that the living category may break down at a finer level. In fact, selective deficits for animals (Blundo et al., 2006, Caramazza & Shelton, 1998) and fruit/vegetables (Hart et al., 1983, Samson & Pillon, 2003), have been observed. A more recent account of the model (see Borgo and Shallice, 2001), has subsequently proposed that the sensory-functional hypothesis may apply to sensory-quality categories, such as edible substances, materials and liquids. Moreover, in order to account for the fact that knowledge about living things seems to break down in animals and fruit/vegetables, it has been proposed that fruit/vegetables are more efficiently described by colour with respect to animals (Cree & McRae, 2003), which would explain the discrepancies observed in the aforementioned studies.

1.3.2 *The Sensory-motor model or GRAPES*

The sensory-motor model (Martin, 1998; Martin, Ungerleider & Haxby, 2000) had its roots in the sensory-functional hypothesis, with two main differences: i) it proposes that motor information was the relevant one for describing tools; ii) it suggests that the organization of semantic memory is property-specific, rather than modality-specific. Its most recent update is the GRAPES model (*grounding representation in perception, action and emotion*) (Martin, 2016), which simply specifies that information concerning motor properties is not thought to be stored in primary sensory-motor regions, rather in regions that overlap with those. Specifically, the main claims of this model are two: first, Martin proposes that mental representations are grounded in brain regions overlapping with those supporting perception and interaction with object concept. For instance, information about the colour of an object should be stored in regions overlapping with visual regions for colour processing, and information regarding its shape should be stored in regions close to those for the processing of shapes. This proposal builds on the results derived from research conducted on congenitally blind individuals (Amedi et al., 2007; Pietrini et al., 2004). In such studies, these individuals have been found to be able to recognize tactically objects that they had never seen, and the region involved in this process was the ventral occipital cortex (shape recognition). Two inferences can be derived from this evidence: 1) the organization of semantic knowledge is defined as property-specific; and 2) this property-specific information, is stored in an organized manner, according to the anatomical constraints of our nervous system. In addition, this model also accounts for the fact that information is continuously acquired about object concepts, and this gain of information updates what we already know about that object concept.

According to Martin, the semantic organization is thought to involve multiple regions, as many as are the properties. This claim is consistent with previous studies on both patients and healthy controls. For instance, an interesting neuropsychological double dissociation supports the proposal of a property-specific organization. On the one hand, *achromatopsia* is the inability to perceive a colour due to an acquired blindness, with the ability to imagine a colour being intact. The lesion site associated with this condition is typically the lingual gyrus in the occipital lobe, a visual area (e.g., Shuren, Brott, Schefft, & Houston, 1996). On the other hand, *colour agnosia*, consists in the impairment of colour-related information, in the absence of visual deficits, and it is associated with the lesion the posterior ventral temporal cortex involved in semantics. Studies have shown that imagining a colour (Howard et al., 1998) or processing colour-related words (Paulesu et al., 1993), elicits activity in a region devoted to colour processing, the fusiform gyrus. Moreover, the same region is involved in judging hue differences (Beauchamp et al., 1999), as well as retrieving colour information in an object-colour matching task (Simmons et al., 2007), supporting the proposal that property-related information is grounded in regions situated within the system devoted to that type of processing.

1.2.3 *The Domain-specific Hypothesis*

Another influential view on semantics is organized, to account for the inconsistencies observed between living things breaking down (in animals and fruit/vegetables), and the predictions of the SFH, suggested that the semantic memory is organized based on how evolutionary pressure has shaped our brains (Distributed Domain Specific Hypothesis, DDSH, Mahon & Caramazza, 2011; Caramazza & Shelton, 1998). Thus, our knowledge is argued to be represented in the brain in categories, rather than modalities, that are relevant for our survival: animals, plants, conspecifics and, perhaps, tools. In this view, a lesion causing a deficit in one of these categories should impair all types of knowledge contributing to that particular category. The authors also argue that categories such as animals and plants, may entail the ‘fight or flight’ mechanism and, therefore, limbic regions should also be involved in semantic knowledge regarding these specific categories (see Caramazza & Shelton, 1998).

In addition, more recently, the authors proposed that the recognition of an object cannot depend on a single brain region but on the connections of this region with other brain regions. In this view, it is more appropriate to talk about a network that integrates the sensory input with its other modality-specific attributes, that is, motor, affective or conceptual. According to this recent account of the DSH, and consistently with the first version of the theory, the existence of innately dedicated neural circuits is restricted to those categories that are relevant for our survival or for our evolutionary history, and different domains are underpinned by different brain regions (e.g. visual and motor for tools, visual and affective for faces). In this view, recognition of items belonging to these categories should depend upon a broad damage of the whole network dedicated to that specific category, or to the ATLs.

1.2.4 *The hub-and-spoke and the connectivity-constrained cognition or C^3 Theory*

The C^3 theory is a recent influential view that extends the proposal of the *hub-and-spoke* model (Rogers et al., 2004; Patterson et al., 2007). The key concept of the hub-and-spoke model is a cross-modal network, with modality-specific knowledge regions, that are called ‘spokes’, encoding information about perceptual, motor and linguistic representations of objects. This information is proposed to converge in a pan-modal hub, consisting of the ventral portion of the anterior temporal lobe (vATL) (e.g., Chen, Lambon-Ralph & Rogers, 2017; Patterson et al., 2007; Rogers et al., 2004). Support to the role of the vATL as a semantic hub comes from several studies (e.g. Lambon Ralph et al., 2007; Binder, 2011; Visser and Lambon Ralph, 2011; Jackson et al., 2016), as well as to the existence of the aforementioned modality-specific spokes (Martin, 2007; Patterson et al., 2007; Barsalou, 2008; Binder & Desai, 2011; Kiefer & Pulvermuller, 2012).

The C^3 (*conncectivity-constrained cognition*) theory expands the hub and spoke model and reconciles well the other theories aforementioned in my thesis. This theory draws together intuitions from other existing theories, unifying them into a model of semantic memory that is supported by literature on patients and by neuroimaging studies. Indeed, this model has been shaped based on the observation of the different types of semantic deficits entailed by different disorders. Specifically, Chen, Lambon Ralph and Rogers (2017) carefully described the type of semantic deficits entail by pathologies such as HSE, SD, temporo-parietal tumor resection (TPT) and visual agnosia. HSE, as described in section 1.1.2, is characterized by a focal damage to the ATL. Based on the hub-and-spoke, this region is thought to entail semantic deficits that are not category-specific. However, these patients do display category-specific deficits for living things, as reported by Warrington and Shallices (1984), for instance. This deficit is argued to be due to the perceptual crowding of the shared features between exemplars of this category and, in the asymmetric variant of the disease, to the involvement of the white matter connecting the ATL to the posterior FG. SD is also taken up as an example: in fact, the initial selective damage of the ATL causes deficits that are not category specific. A deficit for living things may be observed at later stages of the disease, due to the degeneration of occipital regions (see Rogers et al., 2004). Finally, TPT confirmed the existing literature about the involvement of the parietal cortex in semantic knowledge of artefacts (see, for instance, Chao and Martin, 2001) and a similar pattern for animals was observed when simulating the impairment due to the anatomical damage typical of visual agnosia (see Roberts, 2009; Humphreys and Riddoch, 2006), that is a disconnection between the lateral occipital cortex and the FG. In summary, this study shows what predicted by the model, that when the ATL is selectively damaged, this fails to entail a category-specific deficit, because its role is to integrate knowledge converging from other regions in the brain storing modality-specific knowledge.

Moreover, the authors argue that, besides relying on anatomical constraints, semantic memory depends upon learning and experience as well. For instance, compared to animals, that have been to be represented in perceptual and compact regions (such as the FG), tool concepts are likely to be represented by a set of interacting regions because they engage more knowledge concerning praxis (such as IPL and SPL). Indeed, the authors trained a neural network simulating both the connections between regions that are thought to be crucial for specific categories and learning through an error-driven approach with deep learning. Results show that regions previously known to process information about artifacts involves mpFG, pMTG, IPL and SPL, whereas regions associated to information about animals involves the lateral portion of pFG, suggesting that semantic memory is both connectivity-constrained but also by learning and experience.

The debate about how semantic knowledge is organized in the brain is still far from being closed and, in the next section, I am going to show how the category of food can be employed to shed light on the organization of semantic memory.

1.4 *Semantic Memory for Food*

All the hypotheses about how semantic memory is organized on the brain, described in Chapter 1, were mostly based on the observation of category-specific deficits in recognizing animals, and plants (living things) and utensils (nonliving things). In these hypotheses, however, the category of food has been largely overlooked, despite its extreme biological relevance for survival and its hedonic value (LaBar et al., 2001). Our ability to distinguish food from non-food is likely to have its own neural correlates (Small et al., 2004), as suggested by neuroimaging studies (for a review see Rumiati and Foroni, 2016). What is still missing is a study that identifies eventual features that might characterize different types of foods and their brain correlates.

1.4.1 *Semantic deficits for food*

In Chapter 1, I described the single case studies reporting selective deficits for either living things (animals, plants) or nonliving things (utensils, vehicles), that were of critical importance in defining prominent models of semantic memory. Recognition of food has previously been found to be impaired in patients with semantic deficits. In brief, patients were described with impaired recognition of food, associated with impaired or spared recognition of animals (see Borgo & Shallice, 2001; Gainotti & Silveri, 1996; De Renzi & Lucchelli, 1994; Sheridan & Humphreys, 1993; Sirigu et al., 1991; Warrington & Shallice, 1984), or with impaired recognition of animals

(Warrington & McCarthy, 1983). **Table 1.1** describes these cases and is divided in two parts. **1.1a** summarizes the cases with a deficit affecting the semantic knowledge of food observed together with a deficit for living things, such as animals and plants; Table 1.1b summarizes the patients with a deficit affecting their knowledge about food as well with a deficit concerning nonliving things (see Rumiati & Foroni, 2016). Note that, the food items that were used in the assessment of the patients reported in the **Table 1.1** were often different, and include both natural, raw food, such as fruit and vegetables, and transformed, manmade processed food such as pasta or hamburger. This distinction is extremely relevant for my dissertation and will be discussed in detail shortly.

a)

BOTH NATURAL AND TRANSFORMED FOOD IMPAIRED RECOGNITION

Patient	Age	Gender	Authors	Aetiology	Lesion Site	Impaired	Spared
I.N.G	44	F	Warrington & Shallice, 1984	HSE	T bilateral	Food, Animals	vehicles, toys, tools, clothes, body parts, intruments
J.B.R.	23	M	Warrington & Shallice, 1984 Bunn et al., 1997	HSE	T bilateral	NF, TF, animals insects	vehicles, toys, tools, clothes, body parts, intruments
K.B.	60	F	Warrington & Shallice, 1984	HSE	T bilateral	Food, Animals	vehicles, toys, tools, clothes, body parts, intruments
S.B.Y.	48	M	Warrington & Shallice, 1984	HSE	T bilateral	Food, Animals	vehicles, toys, tools, clothes, body parts, intruments

L.A.	34	F	Silveri & Gainotti, 1988; Gainotti & Silveri, 1996	HSE	T bilateral L>R, hippocampus amygdala	NF, TF, animals flowers, musical instruments	body parts, objects
S.B.	19	F	Sheridan & Humphreys, 1993	HSE	Left T edema	NF, TF, animals drinks	objects
FELICIA	49	F	De Renzi & Lucchelli, 1994	HSE	Left FT insula	NF, TF, animals flowers, professions	clothes, tools, kitchne body parts, buildings furniture
F.B.	19	M	Sirigu et al., 1991	HSE	T bilateral	Food, Animals	tools
M.U.	30	M	Borgo & Shallice, 2001	HSE	T bilateral, Frontal bilateral	NF, TF, animals liquid substances, materials	objects

b)

BOTH NATURAL AND TRANSFORMED FOOD SPARED RECOGNITION

Patient	Age	Gender	Authors	Aetiology	Lesion Site	Impaired	Spared
K.E.	32	M	Hillis et al., 1990	Stroke	left F-P	body parts, furniture vehicles, animals clothing	NF, TF
V.E.R.	68	F	Warrington & McCarthy, 1983	Stroke	left F-P	Objects	Food, flowers, animals

Table 1.1 a, b. *All the patients described in these studies were affected by HSE and displayed a disproportionate impairment both at the category of living things, comprehensive of plantlife (flowers, fruit, vegetables) and animals and the category of food, which was, then, assimilated to living things by the SFH*

Based upon these initial observations, the proponents of the SFH hypothesized that food, together with animals, was processed as living things (Warrington and Shallice, 1984). However, the SFH has been challenged by the observation of patients with spared food recognition, while recognition of animals was disproportionately impaired, as in patient K.E., and by patients showing the opposite pattern of impairment, as in patient J.J (Hillis et al., 1990, see **Table 1.1b and Table 1.2a**, as reported in Rumiati & Foroni, 2016). This result is more in line with the DSH, according to which food may represent a domain per se, rather than being either living or nonliving, also due to its evolutionary relevance (Caramazza & Shelton, 1998; Mahon & Caramazza, 2011). However, in contrast with the DSH, food recognition can break down in a finer grain, as single case studies have shown (see **Table 1.2b**; for a review, see Rumiati &

Foroni, 2016; Capitani et al., 2003). These cases led to the hypothesis that natural, unprocessed food may be recognized according to its sensory features (as natural things), while food that has ben organoleptically transformed may be recognized according to its functional attributes (as non-living things) (see Rumiati et al., 2016).[1] This should account for the type of deficits observed for the patients reported in **Table 1.2**.

a)

NATURAL AND/OR TRANSFORMED FOOD DISTINCT FROM ANIMALS

Patient	Age	Gender	Authors	Aetiology	Lesion Site	Impaired	Spared
J.J.	67	M	Hillis & Caramazza, 1991	Stroke	Left T, basal ganglia	NF, TF, body parts furniture, clothing	Animals, vehicles
E.W.	72	F	Caramazza & Shelton. 1998		Left posterior F and P	Animals	NF, body parts, kitchenware clothes, tools

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[1] This is partially in line with what proposed by Borgo and Shallice (2001; 2003) according to whom sensory information, such as colour and texture, but not shape, may affect the recognition of both living things, as already proposed, and some sensory-quality categories (e.g., materials, edible substances, drinks).

b)

NATURAL FOOD IMPAIRED AND TRANSFORMED FOOD SPARED

Patient	Age	Gender	Authors	Aetiology	Lesion Site	Impaired	Spared
M.D.	34	M	Hart et al., 1983	Stroke	Left F, basal ganglia	Fruit/vegetables	vehicles, toys, tools, animals, food, clothes
P.S.	43	M	Hillis & Caramazza, 1991	TBI	Bilateral FT haematoma	Animals, vegetables	food, body parts, clothes vehicles, furniture

Table 1.2 a) *All the patients described in these studies were affected by HSE and displayed a disproportionate impairment both at the category of living things, comprehensive of plantlife (flowers, fruit, vegetables) and animals and the category of food, which was, then, assimilated to living things by the SFH. b) Patient MD and patient PS displayed a pattern of impairment suggesting that food may break down at a finer grain. MD developed, after a stroke causing a damage in the left frontal cortex and in the basal ganglia, a deficit in the recognition of fruit and vegetables. However, the ability to recognize vehicles and manmade objects and other types of food was intact. PS showed the opposite behavioural pattern: after a traumatic brain injury, the patient, suffering from a bilateral frontotemporal heamatoma, was impaired at recognition of animals and vegetables, whereas the ability to recognize manmade objects and vehicles and other type of foods was spared.*

1.4.2 *Recent research on the natural/transformed distinction*

The sensory/functional hypothesis of natural/transformed food is supported by recent research showing that recognition food may break down according to this natural/transform dimension. For instance Rumiati et al. (2016) enrolled patients with primary progressive aphasia (PPA), Alzheimer's disease (AD) and healthy controls to investigated semantic memory for natural and transformed food, and for living and nonliving things. Results showed that, overall, food tends to be recognized better than non-food, consistently with a greater resilience to brain damage for food, in virtue its biological importance. Patients performed worse than controls, however, PPA's accuracy was lower than that of patients with Alzheimer's disease. PPA, in addition, failed to show any category-specific pattern of impairment. Interestingly, patients with Alzheimer's disease exhibited a worse performance for natural versus transformed food, and for living versus nonliving things, consistently with the SFH and with the hypothesis that such patients are more impaired with the living category (see Silveri et al., 1991). Moreover, sensory knowledge proved to be more effective in recognizing food overall.

That food might be recognized depending on whether it is natural or transformed comes has been provided in a study by Pergola et al. (2017) have analysed the N400 component in healthy participants. N400 is a negative deflection of the event related potential (ERP) that emerges 200 to 300 ms after stimulus onset and peaking at 400ms. This component is largely used in EEG studies on semantic memory, and is recognized as a reliable indicator of semantic incongruency (for a review, see Kutas and Federmeier, 2011). Indeed, several studies have documented this effect when violations along the meaningful/nonmeaningful dimensions were made, such as presenting syntactically correct sentences with a semantic violation as in 'I like my tea with milk and tights'. The N400 component has been observed in response to meaningful/nonmeaningful dimensions with isolated words, pseudowords, faces and pictures (for a review see Lau, Philips and Poeppel, 2008) and in lexical-semantic priming experiments, related items showed reduced N400 amplitudes relative to unrelated items (see Kutas and van Patten,1998).

In the study by Pergola and colleagues presented congruent trials with images of natural food paired with sentences describing a sensory property and transformed food paired with sentences describing the functional properties, and incongruent trials pairing natural food with functional sentences, and transformed food with sensory sentences. The N400 was found to be greater for incongruent trials, that is, as described above, when natural food images were paired with functional properties and viceversa transformed food were paired with sensory properties. This confirms the hypothesis that natural food is assimilated to living things, being more efficiently described by sensory properties, whereas transformed foods are more efficiently described by functional properties, as it happens for utensils. Moreover, using EEG, Coricelli et al. (submitted) have shown that the brain tracks the difference between natural and transformed foods as early as at 130 ms, with stimuli being matched for calorie content, discarding the hypothesis that this peak may reflect a difference in the energetic value (which has been already tested elsewhere, see Toepel et al., 2009). Accordingly, based on the above review evidence, we argue that food recognition can be instrumental in testing models of semantic memory, capitalizing on the double nature of food.

In the following chapters, I will describe four studies that add further fuel to this hypothesis by showing that natural and transformed food have neural correlates of their own; I will also suggest a food network associated with food recognition, and that semantic memory for food can shape our behaviour and it can, in turn, be shaped by our life-long experience with food items.

Chapter 2

Brain signatures of lexical-semantic knowledge of food

2.1 Introduction

As outlined in Chapter 1, the study of category-specific semantic impairments in patients with brain lesions has fuelled the debate on how semantic memory is organized. I also argued that food is a key category that can be used to test prominent models of semantic memory, because food shares sensory properties with living things and functional properties with nonliving things. Thus, according to the sensory-functional theory, if concepts are differentially organized in sensory and functional properties, then recognition of natural food, as living items, should rely more on sensory properties, while recognition of transformed food, as nonliving things, should rely more on functional properties. In addition, natural food should be represented in brain regions storing sensory information, and transformed food in regions storing functional knowledge. Specifically, we expect regions such as the lateral occipital cortex (LO) and the fusiform gyrus (FG), as well as other areas involved in sensory processing (e.g., Chao, Haxby, Martin, 1999; Perani et al., 1999), to be associated with knowledge regarding living things and natural food. On the other hand, for recognition of nonliving things and transformed food, we expect an involvement of the inferior frontal gyrus (IFG), the left posterior middle temporal gyrus (pMTG), as well as the superior temporal gyrus (STG), previously associated to knowledge of tools (e.g. Chao & Martin, 2001; Vingerhoets, 2008; Perani *et al*., 1999). This organization should be mirrored in the involvement of white matter tracts. If this turns out to be the case, it would strongly support the view that semantic memory is organized in sensory/functional subsystems.

In order to test these hypotheses, in the present study we assessed semantic knowledge of food (natural and transformed) and non-food (living and nonliving things) in patients with behavioural frontotemporal degeneration (bvFTD), primary progressive aphasia (PPA), Alzheimer's disease, and in healthy controls, using several ad hoc devised tests, and correlated their performance to the local grey matter concentration and the integrity of the white matter tracts.

2.2 Materials & Methods

2.2.1 *Participants*

Fifty-eight right-handed participants took part in the study: ten bvFTD patients (five females), eleven PPA patients (four females), eleven Alzheimer's disease patients (six females), and twenty-six healthy controls (sixteen females). Participants were matched for gender (χ 2 = .82, p = .83), age and education (*ps* = ns) across the four groups (see Appendix A1). Patients were diagnosed by clinical neurologists, based on neuropsychological and neurological evaluations. MMSE (Italian norms from Measso et al., 1993), Addenbroke's Cognitive Examination revised (Pigliautile et al., 2011), the Frontal Assessment Battery (FAB, Apollonio *et al.*, 2003) were administered to all participants; in addition, patients were administered a naming task (Laiacona *et al.*, 1993). Moreover, when possible, also the Pyramid and Palm Trees test (see Gamboz *et al.*, 2009, for normative data on the Italian population), the Camden recognition memory test for faces (Warrington, 1996) (see Table 2.1). Participants read and signed an informed consent. Testing was conducted in accordance to relevant guidelines (Helsinki declaration, 2013) and the study was approved by SISSA ethics committee.

2.2.2 *Experimental Tasks*

Participants were administered with four behavioural experimental tasks following the same order: categorization task, confrontation naming, word-picture matching and the sensory/functional association task. Their responses were recorded by the experimenter on a scoring sheet. The order of items was first randomized within each task and then administered with the same order across participants. Tasks were presented on a computer screen by using Microsoft Powerpoint presentations. Before each task, participants performed an 8-trial practice in order to familiarize with the task, and these responses were not included in the analyses.

Task 1 – Confrontation Naming

This task tests the ability to retrieve the names of visually presented pictures. Each of 72 pictures was presented individually at the centre of the computer screen and participants were asked to name it in a self-paced way. The confrontation naming detects the presence of eventual perceptual, lexical or semantic deficits.

Task 2 – Word-picture matching

This task aims at evaluating the participants' ability to understand nouns. In each of the 72 trials, the participant is required to choose the target picture corresponding to the word uttered by the experimenter among five distractors. This task evaluates the lexical-semantic processing of words and, compared to the confrontation naming, it does not require a verbal output.

Task 3 – Categorization

This task evaluates the participants' ability to categorize stimuli. In each of 144 trials (organized in 4 blocks), two pictures were presented, next to each other. Participants were asked to decide whether the two items belonged to the same category or to different categories. In the same trials, two foods or two non-foods were depicted, whereas in the different trials, one food and one non-food item.

Task 4 – Sensory/functional matching task

This task was specifically designed to test whether pairing a word representing a sensory property with a natural food, and pairing a word describing a functional property with transformed food (congruent trials) would improve accuracy compared to trials in which natural food and transformed food were paired with functional and sensory properties, respectively (incongruent trials). In addition, for each item we presented two filler trials, in which incorrect congruent and incongruent pairings (e.g. cauliflower – sweet, lasagne – breakfast) were presented, in order to avoid participants to respond always in the same manner to the question. Such trials were not considered for the behavioural analyses. The task (36 trials) consisted in two blocks, one pairing words describing sensory features (e.g. 'sweet') and the second block pairing words describing functional features (e.g. 'lunch') with either natural or transformed foods. The best congruent and incongruent pairings, as well as the most suitable words, were selected with a pilot study (see Appendix A1).

2.2.2.1 *Stimuli.*

For Tasks 1-3 seventy-two images depicting food and non-food items were selected from FRIDa database (Foroni *et al*., 2013), with a resolution of 330×330 pixels and colour coding RGB. Non-food stimuli were both living (N = 18) and nonliving things (N = 18), and food stimuli both natural (N = 18) and transformed foods (N = 18). Stimuli were matched for letter length and written frequency across all four categories (CoLFIS, Bertinetto *et al*., 2005). For Task 4, 14 images of food stimuli only were selected (FRIDa, Foroni *et al*., 2013), with 7 natural foods and 7 transformed foods, matched for number of letters, written frequency, arousal and valence. Natural and transformed food stimuli were matched for calorie content (see Appendix A2).

2.3 Data Analysis

2.3.1 *Behavioural analyses*

Independent samples t-test or, when necessary. Mann Whitney U tests were conducted to compare the neuropsychological performance of each patients' group and healthy controls.

Performance on the naming task was analysed using a repeated-measures ANOVA with *Group* (bvFTD, Alzheimer's disease, PPA, healthy controls) as between-subjects factor, *Type of item* (food, non-food) and *level of artificiality* (sensory, functional) as within-subject factors, with multiple comparisons being Bonferroni-corrected. Performance of the four groups on the categorization task and the word-picture matching task was analysed using the Mann-Whitney tests, as data were not normally distributed. Differences between food and non-food and natural and transformed food within each of the groups were analyzed using the Wilcoxon rank sum tests. Results from these latter three tasks are reported in the Appendix A3 and A4. Performance on the sensory-functional matching task was analysed with a repeated-measures ANOVA with *Group* (bvFTD, Alzheimer's disease, PPA, healthy controls) as between-subjects factor, *Type of Food* (natural, transformed) and *type of property* (sensory, functional) as within-subject factors, with multiple comparisons being Bonferroni-corrected.

Regression analyses were conducted between naming performance and caloric content, concerning food items.

2.3.2 *Anatomical analyses*

Voxel Based Morphometry. A Voxel Based Morphometry (VBM) is a whole-brain MRI analysis technique that requires the use of a structural T1-weighted MRI image for each of the participants (Ashburner & Friston, 2000). All the images were acquired with a Philips 3T scanner at the 'S. Maria della Misericordia' hospital in Udine.

VBM was used to correlate local grey matter concentration with our variables of interest, which are participants' accuracies in the experimental tasks. Analyses were performed with SPM12 software package. First, the T1-weighed structural images were reoriented by setting the origin at the anterior commissure for each of the subjects. Subsequently, the preprocessing was carried out by segmenting the images in grey matter, white matter and cerebrospinal fluid. Grey and white matter segments of our participants were, then, used to create a template brain, which consisted in an average of the brains (segmented grey and white matter) of our participants. After this step, the grey matter images obtained for each of the subjects after the segmentation step were co-registered to the template and normalized to the MNI space and smoothed with a 8-mm isotropic Gaussian kernel.

Once completed the preprocessing, we used a covariates only statistical model, with gender and age as nuisance covariates and the accuracies in the experimental tasks as covariates of interest. Moreover, we also performed conjunction analyses (Friston, Penny, Glaser, 2003), in order to test which brain regions correlated with the scores at two categories together. Total intracranial volume for each of the subject was used as global normalisation in the analysis, for which we chose the ANCOVA option.

Tract based spatial statistics. The analysis of the diffusion tensor imaging data was performed using the FMRIB diffusion toolbox (FSL software, Smith *et al.*, 2004; 2006). First we generated binary masks for each of the images of our participants, by means of the brain extraction tool (version 4.1) (Smith, 2002), with fractional threshold = 0.1 and vertical gradient, g = 0. Subsequently, we performed the eddy current correction on the original images of each of our participants. Then, using the brain extracted mask and the b value and the b vector, we obtained fractional anisotropy (FA) for each of our participants.

Upon completion of the preprocessing, the brain extracted FA images of all participants were used as the input images for TBSS processing (Smith et al., 2006). First, we performed a voxelwise nonlinear registration of all participants' FA to a standard image provided by the FSL software. The FA images obtained in this way were, then, averaged to create a mean FA image, which was subsequently implied to create a skeleton of the tracts of white matter. This procedure labels the skeleton voxels with maximum FA intensity along the perpendicular direction (breath) of a white matter tract; we used a FA threshold of 0.3 to distinguish grey from white matter (Smith et al., 2007). Subsequently, the mean skeleton was applied to the registered FA image of individual participants. Then, we projected the maximum FA values on the skeleton for our subsequent statistical analysis by using the SPM basic models function to design a covariates only statistical model, mirroring the model used to analyse the VBM data (e.g. Chang et al., 2012). In order to identify, based on the statistical parametric map obtained, the white matter tracts involved, the diffusion tensor imaging-based atlases by Thiebaut de Schotten *et al.* (2011a, b) and by Oishi *et al.* (2008) were used.

2.4 Results

2.4.1 *Behavioural analyses*

Patients were all outperformed by healthy controls at the MMSE [bvFTD ($t_{10.34}$= -3.15, $p < .001$), Alzheimer's disease ($t_{12.39}$= -5.75, $p < .001$), PPA ($t_{10.68}$= -4.61, $p = .001$)] and the FAB [bvFTD (t_{10}= -4.9, $p = .001$), Alzheimer's disease ($t_{11.78}$= -4.77, $p < .001$), PPA ($t_{10.10}$= -5.90, $p < .001$)].

Moreover, bvFTD show a higher MMSE score with respect to PPA patients ($t_{16.7}$= 2.2, p =.04).

bvFTD patients performed worse than controls at each of the ACE-R subscales administered (ps <.03), except for the subscale of the ACE-R testing language (t_{9}= -1,7, p = .12). Alzheimer's disease patients did not perform significantly worse than controls only at the ACE-R visuospatial subscale (t_{10} = -1.1, p = .3), whereas PPA patients performed worse than controls at all of the subscales (ps < .001). bvFTD patients performed better than Alzheimer's disease patients only at the ACE-R memory subscale (t_{19} = 2.2, p = .04), better than PPA patients at the fluency (t_{19}= 2.6, p = .02), language (t_{19} = 3.7, p = .002), visuospatial (t_{19}= 2.8, p = .01) and total (t_{19}= 2.9, p = .01) scores of the ACE-R. Moreover, PPA performed worse than AD at the subscales of fluency (t_{20}= 2.6, p = .02) and language (t_{12}= 4.7, p = .001), and also at the total score (t_{20}= 2.11, p = .05).

We also compared patients only at the Pyramid and Palm Trees Test, at the Camden test and at a picture naming. However, not all of our patients were able to complete these tests (see table 1). bvFTD and Alzheimer's disease patients did not differ significantly at any of these tests (ps > .05), whereas PPA patients performed significantly worse than bvFTD (t_{10}= 4.25, p = .002) at the PPTT. Moreover, PPA patients' naming performance (Laiacona) was significantly worse than both bvFTD (U= 10.5, p = .03) and Alzheimer's disease (U= 7.0, p = .02). For details, see Table 2.1 (in the table, Alzheimer's disease is shortened as AD and healthy controls as HC).

Neuropsychological assessment: patients and healthy controls

	Group	N	Mean	Std. Dev	Std. Error Mean
MMSE	bvFTD	10	25.79	4.00	1.27
	AD	11	22.95	3.38	1.02
	PPA	11	20.61	6.60	1.99
	HC	26	29.96	1.73	0.34
ACE_orientation	bvFTD	10	15.80	2.37	0.81
	AD	11	14.18	2.04	0.62
	PPA	11	11.91	5.52	1.66
	HC	26	18.00	0.00	0.00
ACE_memory	bvFTD	10	14.00	5.98	1.89
	AD	11	8.91	4.37	1.32
	PPA	11	10.36	7.21	2.18
	HC	26	23.31	2.65	0.52
ACE_fluency	bvFTD	10	6.40	2.88	0.91
	AD	11	6.18	2.52	0.76
	PPA	11	3.18	2.79	0.84
	HC	26	11.63	2.13	0.42
ACE_language	bvFTD	10	23.40	4.22	1.33
	AD	11	24.09	1.97	0.59
	PPA	11	14.82	6.26	1.89
	HC	26	25.73	0.45	0.09
ACE_visuospatial	bvFTD	10	14.10	1.45	0.46
	AD	11	14.18	5.34	1.61
	PPA	11	10.27	4.20	1.27
	HC	26	13.92	0.39	0.08
ACE total	bvFTD	10	72.70	13.94	4.41
	AD	11	65.73	11.04	3.33
	PPA	11	50.55	21.08	6.36
	HC	26	94.81	4.56	0.89
FAB	bvFTD	9	12.00	2.74	0.91
	AD	11	11.64	3.38	1.02
	PPA	10	9.20	3.91	1.24
	HC	26	16.73	1.10	0.28

Neuropsychological assessment: patients only

		N	Mean	Std. Dev	Std. Error Mean
PPTT	bvFTD	7	48.14	4.06	1.53
	AD	2	43.50	7.78	5.50
	PPA	3	34.20	7.33	3.28
RMT	bvFTD	6	18.33	4.63	1.89
	AD	8	16.25	2.71	0.96
	PPA	3	17.40	2.70	1.21
NAMING (Laiacona)	bvFTD	10	58.30	5.38	1.70
	AD	10	57.80	3.85	1.22
	PPA	6	40.83	15.54	6.34

Table 2.1. *Neuropsychological information (mean, standard deviation and standard error of the mean) for each of our participants' groups.*

Task 1-Confrontation Naming. Thirty out of thirty-two patients performed this task (two patients were not able to complete it). The repeated measures ANOVA revealed *first*, a significant main effect of *Group* [$F_{(3, 33)} = 41.93$, $p < .001$, $\eta 2$ .71], with healthy controls outperforming bvFTD ($p < .001$, 1.85, 6.05, 95% of CI), Alzheimer's disease ($p = .006$, .34, 4.60, 93% of CI) and PPA ($p < .001$, 6.56, 10.94, 95% of CI) patients. PPA patients performed significantly worse than both Alzheimer's disease ($p <.001$, -8.02, -2.04, 95% of CI) and bvFTD ($p = .012$, -7.37, -0.62, 95% of CI) patients, whereas these latter groups did not differ from each other. *Second*, we observed a significant main effect of the *Level of artificiality* [$F_{(3, 33)} = 14.99$, $p < .001$, $\eta 2 = .23$], with artificial items (transformed food, nonliving things) being overall named better than natural entities (natural food, living things) (.37, 1.13, 95% of CI). *Third,* a significant *Type of item * Group* interaction was found [$F_{(3, 33)} = 2.92$, $p = .04$, $\eta 2 = .14$], with bvFTD patients naming food significantly better than non-food, whereas the other groups did not show this difference. Finally, we found a significant interaction *Type of item * Level of Artificiality* [$F_{(3, 33)} =23.42$, $p < .001$, $\eta 2 = .31$], with transformed food being named significantly better than natural food ($p < .001$, .56, 1.71 95% of CI), whereas the opposite pattern was observed for natural items, with nonliving things named worse than living things ($p = .01$, -1.53, -.21, 95% of CI).

Task 2-Word-picture matching. The Mann Whitney test showed that healthy controls outperformed patients, with PPA displaying a worse performance with respect to Alzheimer's disease and bvFTD patients (for details, see Appendix A3).

Task 3-Categorization. Twenty-nine out of thirty-two patients were able to complete this task. The Mann Whitney test revealed no significant difference at any of the categories considered between the three patients' groups (for details and Wilcoxon rank sum data see Appendix A4).

Task 4-Sensory-functional matching. The repeated measures ANOVA revealed *first*, a significant main effect of *Group* [$F_{(3, 34)} = 38.31$, $p < .001$, $\eta2 = .31$], with healthy controls outperforming bvFTD (p =.001, .29 .1.58, 95% of CI), Alzheimer's disease ($p = .003$, .22, 1.47, 95% of CI) and PPA (p =.05, 0. 1.23, 95% of CI). We found a main effect of *type of food* [$F_{(3, 34)} = 8.35$, $p = .006$, $\eta2 = .13$], with transformed food trials showing a better performance than natural food trials (.1, .32, 95% of CI). We also found a significant interaction *type of food * property* [$F_{(3, 34)} = 7.37$, $p = .009$, $\eta2 = .12$] with a better performance at natural food in the sensory block if compared to the functional block ($p = .01$, with .09, .68 95% of CI). In addition, a significant three-way interaction emerged between *type of food * property * group* [$F_{(3, 34)} = 5.60$, $p = .002$, $\eta2 = .24$], with bvFTD and PPA performing better at natural food trials in the sensory block (congruent), with respect to natural food trials in the functional block (incongruent), [($p = .002$, .44, 1.76 95% of CI) and ($p = .048$, .01, 1.27, 95% of CI) respectively]. Conversely, Alzheimer's disease patients do not show differences between congruent and incongruent trials for either natural, either transformed food, while controls perform almost at ceiling, not showing any difference.

Regression analysis

We carried out a regression analysis between naming performance and caloric content for food trials only. Interestingly, only in bvFTD calorie content significantly predicts naming transformed food accuracy [F (1,17) = 4.38, $r^2 = .216$, $p = .05$].

2.4.2 *Anatomical analyses*

2.4.2.1 *VBM*

Task1-Naming task. When naming natural food was considered, peaks ($p < .001$ uncorrected) were found in the right cerebellum, left and medial orbitofrontal cortex (OFC), left insular cortex and left inferior temporal gyrus (ITG), while naming transformed food correlated with the right superior temporal gyrus (STG) and right insular cortex (*p* <.001 uncorrected). Naming performance for living things peaked in the right cerebellum (*p* <.001 uncorrected), and for nonliving things correlated with two clusters in the posterior parietal cortex (PPC: the cuneuns and precuneus cortices, *p*FWE < .05). Performance at both natural food and living things peaked in the left cerebellum and a peak in the right lateral occipital cortex (LO), whereas naming both transformed food and nonliving things peaked in the pars orbitalis of the right inferior frontal gyrus (IFG). (Figure 1, A3 a for coordinates and cluster size).

Finally, the neural correlates of overall naming food comprised a significant cluster in the OFC and in the inferior temporal cortex (ITC) bilaterally, as well as a significant cluster in the medial posterior cingulate cortex (PCC), see Figure 2.1.

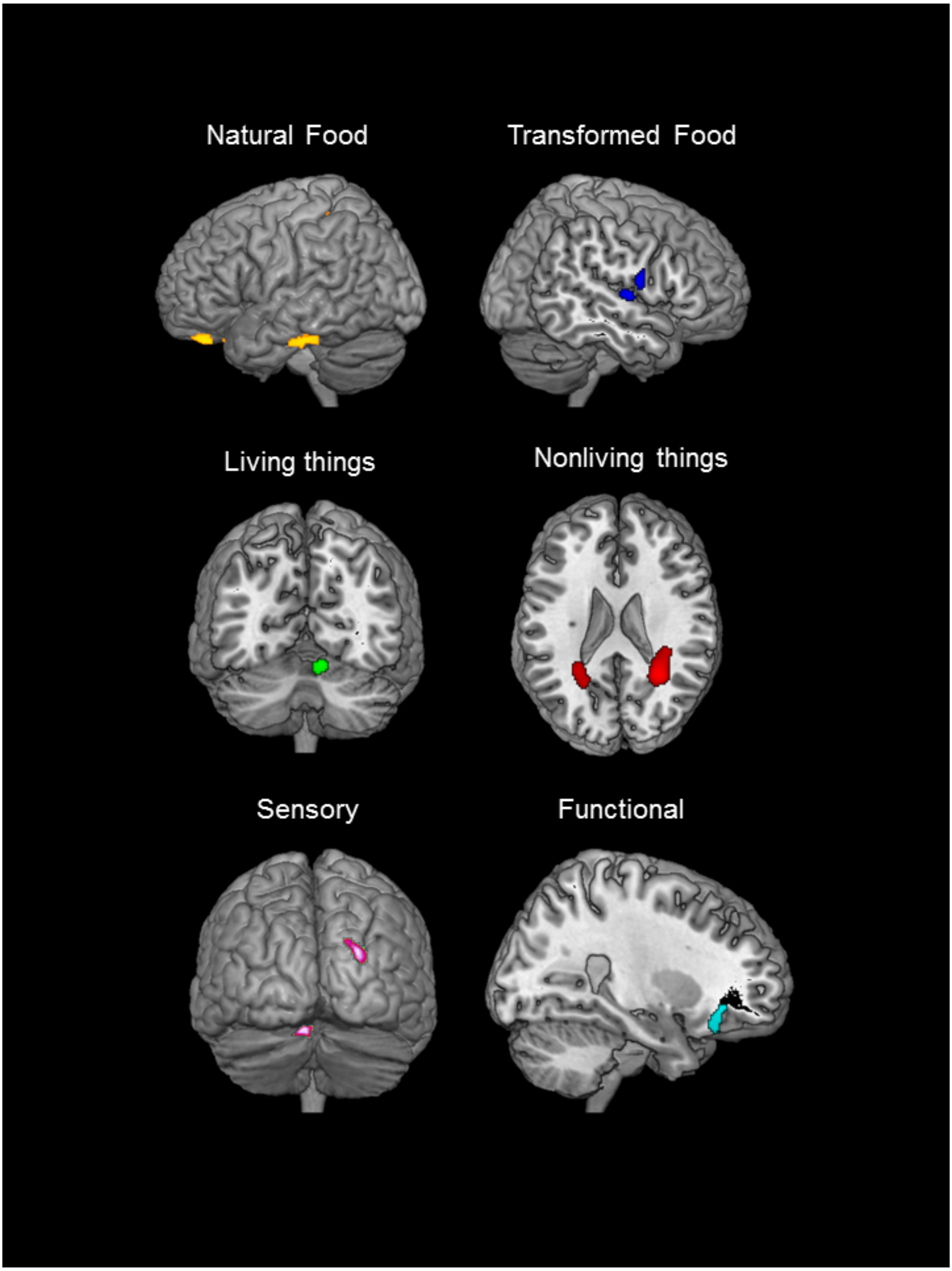


Figure 2.1. *Peak and clusters correlations for natural (yellow), transformed food (blue), living (green), nonliving (red) things, sensory (pink), functional knowledge (cyan).*

Task2-Word-Picture matching task. Recognition of natural food significantly correlated with large clusters in the cerebellum and in the left OFC bilaterally (*p*FWE < .05), consistently with what observed in the naming task. Recognition of transformed food, on the other hand, significantly correlated with clusters in the OFC, insular cortex, the caudate and medial subcallosal cortices in the right hemisphere, and with clusters in LO, extending to the angular gyrus (AG) and the posterior middle temporal gyrus (pMTG) in the left hemisphere. See Figure 2.2, and Table A6 in Appendix A.

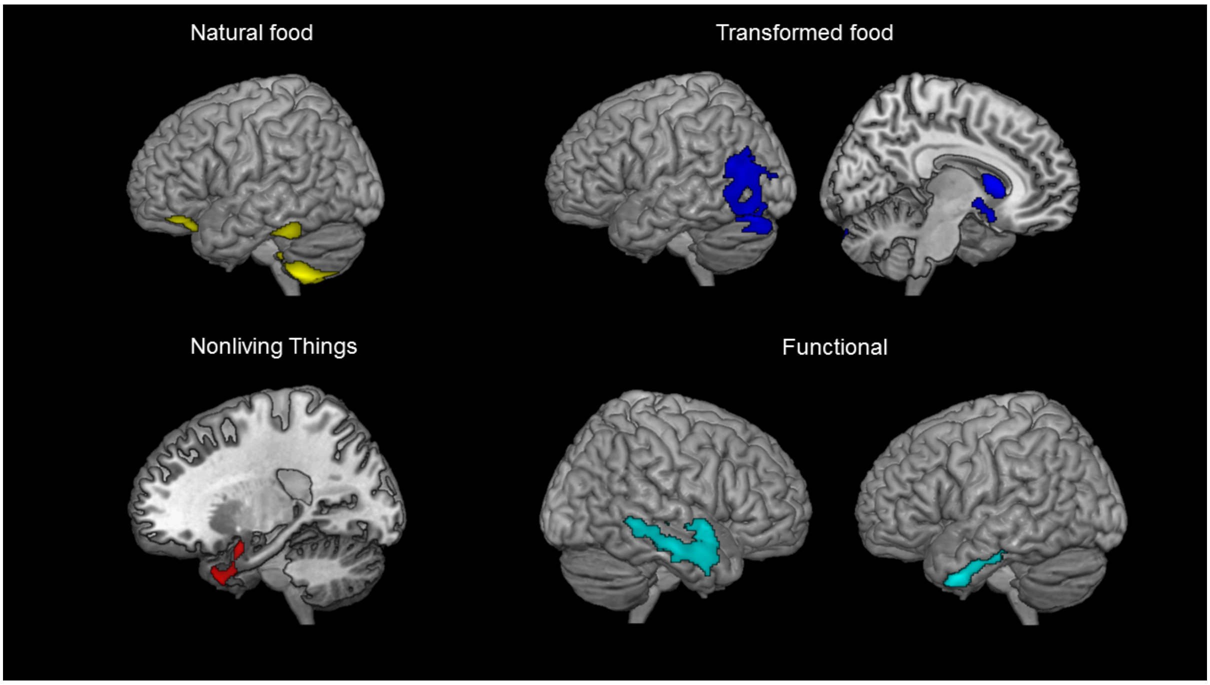


Figure 2.2. *Correlations for natural (yellow) vs transformed food (blue) and functional (cyan) emerged with the VBM for the word-picture matching task.*

While for living things no suprathreshold clusters emerged, recognizing nonliving things correlated with the left anterior STG (see Table A3 for coordinates and cluster size). Performance on both natural food and living things (‘sensory knowledge’) showed no suprathreshold correlation, whereas performance at both transformed food and nonliving showed a significant correlation in the MTG and in the medial cingulate gyrus and in the most anterior portion of the caudate nucleus (see A6). The neural correlates of overall recognition of food included a significant cluster in the inferior portion of the right cerebellum and in the anterior cingulate cortex (ACC) extending posteriorly (see Figure 2.3).

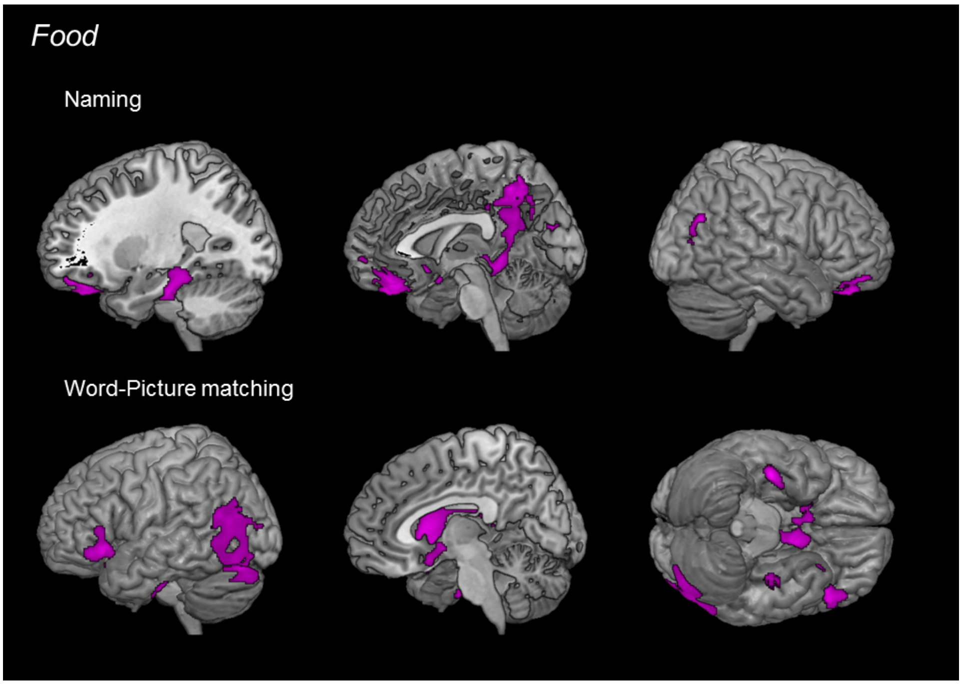


Figure 2.3. *Correlations for food (overall) in violet. In the upper quadrant, correlations between naming food accuracy and local grey matter concentration are reported. In the lower quadrant, I report the correlations with accuracy for food at the word-picture matching task.*

Task 3-Categorization task. This task was completed by twenty-nine out of thirty-two patients. Accuracy in trials assessing sensory knowledge (that is requiring to correctly categorize either natural foods as belonging to the same category, either living things as belonging to the same category, or natural foods as belonging to a different category as living things) significantly correlated (pFWE < 0.05) with clusters in the left anterior FG, and, bilaterally, in the OFC, in the PHG and in lateral occipital cortex (see figure in the Appendix A7a).

Task4-Sensory-functional matching task. This task included either natural or transformed food. In the sensory block, we found a peak in the right LO cortex ($p < .001$ uncorrected) for natural food, and one in the medial PCC for transformed food, a brain region usually found for semantic knowledge with visual/perceptual stimuli but related to a-modal sensory processing. In the functional block, natural food performance peaked in the thalamus, and transformed food correlated with a large cluster in the right temporal cortex (bilateral PHG, right FG) and the right OFC, regions implicated in processing the energetic value, that is a functional feature of food.

No significant correlation was found for sensory knowledge of food (natural+transformed), whereas functional knowledge of food (natural+transformed) correlated with the right temporal cortex, extending from the most anterior part to the temporo-occipital division of the MTG. See Figure in the Appendix A8a.

2.4.2.2 *TBSS*

Task 1-Naming task. Naming natural food significantly correlated with FA in the white matter subjacent the right superior parietal lobule (p uncorrected =.02), and naming transformed food significantly correlated with the left cingulum and corpus callosum (p uncorrected = .01), and the white matter subjacent the fornix in the right hemisphere (p uncorrected = .009). Naming living things correlates with the inferior fronto-occipital fasciculus (p uncorrected = .007) in the left, and the internal capsule and white matter subjacent the fusiform cortex in the right (p uncorrected < .03). For nonliving things, a correlation was observed with the right arcuate anterior segment (p

uncorrected = .001) and fornix (*p* uncorrected = .003), and in the corpus callosum bilaterally (*p* uncorrected =.02).

At the conjunction analysis, sensory knowledge correlates with the left corpus callosum, and the right arcuate segment (*p* FWE < .001) and corticospinal tract. Functional knowledge results in a correlation with the left inferior longitudinal fasciculus and arcuate posterior segment (*p* uncorrected = .002), and the right cingulum (*p* FWE = .01).

Concerning food overall, we found a correlation between naming performance and FA in both the left (*p* FWE ,< 05) and the right (*p* uncorrected = .01) splenium of corpus callosum, in the right corpus callosum and in the right cingulum (*p* uncorrected =.009), in the inferior longitudinal fasciculus bilaterally (*p* uncorrected < .01), in the posterior thalamic radiations bilaterally (*p* uncorrected < .01), in the right superior corona radiata (*p* uncorrected = .003, for details see Appendix A5b).

Task 2-Word-Picture matching task. For natural food, no correlation was observed, whereas recognition of transformed food correlated with FA in the right cingulum (*p* uncorrected =.006), as was the case for functional knowledge in the naming task. Recognizing living things correlated with the anterior corpus callosum bilaterally (*p* uncorrected = .001), whereas recognition of nonliving things correlated with FA in the right inferior longitudinal fasciculus, and in the posterior corpus callosum bilaterally (*p* uncorrected = .001), as in the naming task.

For ‘sensory knowledge’ no correlations were observed. Instead, ‘functional knowledge’ correlates bilaterally with FA in the bilateral corticospinal tract, with the cingulum (anterior portion) and the inferior frontal longitudinal fasciculus, as in the naming task (*p* FWE < .001, *p*

<.001 uncorrected, for details and other correlations see Appendix A6b). A correlation between FA in the right anterior cingulum and food recognition was observed ($p < .01$ uncorrected).

Task 3-Categorisation task. The white matter tracts identified confirmed the findings from the VBM analysis on this task as far as sensory knowledge is concerned: categorising living things and natural foods correlates with the left arcuate segment, left inferior longitudinal fasciculus and, with the anterior corpus callosum bilaterally. Full results are explored in the discussion section and are reported into detail in the Appendix A7b.

Task 4-Sensory/functional matching task. The white matter tracts identified confirmed the findings from the VBM analysis at this task. Results are explored in the discussion section and are reported into detail in the Appendix A8b.

2.3 Discussion

In this study, we assessed whether the knowledge about natural food and living things, and knowledge about transformed food and nonliving things, is organized according to sensory and functional properties, as posited by the sensory/functional hypothesis (SFH, Borgo & Shallice, 2001, 2003; Warrington & McCarthy, 1987; Warrington & Shallice, 1984). Our results across different tasks are well in accordance with the SFH, with correlations being found between atrophy of ‘sensory’ regions and reduced ability to recognize natural food and living things, and between atrophy of ‘functional’ regions and reduced ability to recognize transformed food and nonliving things. In the following, we will explain this pattern of results capitalizing on VBM and TBSS analyses.

2.3.1 *Natural food and living things*

One of the main results that emerged from the VBM analysis is that the reduced ability to recognize natural food mainly correlates with atrophy in sensory regions of the cortex such as LO, cerebellum, ITC, thalamus, and primary somatosensory cortex, which have been repeatedly found associated to sensory processing (Martin, 2016; Alitto & Userey, 2003; Chao, Haxby & Martin, 1999). The TBSS analysis showed that natural food recognition implicates the anterior arcuate fasciculus, which connects the posterior temporal cortex to the premotor cortex, close to the primary somatosensory cortex highlighted by the above mentioned VBM analysis. The anterior corpus callosum (CC) turned out to be also involved in natural food recognition. This tract is implicated in semantic processing and in sensory-motor tasks (for a review see Gazzaniga, 2000). We argue that the involvement of the above tract might depend on natural food still needing to be prepared, as also suggested by a recent EEG study (Coricelli et al., submitted). In this study with healthy individuals, a peak in the waveform was observed as early as at 130 ms from visual onset of natural food stimuli in the premotor cortex. Indeed, natural food is generally perceived as less readily edible than transformed food (FRIDa, Foroni et al. 2013).

Results from the VBM conjunction analysis, exploring recognition of both natural food and living things in each of our experimental tasks (Task1-3), confirm that this information is represented in sensory regions (LO, cerebellum, bilateral FG and ITC). Moreover, the analyses on Task 4 (requiring to judge the congruency of natural foods with matched sensory words) confirm and extends these results, showing a correlation between performance and atrophy in superior LO, AG, intracalcarine cortex, temporoccipital MTG regions. The TBSS conjunction analysis investigating lexical-semantic processes of both natural food and living things, showed an involvement, among other tracts, of the uncinate fasciculus, that connects the anterior temporal lobe with frontal regions. The uncinate fasciculus was also involved in Task 4, as described above, besides having previously been found involved in picture naming and word comprehension tasks (e.g., Catani et al., 2013).

When we analysed living things recognition alone, the VBM returned clusters in the right cerebellum, previously found involved in semantic processing (Xiang et al., 2003), but also in shape versus texture discrimination in semantic tasks (see Perani et al., 1999). Moreover, a correlation was observed with the inferior frontal occipital fasciculus (IFOF); this tract connects the occipital lobe (inferior and medial) with the inferior orbitofrontal cortex (Catani & Thiebaut de Schotten, 2008), a higher order region involved in assigning a behavioural value to a stimulus (e.g., a plant).

2.3.2 *Transformed food and nonliving things*

On the other hand, recognition of transformed food is mainly affected by atrophy in functional associated regions (e.g., IFG, MTG, AG, and STG among the others, see Martin, 2016). The TBSS highlighted the involvement of the cingulum bilaterally, a tract that has been associated to high calorie food processing (e.g. Frank et al., 2010), and the corpus callosum, which is involved in motor function (see Gazzaniga, 2000), in ideomotor apraxia in patients with Alzheimer's disease (Cimino-Knight et al., 2016), as well as in transfer of semantic information (Gazzaniga, 2000). Information about nonliving entities and transformed foods together (conjunction analysis) is coded in functional related regions (IFG, STG, MTG, posterior parietal cortex). Moreover, an impaired performance at matching functional words with transformed food items (Task 4) correlates mainly with atrophy of the PHG (bilaterally) and right ITC, regions previously associated to high calorie food processing (see van der Laan et al., 2011), thus supporting the hypothesis that the energetic content, being a functional information, is relevant for transformed food recognition. The TBSS conjunction analysis revealed that the left arcuate posterior segment and the right cingulum correlate with the recognition of transformed food and nonliving things together, consistently across different tasks, together with the right fornix and inferior longitudinal. In addition, we found a consistent involvement of the IL fasciculus. This white matter tract encompasses the regions we found involved in functional knowledge with the VBM analysis (MTG, STG).

Recognition of nonliving things correlates with atrophy of the precuneus cortex, that has been associated with tool information (see Chao & Martin, 2001) and of the STG (Perani et al., 1999). Consistently, the TBSS highlighted the involvement of the corticospinal tract bilaterally (Makin et al., 2009), the corpus callosum and the right fornix, which are both involved in the motor system (e.g., Qualls-Creekmore et al., 2017; Gazzaniga, 2000; Gaffan & Harrison, 1988), and the left inferior longitudinal fasciculus, involved in language processing (e.g. Ivanova et al., 2016; Mandonnet et al., 2007).

The present findings strongly support the initial hypotheses that food breaks down in natural and transformed foods, and that this distinction depends upon a sensory/functional organization of semantic memory. Interestingly, behavioural results of the sensory-functional task, that was intentionally designed to test the sensory-functional hypothesis using food as a test category, show that bvFTD and PPA patients, but not Alzheimer's disease patients, performed better in trials where sensory words are paired with natural food, probably due to the greater impairment at correctly categorizing natural food in the latter group. Moreover, these results are in line with recent studies, supporting the relevance of the natural/transformed food distinction (Pergola et al., 2017; Coricelli et al., submitted). In a recent ERP study, Pergola et al. (2017) found that, in normal weight individuals, the N400 component, usually modulated by semantic or syntactic incongruency, was larger for sensory primes paired with transformed foods and functional primes paired with natural foods. Moreover, it seems that the brain is able to track the difference between natural and transformed food as early as around 130 ms (Coricelli et al., submitted).

2.3.3 Food network

Our findings allow us also to identify the *overall brain network* of regions that represent the semantic knowledge about food. Specifically, patients' performance with food correlates with OFC e ITC - especially the posterior fusiform cortex - LO and the white matter tracts connecting these regions, such as the IFOF, connecting occipital areas with the OFC. This network (OFC, ITC, MTG, LO) is responsible, together with the temporal lobes, of processing information concerning food and, by assigning a value to the stimulus (OFC, e.g. Rolls, 2000), to plan how to act upon it (Otto & Eichenbaum, 1992; Schoenbaum et al., 2003). In fact, the IFOF puts temporal and frontal regions in communication. This result suggests that food may overall be processed as an extremely salient stimulus thanks to both sensory and functional properties.

Behaviourally, transformed food was overall named significantly better than natural food, consistently with other studies showing an advantage for this category (Rumiati et al., 2016; Aiello et al., under review). Another interesting result is that only bvFTD patients name food significantly better than non-food and that their performance, particularly with transformed food, significantly correlates with calorie content. This has been not observed with any of the other groups. This result is interesting and deserves to be further investigated, since bvFTD is known to cause several eating abnormalities, among which a strong preference for foods that are palatable and high in calorie content (for a review see Aiello et al., 2016).

Taken together, our results highlighted a set of cortical regions and white matter tracts involved in semantic processing, and add evidence on current models of semantic memory. They confirm and extend the SFH theory, since they show a set of regions (e.g. bilateral OFC, FG), connected by white matter tracts (e.g. the uncinated fasciculus), that are associated with sensory knowledge, and a set of cortical regions (IFG, STG, MTG, posterior parietal cortex), connected by white matter tracts (e.g. the arcuate fasciculus and the inferior longitudinal fasciculus), associated with functional knowledge.

Chapter 3

How experience modulates semantic memory for food: evidence from elderly adults and centenarians

3.1 Introduction

As discussed in the first chapter, semantic knowledge is shaped by experience. The studies that have tested this hypothesis have to date been limited to a specific instance of experience, that is *expertise*, defined as an exceptional skill or performance in a given domain that requires extensive training (for a review, see Hoffman' 1988). Expertise has also been found to entail specific patterns of neural activity, such as visual tuning, attention and memory (Haerl et al., 2010; Krawczyk et al., 2011; Bilalic et al., 2012, but, for a review, see Harel, Kravitz and Baker, 2013). Importantly, training may also be achieved in a limited amount of time, as apparent in the study by Gauthier and Tarr (1997) in which participants were trained to become experts on an invented category of objects, the *Greebles*. Compared to novices, experts' intensive training improved both accuracy and reaction times in a recognition task. Specifically, studies on expertise have investigated differences in semantic memory of experts - truly exceptional people at a specific domain of knowledge (Ericsson and Lehmann, 1996) (e.g., ornithologists, as in Rosch et al., 1976; Johnson and Mervis, 1997; Tanaka, Curran and Scheinberg, 2003; dog show judges, see Robbins and Mckone, 2007; car experts, as in Haxby, 2001 and chess experts, as reported by Krawczyk et al., 2011) - by comparing their performance to that of novices or even naïve participants - defined as *'totally ignorant of a domain'* in Hoffman's taxonomy. Expertise has been consistently found to enhance the ability to list features of exemplars at the subordinate level (e.g., 'robin' rather than 'bird'), to categorize and name exemplars of one's domain of expertise (e.g. Tanaka and Taylor, 1991), and to recognize complex[9] (Murphy, 1993) or novel objects (e.g. classes of objects created with algorithms, see Gauthier and Tanaka, 1997 and Op de Beeck et al., 2006).

However, individuals may possess considerable experience in a given domain and yet they might not be considered experts (Jacoby et al., 1986). Their *experience* corresponds to the knowledge they acquired over a number of years and, as such, it depends on the degree or frequency with which they have been exposed to a stimulus, rather than on the amount of training or practice.

As part of experience, cultural knowledge is likely to play a role as well in shaping semantic memory, as revealed by ethno-scientific studies. For instance, Dougherty (1978) observed that the Tzeltal population's recognition of plants and animals occurs at a more specific level (*folk genera*, e.g., oak) rather than at the superordinate level (e.g. *tree*). In addition, it has been shown that memory and similarity judgments were influenced by cross-cultural factors in two different tribes (Roberson et al., 2003).

Moreover, as different age-cohorts are likely to be exposed to different cultural and socio-economical conditions, some types of knowledge change across generations (Ryder, 1963; McCrae et al., 1999; Twenge and Campbell, 2001). In Poon and Fozard's study (1978), young and elderly adults were presented with objects that, compared to commonly familiar stimuli, were either obsolete and unfamiliar to young adults but familiar for elderly adults or, *vice versa*, too modern or unfamiliar to elderly adults but familiar to young adults. These authors found that naming of either group was influenced by the degree of familiarity with the object categories. Likewise, Bäckman and Karlson (1985) investigated the effect of datedness of information in two different age groups, by asking young adults and old adults questions about events that took place in the period from 1930 to 1930, and from 1970 to 1985. Similarly to Poon and Fozard's findings, they observed that elderly adults performed better on dated information and young adults on contemporary information. Taken together these results suggest that investigating semantic memory in different age-cohorts may be a good model for exploring the relationship between semantic knowledge and experience.

In the present study, instead of expertise, we assessed the role of experience in food recognition. To this end we administered different semantic tasks using food and non-food stimuli to participants of three different age cohorts (Young Old, aged 36-74, Old Old, aged 73-91, and Centenarians aged 100-108), and asked them to report on the dietary habits held throughout their life. We hypothesized that the participants belonging to the different age-cohorts went through different eating experiences that, in turn, differentially shaped their semantic memory about natural and transformed foods. In addition, the enrolment of the different age cohorts was expected to inform us on how semantic memory declines throughout aging. More predictions were made with respect to the type of task and the type of stimuli used. On one hand, based on the combined evidence on naming abilities and ageing, we expected particularly participants' naming to decline (see e.g., Au et al., 1993; Nyberg et al., 2003; Rönnlund et al., 2005, Gondo & Poon, 2007, Salthouse, 2014). As to the stimuli, we expected food representations being more resilient to detrimental processes, as recently demonstrated (Rumiati et al., 2016). Moreover, the full design of all tasks included also non-food items distinguished in living things and nonliving things.

3.2 Materials and Methods

3.2.1 *Participants*

The study enrolled 61 participants, belonging to three groups: 24 Young Old adults (13 F, age range 51-74), 19 Old Old adults (13 F, 75-91) and 18 Centenarians (12 F, 100-108). The inclusion criteria were: participants were not affected by neurodegenerative diseases, were native Italian speakers and had at least five years of education (except for three Centenarians, who did not reach 3 years of education). Participants were administered the MMSE (Folstein et al., 1975). A raw MMSE score > 25 was accepted for Young Old and Old Old adults, while a MMSE score > 20 was accepted for Centenarians. Three Centenarians had significantly lower MMSE scores, due to motor deficits and weakness that made it impossible for them to perform some tasks. However, they were screened by a neurologist and were diagnosed as cognitively normal according to the Criteria of the Diagnostic and Statistic Manual of Mental Disorders - IV (APA, 1994) (for the full screening protocol, see Tettamanti & Marcon, 2018; in press). Moreover, participants were screened for deficits affecting vision and deafness. Participants signed an informed consent form and were tested in accordance to the relevant guidelines for experiments involving human subjects as stated by the declaration of Helsinki (2014). The study was approved by SISSA's Ethics Committee.

3.2.2 *Experimental Tasks & Procedure*

All participants (N = 61) were administered with the following experimental tasks in a fixed order: categorization, picture naming and word-picture matching. Tasks were presented on a computer using Microsoft PowerPoint presentations controlled by the experimenter. The experimenter recorded the participants' responses on a dedicated scoring sheet. Before each task, participants performed an 8-trial practice in order to familiarize with the task.

3.2.3 *Experimental Stimuli*

Seventy-two images representing both food and non-food items were used in the study, with 18 photographs of transformed foods, 18 of natural foods, 18 natural non-edible objects and 18 kitchen utensils. All the images were selected from FRIDa database (resolution: 330×330 pixels; Foroni et al., 2013). The corresponding names were matched for number of letters and written frequency (see Rumiati et al., 2016). Age of acquisition and familiarity rates about these stimuli were derived from a norming study described in Rumiati et al. (2016).

Task 1 – Categorization

This task investigates the ability to categorize both food (natural and transformed) and non-food items. The experiment contained 144 trials arranged in 4 blocks, with each trial consisting in two pictures. Each block contained 36 trials, with half of the trials consisting two items belonging to the same category (N = 18, same trials), and the other half consisting of two items belonging to different categories (N = 18, different trials). Participants were asked to decide whether the two items were either two foods (natural or transformed) or two non-foods, or whether they were a food and a non-food.

Task 2 – Confrontation Naming

This task taps the ability to retrieve name of the item depicted in the picture. The same 72 pictures of the categorization task were used. Each image was presented at the centre of the computer screen. Participants were asked to name the picture.

Task 3 – Word -Picture matching

This task aims at evaluating the ability of an individual to comprehend nouns. On each trial, the experimenter uttered the name of an item and the participant was required to point to the target among six pictures of which five were distractors (a semantic distractor belonging to the same category as the target, and the remaining to the other categories). For instance, for natural food, in addition to the apricot as a target, and a mandarin as a semantic distractor, there were four more distractors: a knife, a leaf, a slice of pizza and a root. The six pictures were randomly placed in each of the six possible locations, three on the upper part of the screen and the other three on the lower part. A total of 72 trials were administered, with the target items being the same as in Tasks 1-2.

3.2.4 *Data Analysis*

Central tendency analyses were performed on the data for each of the tasks (B1).

For the naming task, we performed a repeated-measures MANCOVA with Group (Young Old adults, Old Old adults, Centenarians) as between-subjects factor, Type of item (food, non-food) and Level of artificiality (sensory, functional) as within-subjects factors and Education level and MMSE score as covariates. To further investigate the interaction group x Type of item x Level of artificiality, we ran two MANCOVAs Group x Level of artificiality, separately for the food and non-food type of stimulus. Multiple comparisons were Bonferroni-corrected. For the categorization and the word to picture matching tasks we ran, due to the lack of normality of the data, Mann-Whitney tests to compare the overall performance of three groups and Wilcoxon rank sum tests to investigate the differences in the performance at food and non-food and natural and transformed food within each of the groups.

In addition, we also analysed the data using generalized linear mixed models with binomial family (see, for instance, Jaeger 2008), with accuracy as dependent variable, age group x stimulus type as fixed factor, education as a covariate and id as random factor for food vs. non-food. In order to explore the differences between natural and transformed food, we used a similar model, with age group x food type as fixed factor. Multiple comparisons were Bonferroni corrected and post-hoc analyses were performed with a Tukey test.

A series of regression and correlation analyses was calculated between naming of food and the psycholinguistic variables (frequency of use, word length, age of acquisition and familiarity) in each of the groups of participants in order to understand the role of each of these variables during aging. In addition, for food items only, naming performance was also correlated with the caloric content. These analyses focused on food only since food is the category for which, even thought we could not manipulate expertise, we could assess the level of experience with.

For what concerns the naming task, regarding food items, we also analyzed semantic error types (anomias, semantic and verbal paraphasias, visual errors, good circumlocutions, poor circumlocutions) to investigate their lexical or semantic origin.

Finally, for both natural foods (raw fruit and vegetables) and transformed foods (pasta, sweets and cakes, processed meats), we asked Centenarians and a subset of our younger participants (aged 70-91) how 'often', 'seldom', or 'never' they consumed a particular item in their life. The aim was to investigate whether eating habits influence food recognition. Based on these data, a bivariate linear regression was carried out to investigate the quantitative relationship between naming performance and dietary habits and the bootstrap method (Efron & Tibshirani, 1993) was applied to the regression coefficient to estimate the confidence interval. All analyses were performed with statistical software PASW Statistics for Windows, Version 18.0. Chicago, SPSS Inc.

4.3 Results

The group of Young Old adults and the group of Old Old adults were matched for education [*t* (41) = -.66, *p* = .51] and MMSE (*t* (41) = -.12, *p* = .26), while Centenarians' MMSE scores were significantly lower compared to both Young Old [*t* (40) = -4.12, *p* <.001] and Old Old [*t* (25.5) = -4.25, *p* <.001] adults. Moreover, their education level resulted marginally, but not significantly, lower than those of the Young Old adults [*t* (40) = -1.70, *p* = .10] and of the Old Old adults [*t* (40) = -1.82, *p* = .07]. See Table 1.

Age, Education and MMSE Mean and Range Across the three Age groups

	Young Old Adults	**Old Old Adults**	**Centenarians**
	N = 24 (15 F)	N = 19 (13 F)	N = 18 (12 F)
Age	67.75 (± 6.69)	79.15 (± 1.00)	102.38 (± 2.33)
range	(51-74)	(75-91)	(100-108)
Education	8.79 (± 2.35)	9.52 (± 4.81)	7.22 (± 3.20)
range	(5-13)	(5-18)	(2-13)
MMSE	28.27 (± 1.87)	27.47 (± 2.01)	23.20 (± 4.33)
range corrected	(24-30)	(24-30)	
range raw	(26-30)	(24-30)	(12-30)
	ns	ns	*ps* <.001

***Table 3.1**. Mean age, education and MMSE of the three age groups.*

3.3.1 *Effect of Group on lexical-semantic processing*

Naming. We observed a significant main effect of *Group* [*F* (2, 56) = 50.95, MSE = 721.22*,* $p< .001$, $\eta^2 = .65$], with Centenarians being outperformed by both Young Old [$p< .001$, CI (-16.91, -10.14])] and Old Old adults [$p< .001$, CI (-16.38, -8.92)], with Old Old and Young Old adults not differing between each other [$p = 1$, CI (-1.99, 3.74)], and a significant interaction *Group*Stimulus type*level of artificiality* [*F* (2, 56) = 38.04, MSE = 19.02, $p< .001$, $\eta^2= .24$]. No other effects emerged and, in particular, food and non-food items were named with the same accuracy by all three groups. To further investigate the interaction *Group x Type of item x level of artificiality*, we run two MANCOVAs *group* x *level of artificiality*, separately for the *food* and *non-food* items.

Naming food items (natural, NF and transformed, TF). The analysis showed a main effect of Group [*F* (2, 56) = 55.5, MSE = 407.09, $p< .001$, η2= .55] as well as a significant *Group x level of artificiality* interaction [*F* (2, 56) = 8.36, MSE = 12.68*,* $p< .01$, $\eta^2 = .23$]. Transformed foods were named better than natural foods by Young Old adults [$M_{NF} = 15.41 \pm .25$; $M_{TF} = 16.75 \pm .37$; $p < .01$, 95% CI (.62, 2.3)] and Old Old adults [$M_{NF} = 14.63 \pm .37$; $M_{TF} = 16.15 \pm .45$; $p < .01$, 95% CI (.57, 2)] whereas centenarians named natural food ($M_{NF} = 9.83 \pm .78$) significantly better than the transformed one [$M_{TF} = 8.61 \pm .69$, $p = .02$, 95% CI (.15, 2.1)] (see Figure 1). Please note that the difference in Young Old adults and Old Old adults were not significant when a generalized linear model with binomial family was run (See Appendix B9).

Naming non-food items (living and non-living). The MANCOVA revealed, beyond the main effect of Group [F (2, 36) = 32.27, MSE = 316.93, $p < .001$, η2= .34], a main effect of *level of artificiality* [F (1, 36) = 36.0, MSE = 9.66, $p = .03$, η2= .07], with non-living things being overall named more accurately than living things. A significant *Education level * non-food type* interaction was also observed, possibly due to the fact that some of the non-food items used were more difficult than others for our participants (see Appendix B1 for means and standard deviations).

Word-Picture matching. The Mann-Whitney test confirmed that Centenarians performed significantly worse than Young Old (food, $U = 24$, $p < .001$, non-food, $U = 23.3$, $p < .001$) and Old Old adults (food, $U = 23.3$, $p < .001$, non-food, $U = -23$, $p < .001$), whereas these two groups did not differ between each other (food, $U = 204$ $p = .1$, non-food, $U = 189.3$, $p = .09$). Moreover, no difference was observed between food and non-food in Old Old adults ($Z = -.38$, $p = .37$), in Centenarians ($Z = -.68$, $p = .3$), and in Young Old adults, who perform at ceiling ($M_{TF} = 36 \pm 0$, $M_{NF} = 36 \pm 0$).

Concerning food items, Centenarians performed significantly worse in both natural and transformed food recognition with respect to Young Old adults (NF: $U = 48$, $p < .001$; TF: $U = 36$, $p < .001$) and Old Old adults (NF: $U = 44$, $p = p < .001$; TF: $U = 33.3$, $p < .001$), whereas these two groups did not differ from each other ($U = 216$, $p = .26$, for both categories). Wilcoxon rank sum tests revealed that Young Old performed at ceiling at both natural and transformed food ($M_{NF} = 18 \pm 0$; $M_{TF} = 18 \pm 0$) and that Old Old adults did not show any difference in performance (M_{NF}

= 17.94 ± .03; M_{TF} = 17.89 ± .11; $Z = -.43$, $p = .66$). By contrast, Centenarians recognized natural food significantly better than transformed food (M_{NF} = 16.72 ± .28; M_{TF} = 13.3 ± .47; $Z = -2.62$, $p = .01$). This analysis was repeated with a generalized linear model with binomial family, confirming the centenarians' greater impairment in recognizing transformed food. This analysis also showed a difference in Old Old adults' performance, with natural food being better recognized than transformed food (see Appendix B9). However, as shown by the mean values, Old Old adults performed at ceiling with both categories.

For what concerns non-food items, beyond the worse group performance of Centenarians, no significant differences were observed (see Appendix B2 for details and B1 for means).

Categorization task. Since all of the three groups showed a ceiling effect, results concerning the categorization task are reported in the Appendix B (B8).

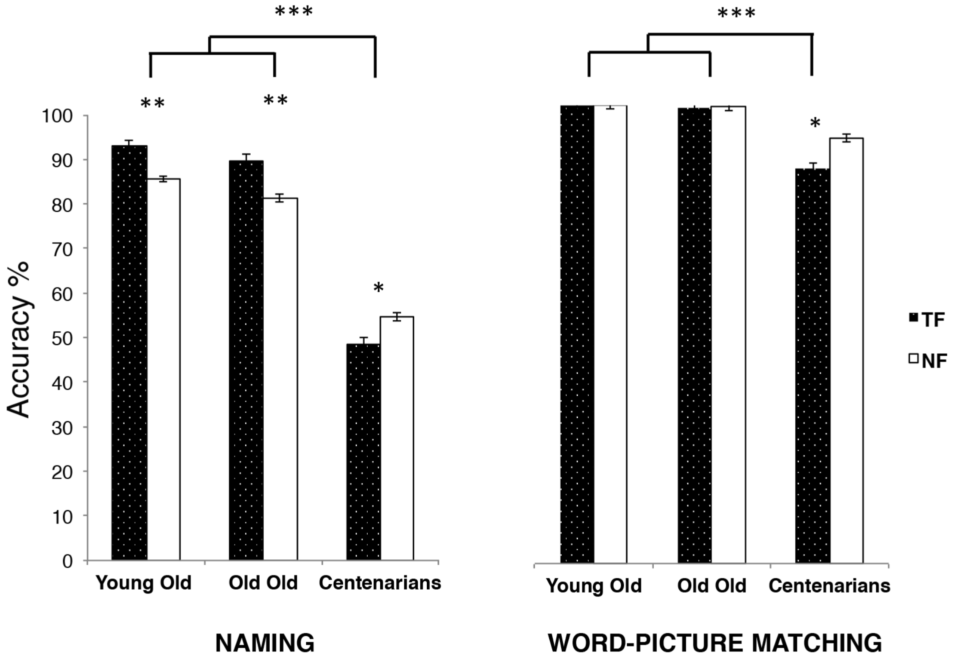


*Figure 3.1. Mean accuracy for natural vs. transformed food across the three groups and for two the tasks. In the naming task, besides the group effect, with Centenarians performing significantly worse than Young Old and Old Old adults, there is a significant Type of food * Group interaction, with Young Old and Old Old adults showing and advantage for transformed food and Centenarians showing the opposite pattern. In the Word-Picture matching task we observe a similar patter, with Centenarians performing significantly worse than both Young Old and Old Old and showing a significantly better performance at natural versus transformed food, whereas the other two groups did not show any difference (*** p < .001, ** p < .01, * p < .05).*

3.3.3.2 *Error Analysis for the naming task*

Consistently with the accuracy results, the error analysis using the Wilcoxon test revealed that Centenarians made significantly more semantic errors for transformed food than for natural food ($M_{NF} = 2.44 \pm 1.38$, $M_{TF} = 4.39 \pm 2.25$, $Z = -2.60$, $p = .01$), whereas the Young Old adults ($M_{NF} = 1.42 \pm 1.26$, $M_{TF} = 0.68 \pm 0.50$, $Z = -2.121$, $p = .03$) and Old Old adults ($M_{NF} = 0.45 \pm 0.72$, $M_{TF} = 0.20 \pm 0.50$, $Z = -1.987$, $p = .05$) made more semantic errors for natural food (for details, see Supplementary Information, S3 and S4).

(for details, see Appendix B3 and B4).

3.3.3 *The role of psycholinguistic variables in the three different age cohorts*

3.3.3.1 *Naming food items*

Correlational analyses between psycholinguistic variables and food naming in the three groups, can be found in Table B5 of the Appendix B. These analyses showed no significant correlations between naming performance and any of the psycholinguistic variables for the Young Old adults, whereas a positive correlation was observed for familiarity in the Old Old adults; for what concerns Centenarians' food naming performance, it positively correlates with familiarity and frequency and negatively with age of acquisition, suggesting that psycholinguistic variables are characterized by a differential resilience to the degradation of semantic memory: specifically, familiarity seems to strongly influence the performance after 75 years of age, whereas after 100 years also frequency of use and age of acquisition have an effect. Regression analyses were performed on the food naming accuracy on the 36 food items for each of the age groups, using familiarity, frequency, number of letters and age of acquisition as predictors (see S6). The model resulted significant for Centenarians only [F (4, 30) = 3.66, with $p = .01$ and $r^2 = .33$], with none of the single variable adding statistical significance.

4.3.3.2 *Naming of natural and transformed foods*

In Centenarians, these analyses showed a significant positive correlation between naming natural food and familiarity (r = .68, p < .01), and a significant but negative correlation between naming natural food and age of acquisition (r = -.33, p = .02). None of these correlations resulted significant in the other two groups.

Caloric content negatively correlated with naming natural food in Old Old, but not in Young Old adults or Centenarians, while it positively correlated with transformed food in the Young Old adults and the Old Old adults but not in Centenarians (see Table 3.2). Regression analyses were performed on both natural and transformed food naming performance using only age of acquisition and familiarity as predictors, since none of the other psycholinguistic variables significantly correlated with the performance (see B7). The model resulted significant for Centenarians only [F (2, 17) = 7.3, r^2 = .49, p = .01] and concerning just natural food, with only familiarity adding statistical significance (β = 43.75, p = .03).

Correlation Analyses between Natural Food Naming Accuracy, Psycholinguistic Variables and Calorie Content

	Written Frequency	**Letters**	**AofA**	**Familiarity**	**Calorie Content**
Young Old adults	*r* = .30	*r* = -.25	*r* = .12	*r* = -.06	*r* =-.19
	p = .24	*p* = .32	*p* = .63	*p* = .82	*p* = .44
Old Old adults	*r* = .35	*r* = -.13	*r* = -.15	*r* = .35	*r* = -.47
	p =.18	*p* = .60	*p* = .57	*p* =.16	*p* =.05
Centenarians	*r* = .43	*r* = -.02	*r* = -.55**	*r* = .68**	*r* = -.37
	p =.08	*p* = .92	*p* =.03	*p* <.01	*p* =.14

Correlation Analyses between Transformed Food Naming Accuracy, Psycholinguistic Variables and Calorie Content

	Written Frequency	**Letters**	**AofA**	**Familiarity**	**Calorie Content**
Young Old adults	*r* = .00	*r* = -.01	*r* = -.20	*r* = .29	*r* =.49
	p = .99	*p* = .97	*p* = .43	*p* = .25	*p* = .04
Old Old adults	*r* = .11	*r* = .00	*r* = -.35	*r* = .35	*r* = .52*
	p =.67	*p* = .10	*p* = .15	*p* =.15	*p* =.03
Centenarians	*r* = .23	*r* = .33	*r* = -.43	*r* = .29	*r* = .27
	p =.23	*p* = .18	*p* =.08	*p* =.24	*p* =.28

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Table 3.2. *Pearson correlations between psycholinguistic variables, calorie content and natural and transformed food naming scores for the three age groups.*

3.3.4 *Dietary Habits*

The life dietary habits were collected for a subset of participants including Centenarians (N = 18) and 19 participants from the two groups of elderly adults (for a total of 19, M_{age} = 78.52 ± 4.66, range 70-91). Participants were asked to rate on a scale ranging from ‘Often’ (scored as 2), to ‘Seldom’ (scored as 1), to ‘Never’ (scored as 0), the extent to which they had eaten a particular type of food in their lifetime. We aggregated the transformed foods (pasta, processed meats, sweets) and the natural foods (raw fruit and raw vegetables), and performed the Wilcoxon signed ranks test. Centenarians (N = 18) confirmed to have eaten natural food significantly more frequently than transformed food ($M_{TF} = 1.48 \pm .10$; $M_{NF}= 1.86 \pm .07$, z = -2.73, $p = .04$), whereas the subgroup of elderly adults showed no differences ($M_{TF}= 1.93 \pm .05$; $M_{NF}= 2 \pm .00$) (see Figure 3.2). Moreover, we performed a Mann-Whitney test comparing the frequency of consumption of both natural and transformed food in the two groups, which revealed that the subgroup of elderly adults ate transformed food more frequently with respect to centenarians ($U = 41.50$, $p <.001$).

To test whether the frequency of consumption effectively predicted Centenarians' naming accuracy, a bivariate linear regression with a 'frequency index' [freq_{NF}- freq_{TF}] – that is a difference in the frequency of consumption between natural and transformed food – was used as independent variable and an 'accuracy index' [naming accuracy $_{NF}$ – naming accuracy $_{TF}$] the naming accuracy on the two categories, that is the difference in naming transformed and natural food. The regression model resulted significant [F (1, 35) = 4.98, $p = .03$, $r^2 = .13$], with frequency of consumption effectively predicting naming performance. Moreover, the bootstrap method (100000 iterations) was applied to estimate the confidence interval for the regression parameter, which resulted significantly different from 0 (p =. 02, CI [.02, .18]).

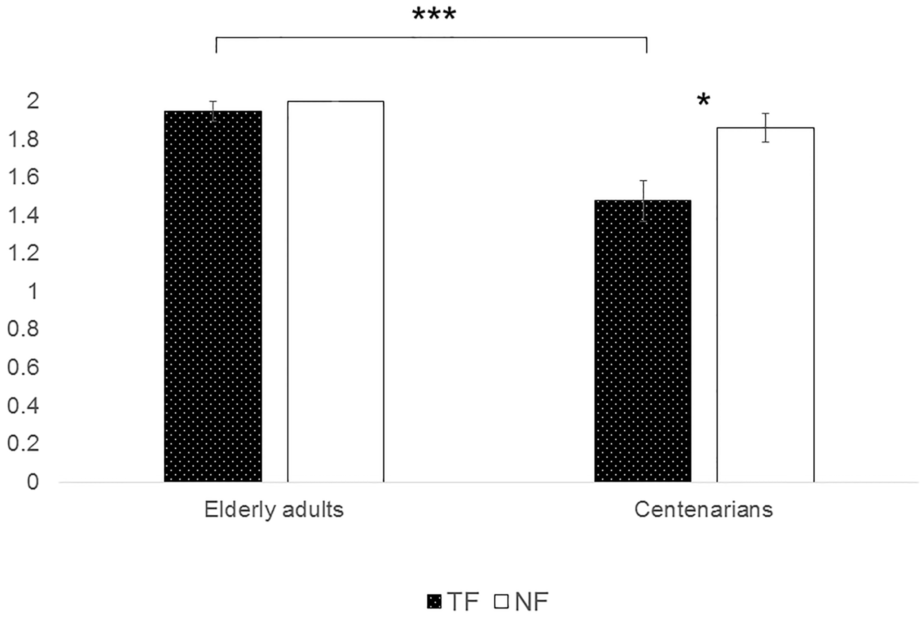


***Figure 3.2**. Dietary habits for Centenarians and Elderly Adults. Wilcoxon tests revealed that, compared to younger elderly adults, Centenarians have eaten significantly less frequently transformed foods than natural foods (* p < .05, *** p < .001).*

4.4 Discussion

The main findings of the present study are the following. Food recognition degrades differently depending on the age of the participants but also on the level of transformation of the food items. Specifically, compared with Young Old and Old Old adults who named transformed food significantly better than natural food, Centenarians named natural food better than transformed food. This pattern of results was replicated in the word-picture matching task, suggesting that the degradation is at the representational level, and not at the output level. Consistently, the analysis of the naming errors revealed that Centenarians made more semantic errors with transformed food than with natural food, whereas Young Old adults and Old Old adults displayed the opposite pattern. In the next section we will discuss these results in turn.

First, experience affects food recognition: Centenarians reported to have consumed transformed food less frequently than natural food in their life, a pattern that was not observed in Young Old and Old Old adults. Results from the regression and bootstrap analyses corroborated the interpretation that the frequency of food consumption effectively predicted Centenarians' naming accuracy. Experience of specific types of food may be considered as a category learning process that has been shown to affect object recognition (e.g., Tanaka & Gauthier, 1997), even if such process took place in a large span of time, as in the case of our participants. Our results resemble those observed in the study by Poon and Fozard (1978) about obsolete and contemporary object naming in young and elderly adults. If experience is really at stake in our study, as the data strongly suggest, future centenarians should show a similar but inverse pattern of performance, being better than contemporary centenarians at recognizing transformed food.

Second, our study also shows that semantic declines later life, as observed in the naming task, and that this decline is particularly sharp in the 10th decade of life. Interestingly, also the significance of different psycholinguistic variables such as age of acquisition, familiarity and word frequency of food items increases with ageing. For instance, in Centenarians, food items that are less familiar, less frequent and acquired later in life are more difficult to be recognized. This is consistent with the decline of episodic memory affecting first recent events while leaving long-term memories better preserved (see Hedden & Gabrieli, 2004, for a review). This pattern of degradation is consistent with the correlation analyses that revealed a significant positive correlation between natural food naming performance and familiarity, and an inverse correlation with age of acquisition, which was not observed for transformed food items. In addition, when we considered caloric content, found to predict food naming performance (Rumiati et al., 2016), we observed that it positively correlated with naming transformed food in Young Old and Old Old adults, but not in Centenarians. The richer energetic content of transformed food seems to be highly salient for the Young Old and Old Old groups (see also Rumiati et al., 2016) and less so for Centenarians, possibly because these individuals need less energy (e.g., Diamond, 1991), or because of their lower familiarity with this food category. In contrast, participants' naming performance on natural food items, that are lower in calories than transformed foods, does not correlate with their caloric content. Thus our findings suggest that the distinction between natural and transformed food is biologically relevant, as suggested elsewhere (Foroni & Rumiati, 2017; Rumiati & Foroni, 2016; Foroni et al., 2016; Pergola et al., 2016; Wobber, Hare and Wrangham, 2009; Carmody and Wrangham, 2009) and as shown by the studies presented in the previous chapters.

This study has some limitations. As healthy centenarians are rare, our sample size is inevitably small. Moreover, there is a gap in our sample as we excluded the participants with more than 91 years of age, while in other studies (e.g., Barzilai et al., 2001), people above 95 were considered as 'centenarians'. As we aimed at testing group-specific effects, we avoided overlaps between the Old Old and the Centenarians groups. In addition, Young Old and Old Old adults perform at ceiling in the word-picture matching task, which limited us to draw conclusions only concerning centenarians. As a last point, due to the length of the battery and the fragility of the participants, in particular Centenarians, we limited the neuropsychological testing to the MMSE.

Chapter 4

Episodic memory for natural and transformed food

4.1 Introduction

In several domains of cognitive neuroscience, from attention to perception, from language to human development, an advantage for living versus non-living things has been reported, with living things holding a special sway over human cognition (New et al., 2007; Laws, 2000; Opfer & Gelman, 2011). In particular, it has been proposed that human evolution has led to the development of specialized neural mechanisms for recognizing living things as they are more relevant for survival (the Domain Specific Hypothesis, Caramazza & Shelton, 1998). Recently, this distinction has been argued to apply also to episodic memory, with several studies showing that living things are better remembered than non-living things. This "*animacy effect"* has been observed with both words and pictures and different tasks such as free recall, recognition tasks and paired-associates task (Bonin et al., 2014; 2015; Nairne et al., 2013; van Arsdal et al., 2013; 2015; 2017; Xiao et al., 2016). Moreover, this effect seems to survive even after controlling for different variables such as familiarity, age of acquisition, frequency, words length, emotional arousal and, in the case of pictures, also visual complexity (Bonin et al., 2014; 2015).

The advantage of living versus non-living things in episodic memory has been attributed to different mechanisms. For instance, living things may draw more attention than non-living stimuli (New et al., 2007), or may share more semantic features than non-living objects (the "structural similarity hypothesis", Humphreys & Forde, 2001) and as such be easier to memorize. Very recently, these two hypotheses have been directly compared in an fMRI study (Xiao et al., 2016). By using both univariate and multivariate pattern analyses, these authors found that compared to non-living words, living words show a greater overlap in semantic features and in neural representations which, in turn, seem to account for the animacy effect in memory.

By and large, the animacy effect has also been ascribed to the importance of animates things in evolutionary terms. According to Nairne et al. (2016; 2017) our cognitive systems are tuned to detect and remember animate things because recognizing and remembering conspecifics, animals and plants may have had a special adaptive value during human evolution, as first proposed in the context of recognition and conceptual knowledge (Caramazza & Shelton, 1998).

It has recently been proposed that the semantic knowledge about natural food (i.e., fruit/vegetables) and transformed food (i.e., food that underwent thermic or non thermic processing) may follow the living/non-living distinction (for a review see Rumiati & Foroni, 2016). The double dissociation after brain damage in the ability to recognize living things and non-living things has led to suggest that semantic knowledge is organized in two subsystems: recognition of living things preferably relies on sensory features and recognition of non-living things preferably relies on functional features (the Sensory-Functional Theory, Warrington & Shallice, 1984). According to this view, concepts about natural foods, such as apples, tomatoes, carrots, would be best characterized by sensory information (e.g., taste, colour, texture, etc. i.e. tomato is red), while concepts about transformed foods, such as pasta, cakes, pizza because they are handmade, could be best characterized by functional information (e.g., the occasion on which a particular food is normally consumed, the procedures followed for its preparation, etc.; i.e. pasta is eaten at lunchtime; Rumiati & Foroni 2016).

This hypothesis has received support from an EEG study in which Pergola et al. (2017) found a larger N400 - an event-related electrophysiological marker of semantic discordance - for natural food after presenting functional primes (e.g., “It is suitable for a wedding meal”) and, *vice versa*, a larger N400 for transformed food after sensory primes (e.g., “It tastes sweet”). These data overall suggest that concepts about natural foods are less consistent with functional attributes and more with sensory attributes, like living things; on the other hand, concepts about transformed/man-made foods are less consistent with sensory attributes than with functional attributes, like non-living things.

Based on the evidence reviewed above, one would expect that natural food should be better remembered than transformed food. However, the scenario involving food might be far more complex. Both natural and transformed foods may indeed have an evolutionary meaning and be equally remembered. Furthermore, Rumiati et al. (2016) showed that transformed food recognition is more resilient to brain damage compared to natural food in patients with Alzheimer disease, possibly due to its higher calorie content (Rumiati et al., 2016), an evidence that seems to suggest than transformed food may be more relevant (and thus better memorized) than natural food.

In this study we sought to investigate episodic memory for natural and transformed food. This issue was investigated first in healthy young participants (Experiment 1). Furthermore, since episodic memory is extremely sensitive to aging and neurodegenerative diseases, we investigated this issue in a sample of centenarians, patients with Progressive primary aphasia and Alzheimer's disease (Experiment 2). With this latter experiment, we aimed at evaluating whether natural or transformed food are equally resilient to forgetting. In addition, since the animacy effect in memory has never been investigated in these clinical populations, in Experiment 2, we also explored memory for living and non-living things.

4.2 Materials and Methods

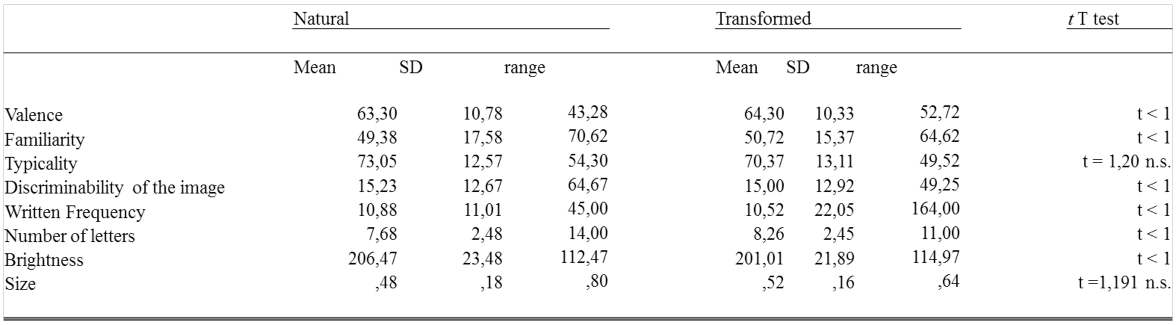
4.2.1 Experiment 1

4.2.1.1 Participants and experiment design

Sixteen subjects (mean age = 28 ± 3.1 years) participated in this study. The participants were first presented with food pictures and had to categorize each one as a natural or a transformed food. They were given a brief definition of what is meant by "natural food" versus "transformed food" (e.g., a natural food has not underwent an organoleptic transformation). Pictures were presented on a computer though the software E-prime (Pittsburgh; Psychology Software Tools Inc.). Each trial began with a fixation point (+) displayed in the middle of the screen for 300ms. A picture was then displayed in the middle of the screen and remained there until the participant responded. Response times (RT) were recorded. The categorization task was followed by two tasks on executive functions, the Stroop Colour & Word Test and the copy of the Rey Osterrieth Complex Figure Test, chosen as distractor tasks. Fifteen minutes after the categorization task, subjects were asked to perform an unexpected memory test. In particular, they were given a recognition test and asked to judge whether a picture was old or new. In this test, 66 pictures were of old items (33 natural and 33 transformed foods) and 66 were of new items (33 natural and 33 transformed foods) randomly mixed and presented one by one on a computer.

The study was approved by the SISSA's Ethics Committee.

Stimuli. A total of 132 pictures were selected from the FRIDa database (Foroni et al., 2013). Pictures depicting natural and transformed food were used. The two stimuli set were matched for valence, familiarity, typicality, discriminability, written frequency, number of letters, brightness and size. The statistical characteristics of the controlled variables are presented in Table 4.1.



	Natural			Transformed			*t* T test
	Mean	SD	range	Mean	SD	range	
Valence	63,30	10,78	43,28	64,30	10,33	52,72	t < 1
Familiarity	49,38	17,58	70,62	50,72	15,37	64,62	t < 1
Typicality	73,05	12,57	54,30	70,37	13,11	49,52	t = 1,20 n.s.
Discriminability of the image	15,23	12,67	64,67	15,00	12,92	49,25	t < 1
Written Frequency	10,88	11,01	45,00	10,52	22,05	164,00	t < 1
Number of letters	7,68	2,48	14,00	8,26	2,45	11,00	t < 1
Brightness	206,47	23,48	112,47	201,01	21,89	114,97	t < 1
Size	,48	,18	,80	,52	,16	,64	t =1,191 n.s.

Table 4.1. *Dimensions according to which natural and transformed food in Experiment 1 have been matched, descriptive statistics and relevant comparative statistics.*

In addition, Likert-type animacy ratings on food pictures used in the experiment were collected on an independent sample of participants (*mean age* = 24.65, *SD* = 3.5; *mean education* = 16.15 years *SD* = 2.4). Stimuli were presented on a computer screen and a seven-point Likert-type scale was used to measure animacy judgments. The instruction was to indicate whether the stimulus displayed was a "living being" by selecting one of eight responses from 0 represented "definitely not a living being" and 7 represented "definitely a living being". The analysis showed that natural food was perceived a significantly more "living being" than transformed food [t (38) = 4.35 $p <$ 0.0001]. [t (38) = 4.33 $p <$ 0.0001]. See Figure 4.1.

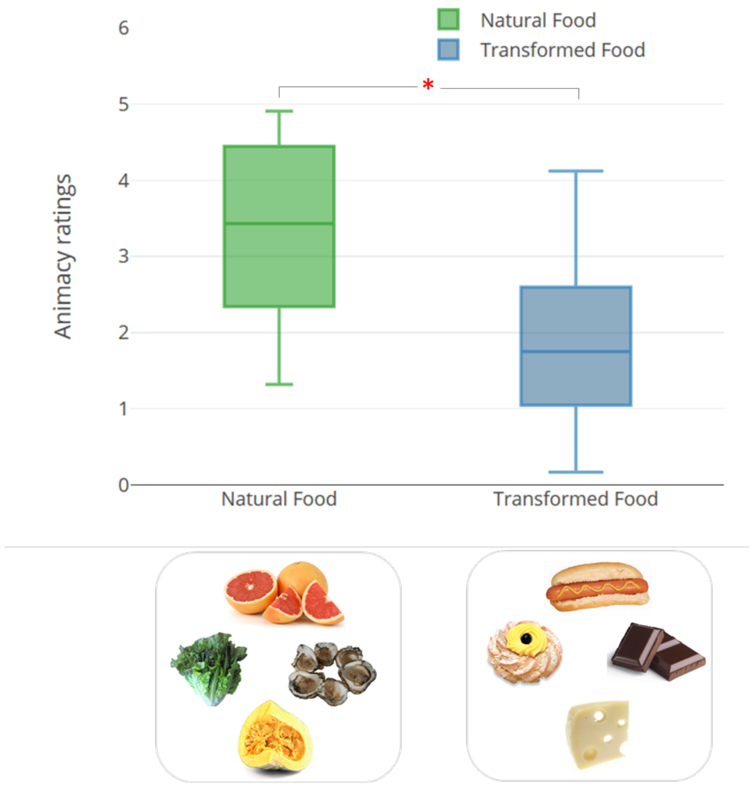


Figure 4.1. *Box plots (displaying the median, lower and upper quartiles, minimum and maximum values) of animacy ratings for natural and transformed food.*

4.2.1.2 Behavioural data analysis

Reaction time, Hits (proportion of old pictures given a “yes” response), False Alarms (proportion of new pictures given a “yes” response) data were analysed according to which category (natural versus transformed) the stimuli belonged to. Moreover, overall recognition performance was analysed using the measure of A_z. The statistic A_z equals the area under the ROC curve and is a monotonic transformation of *d’* (Verde et al., 2006). This non parametric index is a measure of discriminability like *d’* but it can be calculated when subjects have hit or false alarm rates of 1 or 0, and it is preferred over *A’* (Verde et al., 2006). *Az* was computed using Gaetano et al. (2015). Finally, we also performed a correlation analysis on the item level, in order to investigate whether the animacy scores were associated with the degree at which an item was remembered. When variables were normally distributed (as ascertained by Shapiro-Wilk tests) Student's t-test were performed, otherwise a Wilcoxon Rank-Sum test was applied. Correlation analysis was performed using Spearman's rho non-parametric correlation.

4.2.1.3 Results

No difference was observed between Hits for natural and transformed food (*mean* 0.89 *SD* = 0.07; Wilcoxon test, $p = 0.08$). However, the false alarm rate was significantly higher for natural than transformed food (Wilcoxon test, $p = 0.04$). When we computed A_z we observed a significant difference: performance was higher for transformed food compared to natural food (Wilcoxon test, $p = 0.009$). See Figure 4.2 for A_z values and Table 4.2 for Hits, FA and corrected rejections for natural and transformed food. As concerns RTs, no difference emerged between transformed and natural food [t (30) = 0.96 $p = 0.34$]. Overall, these data show that performance is higher with transformed food in terms of signal detection theory. The correlation analysis on the item level, showed that the lower the animacy score, the more the item was remembered (*rho* = - 0.23 *p* = 0.04).

	HITs		FA		correct rejections	
	mean	sd	mean	sd	mean	sd
Natural food	0.90	0.06	0.16	0.06	0.83	0.08
Transformed food	0.94	0.07	0.09	0.09	0.91	0.08

Note. Omissions are not possible in this task.

Table 4.2. Experiment 1*. HITs, FA and correct rejections for Natural and transformed foods.*

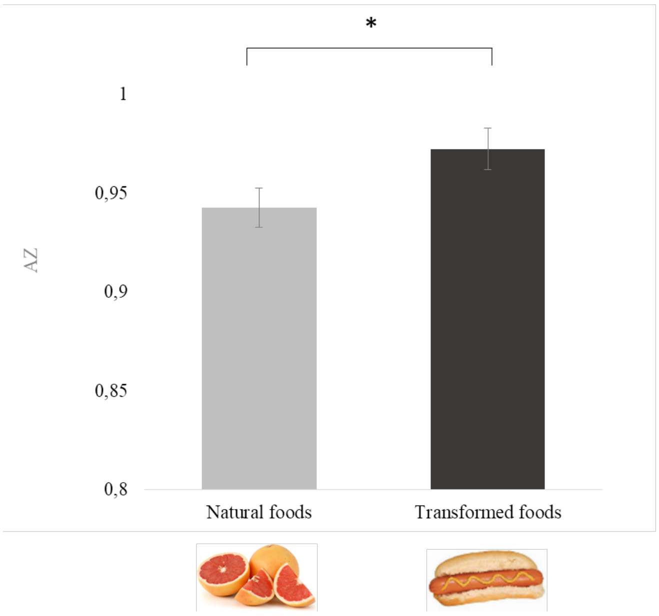


Figure 4.2 Experiment 1. *A_z values for Natural and transformed foods. Mean and mean standard errors.*

4.2.2 Experiment 2

To test whether natural and transformed food are equally resilient to memory decline or whether one category is more preserved than the other, we here evaluated episodic memory for natural and transformed food in a sample of dementia-free centenarians and patients with Progressive fluent aphasia (PPA) and Alzheimer disease (AD). Episodic memory declines with aging even in the 10th and 11th decades of life (Brodaty et al., 2016) and impairments of episodic memory are part of the diagnostic criteria for amnestic mild cognitive impairment and Alzheimer diseases (AD) (Dubois et al., 2007). In addition, considering that the animacy effect has never been investigated in these clinical samples, we also evaluated memory for living and non-living things.

4.2.2.1 Participants

Centenarians

A sample of 18 cognitively intact centenarian without dementia took part in the study. Inclusion criteria were the following: participants were not affected by neurodegenerative diseases, were native Italian speakers, and had a MMSE > 20. Three centenarians scored significantly lower on the MMSE, due to peripheral motor deficits and extreme weakness that made it impossible for them to copy the pentagons, write a sentence, and bend and throw the sheet on the ground. However, they were screened by a trained neuropsychologist and a neurologist and were diagnosed as cognitively normal according to the Criteria of the Diagnostic and Statistic Manual of Mental Disorders - IV (APA, 1994) and therefore included in the study. Moreover, participants were screened for deficits affecting vision such as cataract and glaucoma, and audition such as deafness. The study was approved by the SISSA's Ethics Committee.

The group of 18 *centenarians* had a mean age = 102 ± 2.3 years, ranging from 100 to 108 years; mean education = 7.2 ± 3.11 years, mean MMSE = 23.2 ± 4.2.

Patients

Three groups of participants were enrolled: a group of 14 patients with Alzheimer's disease (DAT; mean age 74.1 ± 7.11 years; mean education: 10.2 ± 5.2 years); a group of 17 patients with Progressive primary aphasia (PPA; mean age 72.4 ± 4.5 years; mean education: 9.82

± 4.3 years). The PPA patients fulfilled the criteria established by Gorno-Tempini et al. (2011). Patients were enrolled at Centre for the Medicine of the Aging of the Department of Geriatrics, Neurology and Orthopedics of the Catholic University of Rome. The inclusion criteria were the following: to have at least five years of formal education, to be native speakers of Italian and to have completed the neuropsychological examination. We excluded patients with a history or radiological evidence of cerebrovascular diseases or a history of major psychiatric disorders, alcohol or drug abuse.

A subsample of seventeen healthy controls (mean age: 73.1 ± 6.5 years; mean education: 10.3± 4.49 years) matched for age and education with the patients were included in the study (all *ps* > 0.5). Healthy participants were enrolled only if they scored equal or above 26 on the MMSE. The study was approved by the Catholic University Institutional Ethics Committee and SISSA's Ethics Committee.

The 36 patients underwent a neuropsychological evaluation as part of their routine clinical assessment. Table 1S in the supplementary material summarizes the mean performance of two patients groups on tasks tapping several cognitive abilities including verbal episodic memory, short-term memory, visuospatial analysis, praxis and intelligence.

4.2.2.2 Experimental procedure

Participants performed three neuropsychological tests: a naming task, a categorization task and a word-to-picture matching task, with pictures of foods (natural and transformed) and non-food (living and non-living). The results of these tasks are reported in Rumiati et al., 2016 and Vignando et al., under review. After completing the three tasks, they talked for ten minutes with the experimenter, in order to let the time pass but without increasing the cognitive load. Participants were subsequently administered an unexpected memory recognition task and were asked to respond, upon presentation of each image, whether they had already seen the image during the previous tasks, or not, stating whether the image was ‘old’ or ‘new’. Images were presented on a computer screen using a Microsoft PowerPoint presentation; the order of the slides was first randomized and, subsequently, administered in the same order across participants. The presentation was not timed and was controlled by the experimenter. Participants’ responses were recorded on a dedicated scoring sheet. Before beginning the task, participants performed an 8-trial practice in order to familiarize with the task. The responses given in the practice trials were not considered for the final analyses.

The memory task was comprehensive of 112 food images (natural and transformed), and non-food (living and non-living). Living pictures include natural objects (e.g., orchid, leaf, sunflower, etc.), while non-living pictures included tools (e.g., cleaver, kettle, fork, spoon, etc.). Participants were showed the 72 images they had seen before (18 for each category) and 40 images that were completely new (10 for each category). All images were taken from the FRIDa database (Foroni et al., 2013), with names of old and new pictures being matched for written frequency and number of letters.

4.2.2.3 Behavioural data analysis

As in experiment 1, Hits, False Alarms (FA) and A_z were used to measure the memory performance. The performance was analysed according to the stimuli's semantic categories (natural versus transformed and living versus non-living). Since data were not normally distributed (as ascertained by Shapiro-Wilk tests), we computed non-parametric tests (Wilcoxon test). Finally, for what concerns patients, a series of correlations were run between HITs, FA and A_z for each category (living things; non-living things; natural food and transformed food) and neuropsychological tests in the whole sample of patients, see Appendix B for the results of these analyses.

4.2.2.4 Results

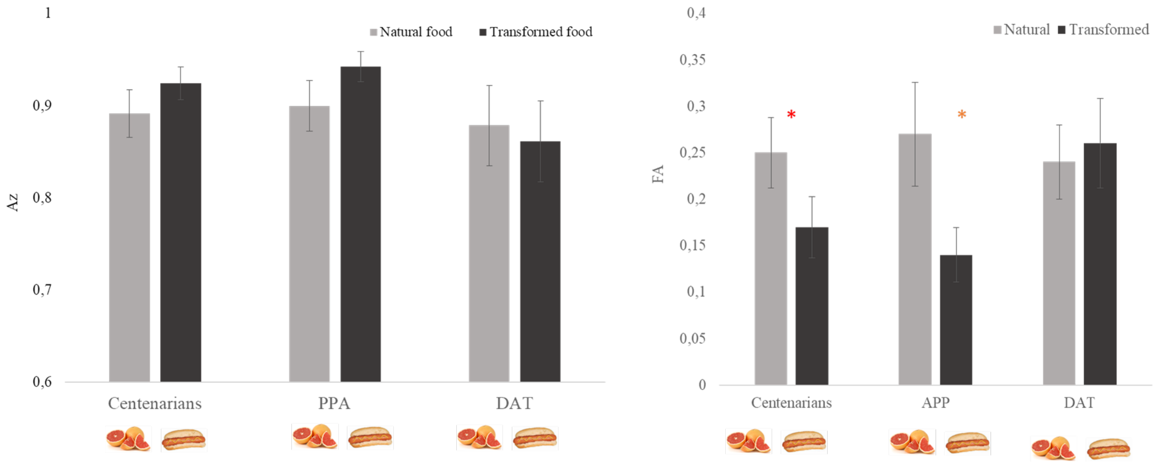
Food recognition memory

Healthy controls performed at ceiling, therefore their data were not considered in the analyses. *Centenarians* showed similar Hit rates for natural and transformed food (Wilcoxon test, p = 0.34), but more FA with natural than transformed food (Wilcoxon test, p = 0.004). When A_z value was computed, no significant differences emerged between the two categories (Wilcoxon test, p = 0.14). Neither PPA nor DAT showed any difference between natural and transformed food, when we considered Hits and A_z (Wilcoxon test, all *ps* = n.s.). For what concerns FA, PPA showed more FA with natural food compared to transformed food (see Table 4.3), however, this difference did not reach standard significance level (p = 0.06). In DAT, a similar level of FA was present for natural and transformed food (p = n.s. see Table 4.3). See Figure 4.3 for A_z values and FA. Table 4.3 shows Hits, FA and corrected rejections for natural and transformed foods.

	Natural food						Transformed food					
	HITs		FA		correct rejections		HITs		FA		correct rejections	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Centenarians	0.87	0.15	0.25	0.16	0.75	0.16	0.85	0.19	0.17	0.14	0.83	0.14
APP	0.92	0.10	0.27	0.23	0.73	0.23	0.92	0.17	0.14	0.12	0.86	0.12
DAT	0.85	0.25	0.24	0.15	0.76	0.15	0.85	0.26	0.26	0.18	0.74	0.18

Note. Omissions are not possible in this task.

***Table 4.3**. **Experiment 2**. HITs, FA and correct rejections for Natural and transformed foods in Centenarians, PPA patients and AD patients.*



* *P* < 0.03 * *P* = 0.06

***Figure 4.3 Experiment** 2. Az values (left panel) and FA (right panel) for Natural and Transformed food in Centenarians, PPA patients and DAT patients. Means and standard errors of means.*

The animacy effect

Healthy controls performed at ceiling, therefore their data were not considered in the analyses. In centenarians, the difference between living and non-living pictures was not significant when we considered HITs, FA and A_z (Wilcoxon test, all ps > 0.25). Both the PPA and DAT groups showed a similar number of Hits for living and non-living things (Wilcoxon test, all *ps* = n.s.). PPA showed more FA with non-living things compared to living things (Wilcoxon test, $p = 0.01$). When we computed A_z, only PPA showed to remember more living compared to non-living (Wilcoxon test, $p = 0.01$). See Table 4 for Hits, FA and corrected rejections for living and non-living things.

	Living						Non Living					
	HITs		FA		correct rejections		HITs		FA		correct rejections	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Centenarians	0.81	0.21	0.14	0.11	0.86	0.11	0.84	0.20	0.13	0.13	0.87	0.13
APP	0.79	0.25	0.11	0.19	0.89	0.18	0.78	0.18	0.24	0.26	0.76	0.27
DAT	0.81	0.22	0.10	0.14	0.90	0.14	0.80	0.27	0.17	0.20	0.83	0.20

Note. Omissions are not possible in this task.

Table 4.4 Experiment 2*. HITs, FA and correct rejections for Living and Non Living in Centenarians, PPA patients and AD patients.*

4.3 Discussion

The goal of the present study was to investigate episodic memory for food and, in particular, whether accuracy would be the same for natural and transformed food (Foroni & Rumiati, 2017; Rumiati & Foroni, 2016; Rumiati et al., 2016). Using a recognition memory task, in Experiment 1 we directly compared the ability to remember natural food and transformed food in healthy young adults. We found that participants showed a similar level of true recognition (HITs) for natural food compared to transformed food, but that they exhibited a higher rate of false alarms for natural food. Indeed, when we measured performance through A_z index, we observed an overall better recognition performance with transformed food than natural food. The correlational analysis on the item level, confirmed this finding, by showing that the lower the animacy score of the item, the better the degree to which it was remembered.

In Experiment 2, we extended the observations of Experiment 1 by testing a sample of 18 dementia-free centenarians and 31 patients with dementia (Alzheimer's disease, Progressive primary aphasia) and age-matched healthy elderly controls. This second experiment aimed at testing memory for natural and transformed food in the presence of an episodic memory decline.

Despite the scarcity of neuropsychological research on centenarians, possibly due to the inherent difficulties in testing them, there is however some evidence that encoding information into episodic memory continues to decline through the 10th and 11th decades of life (Brodaty et al., 2016). For instance, Fairfield et al. (2013) showed that recognition memory for positive and negative images items declined in centenarians compared to older adults, while Inagaki et al. (2009) observed a reduced memory score subtest of the MMSE in 68 centenarians compared to older adults (but see Holtsberg et al. (1995) for different results). Moreover, impairments in episodic memory are part of the diagnostic criteria for amnestic mild cognitive impairment and Alzheimer diseases (AD; Dubois et al., 2007), and have been also described in patients with Progressive primary aphasia even if in this latter case they may be secondary to language disorder (see, for instance, Nilakantan et al., 2017).

Centenarians, PPA and DAT showed similar levels of recognition memory for natural and transformed food (HITs and A_z). However, centenarians, and to lesser extent also PPA patients, showed a higher number of false alarms for natural compared to transformed food, similarly to the tendency observed in healthy participants of Experiment 1. In DAT, however, a similar number of false alarms were observed for natural and transformed food. Older adults and patients with dementia often exhibit enhanced levels of false remembering and, false alarms have been considered as an index of recognition memory impairment (Duarte et al., 2010; Abe et al., 2011). If we consider centenarians, PPA and DAT as characterized by different degree of episodic impairment (in which DAT patients represent the most impaired group), it seems that, at lower memory impairment (as in the case of centenarians and PPA), false alarms are higher for natural food while transformed food is still resilient to the memory' decline. At a more severe memory impairment (as in the case of DAT), also recognition of transformed food became impaired. Of course this is mainly speculative and more studies are necessary in order to test his hypothesis, since the characteristics of our study (different tasks used in Experiments 1 and 2; performance of healthy old adults at ceiling; no episodic memory testing in centenarians) did not allowed us to directly test it.

Overall our results are in line with the observation that transformed food recognition is more resilient to brain damage compared to natural food in patients (Rumiati et al. (2016). Regarding the reason why transformed food may be better remembered than natural food, as already suggested in the introduction, one possibility is that this is due to its higher calorie content (see also Rumiati et al., 2016), which makes this category extremely relevant from a biological point of view. Interestingly, it has been recently argued that appetizing foods might greatly activate hippocampus and induce episodic recollection also due to the greater enjoyment associated to these hedonic stimuli (Stevenson & Francis, 2017), an explanation that may also fit with transformed food. However, it is still possible that the advantage observed for transformed foods is due to their higher visual complexity, which may in turn affect memory performance (Brodeur et al., 2017). Visual complexity is a multidimensional construct influenced by the amount and variety of elements, and their organization, in particular their symmetry (Gartus 2017). We tried to take into account this aspect including, for instance, also natural foods in which more than one element was presented, but, we did not carefully matched the two categories on this dimension. Future studies should disentangle this issue.

Another interesting issue explored in our study regards how episodic memory decline affects the animacy effect. We found that centenarians did not show differences in remembering living versus non-living things, in line with results documented by Bugaiska et al. (2016) who failed to find a difference in remembering living things and non-living things in older adults (aged 60–81 years), compared to young adults (18–37 years). Conversely, PPA showed a significant advantage in remembering living things compared with non-livings and higher numbers of false alarms for non-living things. In DAT, we observed the same pattern, but these differences did not reach significance. These results suggest that when a cognitive degeneration is present, the living category, even if damaged, may still be more resilient to the decline compared to the non-living category in accordance with its proposed evolutionary meaning in episodic memory (Nairne et al., 2016). Interestingly, patients with reduced memory recognition for non-living things scored more poorly on the Rey's words recall memory task, suggesting this category may be more highly demanding compared with living things. It should be noted that this is the first study in which the animacy effect in episodic memory has been investigated in patients with dementia. As such, this research provided new interesting findings that future research needs to further investigate.

We are also aware that our research presents some limitations. First, healthy elderly participants performed near or at ceiling in our episodic task, so it was not possible to assess episodic memory at different ages. Secondly, as in Experiments 2 pictures were matched only according to written frequency and number of letters, we cannot rule out the role of other variables. Finally, living things included only animate objects such as plants and flowers (which are living but not animate) and not conspecifics or animals that are instead traditionally included in this category. Future studies should manipulate also the dimension of "agency" and specifically reassess the animacy effect in episodic memory in patients and healthy elderly controls.

In conclusion our study shows that transformed food is better remembered than natural food. This suggests that this category may be more salient and evolutionary relevant. The natural/transformed distinction appears susceptible to erosion only in the presence of a high degree of episodic memory impairment. Finally, our finding suggests differences in resilience to brain damage for episodic memory of living and non-living concepts, which deserves further investigations.

Chapter 5

Abnormal eating behaviours and semantic deficits in dementia

5.1 Introduction

Dementia entails both cognitive and behavioural deficits. Abnormalities in eating behaviour are commonly observed in patients with FTD, in particular those with the behavioural (bvFTD) and semantic (semantic dementia, SD or svPPA) variants. While bvFTD is mostly characterized by behavioural symptoms, such as inappropriate social behaviours, and disexecutive syndrome with major frontal lobe atrophy, svPPA is characterized by difficulties in lexical-semantic processing typically due to bilateral temporal atrophy (e.g., Mummery et al., 2000).

Different types of eating alterations have been described in FTD patients, such as hyperfagia, pathological sweet tooth, stealing food, and perturbations in eating habits and preferences (see Ahmed et al., 2016, and Aiello et al., 2016, for reviews). Moreover, these eating alterations have been found to correlate with atrophy in several regions such as the right ventral insula, the striatum and the orbitofrontal cortex (OFC), held to be involved in reward and gustatory process (Wooley et al., 2007; Whitwell et al., 2007).

What are the underlying mechanisms that, when damaged, give rise to these symptoms? Aiello et al. (2016) suggested that increasing appetite, hyperfagia, sweet craving, and continuously eating when food is presented, might be secondary to disexecutive functions typically associated to bvFTD, whereas changes in food preferences or food fads might follow a more general semantic disorder, as in svPPA. This hypothesis is mainly based on clinical observations and indirect evidence provided by imaging studies. For what concerns clinical observations, Mendez (2007) reported two patients with semantic dementia and bilateral temporal atrophy, whose eating preferences change with the illness. He first described the case of a 56-year old woman, a life-long vegetarian, who began eating animal products and stopped eating fruits and vegetables probably as a consequence of an impaired ability to recognize such foods. He then described the case of a 54 year-old woman who quit eating fruit and vegetables that she could not recognized anymore, claiming the she could not taste them. Moreover, Thomspon et al. (2016) described two cases of food aversion in two female patients (57 and 58 year-old) with temporal lobe atrophy, semantic deficits (impaired naming, comprehension and memory for faces) and an increasing obsession with their weight, leading to display symptoms typical of anorexia nervosa and bulimia nervosa respectively.

A recent study by Ahmed et al. (2016), investigated the neural correlates of abnormal eating behaviour and sucrose preference in patients with both bvFTD and svPPA. In this study, patients with different types of dementia (bFTD, svPPA, Alzheimer disease AD) and healthy controls were required, after the evening meal, to fast until the morning after, when they were administered the experimental tasks. First, they were offered a breakfast buffet and allowed to eat ad libitum for a maximum of 30 minutes. The total amount of calories and nutrients ingested was subsequently calculated. Secondly, after 4 more hours of fasting, patients were presented with a dessert tasting test: three options, varying in the content of sugars (26%, 39%, 60%) were offered and patients were asked to rate, on a 0 to 10 visual scale, their liking and the sweetness of each dessert. Interestingly, the authors observed different eating patterns in bvFTD and svPPA patients: while the former showed hyperphagia and the largest caloric intake among all groups, the latter exhibited rigid eating behaviour, often refusing to eat the food or eating small amounts of it. Conversely, both groups showed strong sucrose preference. Importantly, different neural networks resulted associated to eating behaviours in patients with bvFTD and semantic dementia, with a similar network associated to sucrose preference, suggesting that different eating alterations may have a different neural substrate in these patients.

The aim of our study is to test whether changes in food preferences and eating habits in patients with dementia correlate with a deficit in lexical-semantic processing, and whether they are both associated with atrophy of temporal regions, to date known to be involved in semantic processing (e.g. Mummery et al., 2000). To reach this aim we enrolled a sample of patients with FTD (bvFTD and svPPA), Alzheimer's disease and healthy matched controls. Participants were asked to perform semantic tasks with food items and non-food items while patients' caregivers (and healthy controls) completed a questionnaire on eating disorders. Structural neuroanatomical substrates of abnormal eating behaviour/semantic deficits were assessed using voxel-based morphometry (VBM).

5.2 Materials and Methods

5.2.1 *Participants*

We enrolled a sample of 23 patients, 12 FTD (7 bvFTD, 5 svSVPPA) and 11 AD patients, as well as 21 healthy controls. Exclusion criteria were the following: visual deficits, hearing deficits, cerebrovascular pathology or brain tumor. Participants underwent a neuropsychological evaluation including MMSE (Italian norms from Measso et al., 1993), Addenbroke's Cognitive Examination revised (Pigliautile et al., 2011), and the Frontal Assessment Battery (FAB, Apollonio et al., 2005). In addition, patients only were administered a naming task (Laiacona et al., 1993). This study was approved by the SISSA ethical committee and patients and healthy controls filled an informed consent.

5.2.2 *Tasks & Stimuli*

Naming Task

Participants were presented with a confrontation naming task, including 72 color photographs, 36 foods and 36 non-foods. Participants were asked to name the object, presented one at a time on a computer screen using Microsoft PowerPoint. The presentation was self-paced by the participant. The experimenter recorded the participants' responses on a dedicated scoring sheet.

Word to picture matching task

Participants were presented with 72 slides (36 food and 36 non-foods), each of which contained six images. When the experimenter named an item, participants were required to point to the corresponding target picture on the screen. The target was placed among five distractors, one of which belonged to the same semantic category. This task is normally used to assess the integrity of object recognition in patients with language disorders, as it allows to diagnose whether the naming deficit is due to failure at the lexicon level or at the semantic level.

Stimuli

72 images depicting both food (e.g., pumpkin, apricot, pizza, cake) and non-food (e.g. knife, chopping board, beehive, sunflower) items were selected from FRIDa database (Foroni et al., 2013), with a resolution of 530×530 pixels and colour coding RGB. Stimuli were matched for letter length and written frequency across all two categories (CoLFIS, Bertinetto et al., 2005). **Figure 5.1** shows examples of the two tasks.

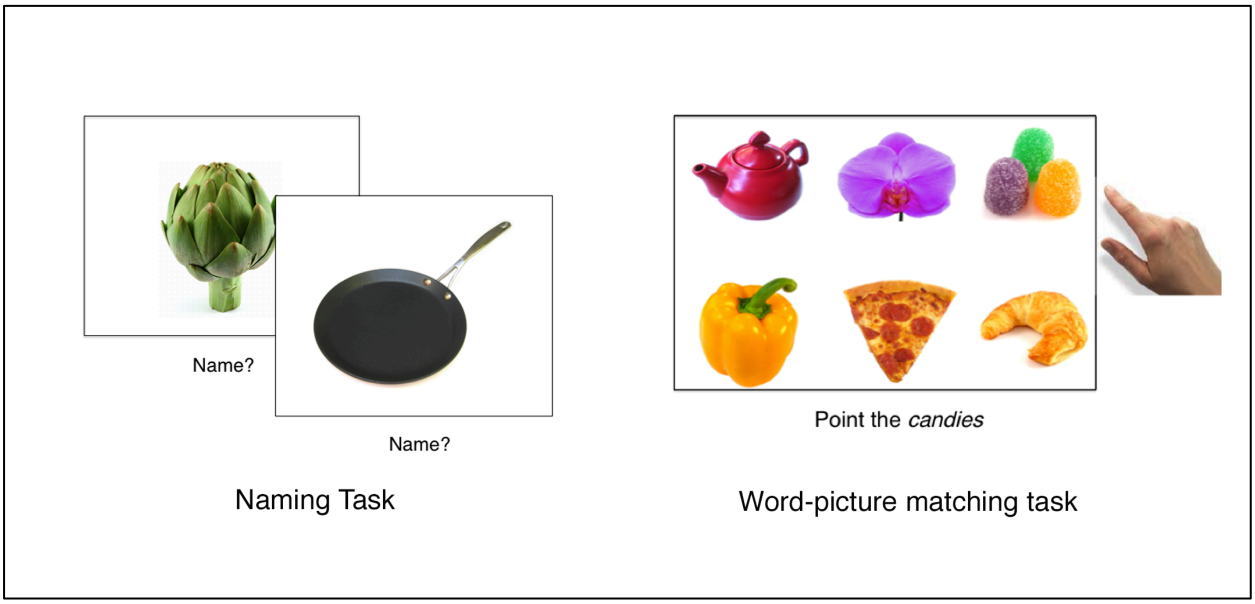


Figure 5.1. Experimental tasks. The naming task requires the participant to name a the object presented on the screen (e.g., artichoke, frying pan). The word-picture matching task requires her to point to the correct target (e.g. candies) named by the experimenter.

APEHQ

Caregivers and healthy controls completed the Appetite and Eating Habits Questionnaire (APEHQ, Ikeda et al., 2002). The full questionnaire can be found in Appendix D1. This questionnaire is comprehensive of 36 items arranged in five subscales, each of which assessing different eating aspects: swallowing, appetite, eating habits, food preference and other oral behaviours. In each section there are several questions, each of which requires to state the frequency of the behaviour on a scale from 0 to3 (0, "never"; 1, "rarely"; 2, "occasionally"; 3, "frequently") and its severity (0, "none"; 1, "mild"; 2, "moderate"; and 3, "severe"9. The score at each question is the product of frequency * severity. The minimum score for each question is 0, whereas the maximum is 9. The first subscale describes difficulties related to *Swallowing,* such as "Has he/she ever had difficulty in swallowing food?". The maximum score that can be obtained at the *swallowing* subscale is 72 as well as at the *appetite* subscale. The latter describes behaviour such as hyperfagia, by for instance asking "Does he/she search for food in-between meals?". The scale *Changes in eating habits* describes specific changes in habits such as that the described by the item "Does he/she want to cook or eat exactly the same food every day? ". The maximum score for this scale is 54. The scale of *changes in eating preferences* describes this dimension by asking questions such as "Has his/her " taste changed in some way (e.g., does he/she eat more meat, more fried food?") and the maximum score is 63. Finally, the subscale investigating the presence of *other oral behaviours,* with questions such as "Has he/she become a heavy smoker or has taken up smoking again?", with a maximum score of 45. Since an Italian validation of this questionnaire is not available, we used a translated version. The questionnaire was translated in Italian and two English native speakers who were bilingual for the Italian language were asked to read the Italian translation and to translate it back to English, in order to make sure that everything had been transposed properly.

5.2.3 *Behavioural Analyses*

Naming data were arcsin transformed, and resulted normally distributed (trough *Kolmogorov-*

Smirnoff test). Therefore, we carried out a repeated measure ANOVA, with *type of item* (food, non-food) as within subject factor and *group (FTD, AD, HC)* as between subject factor. Pairwise comparisons were Bonferroni corrected. For the Word-Picture matching task, we performed non-parametric tests, due to the lack of normality of the data. Specifically, patients' and controls' performance was compared using a Mann Whitney test, whereas the difference between recognition of food and non-food items was evaluated with a Wilcoxon rank sum tests. For what concerns the APEHQ, we carried out Mann Whitney tests. Healthy Controls were excluded from this analysis since their scores at the APEHQ reached floor level, not allowing any statistical comparison. Finally, regression analyses were performed for patients only, in order to explore whether semantic scores resulted significant predictors of the abnormal eating behaviours investigated in the study. In this case, we considered only the category of food since using this category may allow us to capture the relationship between eating disorders and semantic deficit in a more straightforward way.

5.2.4 *Anatomical Analyses*

We collected T1-weighted MRI images for each of the participants. Images were acquired with a Philips 3T scanner in Ospedale S. Maria della Misericordia in Udine. Voxel Based Morphometry (Ashburner & Friston, 2000) was used to correlate local grey matter concentration with our variables of interest: eating disorders and semantic performance. Anatomical analyses were performed with SPM12 software package. T1 weighed images were first segmented in grey matter, white matter and cerebrospinal fluid. A template brain was created by using the grey and white matter segments for each of our participants obtained from the segmentation process. Each of the grey matter images of our participants was co-registered to the template and normalized to the MNI space. Images were smoothed with an 8-mm isotropic Gaussian kernel. Upon completion of the preprocessing phase, we performed two types of analyses. First, data were analysed using two multiple regression models, with covariates only. In both models, the scores on the *swallowing, appetite, eating habits, eating preferences and oral behaviours* were used as covariates of interest, and age and gender were used as nuisance covariates. Moreover, we used participants' total intracranial volume in the global calculation. As normalization procedure, ANCOVA was selected. In the first model, we also entered as a covariate performance at naming, whereas in the second model, we did the same procedure, but with the performance at the word-picture matching task. Subsequently, we conducted two conjunction analyses (Mummery, Patterson, Price, Ashburner, Frackowiak, Hodges, 2000) to determine regions commonly atrophied for both *i)* naming and APEHQ scores at the subscales of *swallowing, appetite, eating habits, eating preferences and oral behaviours* and *ii)* word-picture matching and APEHQ scores at *swallowing, appetite, eating habits, eating preferences and oral behaviours* Since the anatomical analysis does not accept a large amount of zeros in the vectors used as covariates, we added +1 to each data point of the APEHQ.

5.3 Results

5.3.1 *Behavioural analyses*

Demographics

Participants were matched for age [F (2, 41) = 1.76, p = .19], education level [F (2, 41) = 1.33, p = .28] and gender (female = 25; χ *2* = 1.21, p = .751). AD and FTD patients were also compared for onset with and independent samples t-test, revealing no significant differences, but a trend towards significance [t (1,22)=, p = .07], with FTD showing a longer disease onset (mean = 3.1 years, sd = 1.44) with respect to AD (mean = 2.00, sd = 1.32). Table 5.1 summarizes groups' performance on individual neuropsychological tests.

MMSE. Patients' MMSE scores were significantly worse than healthy controls (p <. 001) as expected. No significant difference was observed between FTD and to AD patients (p = .23).

ACE-R. Patients performed worse than healthy controls on most of the subscale, except for , FTD patients, whose performance did not differ from that of controls on the visuospatial abilities tests [F(1,30) = 3.05, *p* = .3], consistently with what reported in the literature (for means, standard errors and range see Table 5.1). Among patients, FTD patients significantly differed from AD patients on the language (*p* = .03) and fluency (*p* = .03) subscales of the ACE-R.

Laiacona Naming test (Laiacona et al., 1993). No significant difference, but a trend, emerged on the picture naming task [$t_{(1,20)}$ = -.18 , p =.08], with FTD having a lower mean score than AD (see Table 5.1 for details).

FTD

	N	Range	Min	Max	Mean	S.E.M.
Age	12	15	66	81	74,92	1,60
Education	12	13	5	18	10,25	1,28
MMSE	12	14,3	15,7	30	24,73	1,40
FAB	12	9	8	17	11,67	0,78
ACE_ao	12	8	10	18	14,75	0,81
ACE_m	12	23	2	25	12,50	2,32
ACE_f	12	8	0	8	4,08	0,82
ACE_l	12	17	9	26	20,00	1,70
ACE_vs	12	16	10	26	15,00	1,11
ACEtot	12	49	41	90	63,83	4,76
Naming	12	67	0	67	45.83	6.59

AD

	N	Range	Min	Max	Mean	S.E.M.
Age	11	22	61	83	73,27	1,96
Education	11	13	5	18	9,73	1,24
MMSE	11	10,6	15,4	26	22,65	0,86
FAB	11	10	6	16	11,36	0,99
ACE_ao	11	8	10	18	14,64	0,68
ACE_m	11	9	6	15	9,64	0,87
ACE_f	11	7	4	11	6,73	0,59
ACE_l	11	5	21	26	24,45	0,51
ACE_vs	11	13	3	16	12,64	1,05
ACEtot	11	31	45	76	68,09	2,73
Naming	11	13	53	66	58,55	1,33

HC

	N	Range	Min	Max	Mean	S.E.M.
Age	21	20	64	84	71,19	1,12
Education	21	13	5	18	12,05	0,91
MMSE	21	1	29	30	29,81	0,09
FAB	21	1	17	18	17,95	0,05

ACE_ao	21	0	18	18	18,00	0,00
ACE_m	21	8	18	26	23,33	0,59
ACE_f	21	8	6	14	11,48	0,51
ACE_l	21	1	25	26	25,71	0,10
ACE_vs	21	0	16	16	16,00	0,00
ACEtot	21	15	84	99	94,67	1,01

Table 5.1. *Neuropsychological assessment results of our participants.*

Semantic performance on food and non-food items

Naming task

The ANOVA on the naming performance showed a significant effect of *Group* [*F* (2, 41) = 29.34, $p < .001$, η^2= .59]. As expected, FTD were significantly less accurate in naming than AD (p = .032, 95% CI [-.427, -.02]) and HC ($p < .001$, 95% CI [-.712, -355]). AD patients were less accurate than HC ($p < .001$, 95% CI [-.51, -1.3]). Moreover, no differences emerged between food and non-food [F (1, 41) = .064, p = .801, η2 = .002] and no significant interaction *item type x Group* was observed [F (2, 41) = .458, p = .636, η2 = .02] (for means and other statistics, see Appendix D2).

Word-picture matching task

Compared to HC, FTD performed significantly less accurately on both food [U = 58.5, z= -2.98, p = .003] and non-food [U = 44.5, z = -3.71, $p < .001$], while AD patients showed a worse performance if compared to HC for the category of non-food only [U = 45.5, z = -3.66 p = .004]. FTD and AD patients did not show any significant difference, between each other neither with food [U = 45.5, z= -1.06, p = -.29], nor with non-food [U= 53.5, z = -.648, p = .64]. As for the naming task, performance of the three groups did not significantly differ between food and non-food stimuli (Wilcoxon rank sum tests, all comparisons $p > 0.5$, for details see Appendix D2).

APEHQ

No significant differences emerged between groups (all comparisons $p > 0.5$). As it can be observed in Table 5.2, patients' scores have a very large range standard error. Therefore, we also provide a qualitative description of score distribution in each group, but also in each single patient (see Appendix D3). For this analysis, we split the FTD group in patients with a diagnosis of sdPPA , on the one hand, and patients with a FTD with a behavioural onset, on the other, in order to appreciate the qualitative differences in their eating behaviour. In particular, we see that on average bvFTD are those with the highest score on the *Appetite* (mean = 13.29 sdPPA = 7.79) subscale, whereas svPPA are those with highest scores on the scales of *Habits* (mean = 17.20, sd = 16.89) and *Preferences* (mean = 13.60, sd = 14.36) subscales. Patients with AD vary substantially from one another.

bvFTD

	N	Range	Min	Max	Mean	S.E.M.	Std. Dev.
Swallowing	7	21	0	21	3,43	2,94	7,79
Appetite	7	71	0	71	13,29	9,89	26,16
Habits	7	14	0	14	6,57	1,81	4,79
Preferences	7	17	0	17	5,71	2,18	5,77
Oral behaviour	7	19	0	19	6,86	2,87	7,60

svPPA

	N	Range	Min	Max	Mean	S.E.M.	Std. Dev.
Swallowing	5	11	0	11	4,20	2,58	5,76
Appetite	5	15	0	15	4,00	2,92	6,52
Habits	5	41	3	44	17,20	7,55	16,89
Preferences	5	35	0	35	12,60	6,42	14,36
Oral behaviour	5	3	0	3	0,60	0,60	1,34

AD

	N	Range	Min	Max	Mean	S.E.M.	Std. Dev.
Swallowing	11	11	0	11	1,00	1,00	3,32
Appetite	11	21	0	21	5,27	2,33	7,73
Habits	11	35	0	35	6,91	3,26	10,82
Preferences	11	68	0	68	13,73	6,65	22,04
Oral behaviour	11	35	0	35	3,27	3,17	10,53

Table 5.2 *Range, minimum, maximum, mean scores, standard error of the mean and standard deviation of patients' groups.*

Regression analyses

Two linear regression analyses were carried out in order to investigate whether the semantic deficit could predict eating disorders (*swallowing, appetite, eating habits, eating preferences and oral behaviours),* with either performance on food picture naming or performance on food word-picture matching items as predictor. In both cases, scores obtained on each of the APEHQ subscales were used separately as dependent variable. In addition, this analysis was carried out separately for FTD and AD patients, in order to uncover possible disorder-specific patterns. Results showed that for the FTD group, naming food was a significant predictor of *changes in eating preferences* accounting for 35% of the adjusted variance [F (1, 10) = 5.32, p = .04, B = -589]. Moreover, performance on the food word-picture matching task significantly accounted for 54% of the adjusted variance [F (1, 10) = 11.86, p = .006, B = -737] for eating habits, and changes 70% of the variance [F (1, 10) = 26.09, p < .001, B = -850] for eating preferences. Importantly, neither performance on food naming, nor that on food word-picture matching could explain the pathological scores in the subscales of swallowing, appetite and oral behaviours (p > .05). However, a trend towards significance (p = .06) was observed between naming non-food and changes in preferences.

However a different pattern was observed in AD patients: performance on food word-picture matching task significantly explained 56% of the variance in a regression model with abnormal *oral behaviours* as dependent variable [F (1, 9) = 11.67, p = 008, B = -751]. A similar result was found when entering as dependent variable the pathological scores at the subscale of *swallowing* [F (1, 9) = 11.36, p = .008, B = -747]. None of the other results were significant. Importantly, these effects were not observed when we considered semantic memory for nonfood stimuli as a predictor (see Appendix D4 for details).

The same models were run with all the participants' scores. Results show that both naming food and word-picture matching scores concerning food trials significantly predicted the *changes in eating habits* and the *changes in eating preferences* scores (see Appendix D5 for details).

The pattern of results described above is supported by Pearson correlations performed on both AD and FTD patients, with a significant negative correlation between deglutition and oral behaviours scores for AD and word-picture matching, and between preferences and habits for FTD (see Appendix D5 for tables and details).

5.3.2 *Anatomical analyses*

APEHQ. We observed a significant correlation between local grey matter concentration in the left insular cortex, left temporal lobe, left caudate nucleus and right fusiform gyrus and the scores at the subscale *changes in eating habits* ($p <. 05$ and $p < .001$, FWE corrected). In addition, another cluster emerged at the level of the posterior cingulate cortex ($p = .032$, uncorrected). See Table 5.4 for coordinates and statistical values. For what concerns the subscale *changes in eating preferences,* a significant correlation with local grey matter concentration in the cuneus and precuneus cortex, in the posterior cingulate cortex and in the subjacent white matter ($p < . 05$, FWE and $p < .001$ uncorrected) was observed. No significant patterns of atrophy were found to be associated with other subscales such as hyperphagia, swallowing and oral behaviours.

Changes in Eating Habits > ALL

Cluster			Peak					Coordinates		
p(FWE-corr)	Cluster size	p(unc)	p(FWE-corr)	p(FDR-c	T	equivZ	p(unc)	x	y	z {mm}
0.132	1266	0.014	0.036	0.229	5.830	4.820	0.000	-18	52	16
			0.549	0.318	4.560	4.000	0.000	-28	-4	36
			0.749	0.331	4.320	3.830	0.000	-24	26	27
0.279	915	0.031	0.042	0.229	5.780	4.790	0.000	-52	-21	-2
			0.25	0.318	5.000	4.300	0.000	-63	-9	2
			0.81	0.377	4.240	3.770	0.000	-51	6	-8
0.106	1370	0.011	0.234	0.318	5.030	4.320	0.000	34	-12	32
			0.347	0.318	4.830	4.190	0.000	30	-12	39
			0.857	0.403	4.170	3.720	0.000	36	-2	27
0.006	2915	0.001	0.246	0.318	5.000	4.300	0.000	-54	-9	-48
			0.282	0.318	4.940	4.260	0.000	-42	-21	-38
			0.32	0.318	4.870	4.210	0.000	-58	-51	-32
0.576	560	0.083	0.263	0.318	4.970	4.280	0.000	28	18	36
			0.352	0.318	4.820	4.180	0.000	32	16	20
			0.641	0.322	4.460	3.930	0.000	28	22	27
0.018	2271	0.002	0.389	0.318	4.770	4.140	0.000	-15	-46	26
			0.521	0.318	4.600	4.030	0.000	-8	2	30
			0.547	0.318	4.570	4.000	0.000	-9	-24	28
0.456	679	0.059	0.407	0.318	4.750	4.130	0.000	36	-30	8
			0.704	0.323	4.380	3.870	0.000	56	-21	2

Changes in Eating Preferences > ALL

Cluster			Peak					Coordinates		
p(FWE-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-c	T	equivZ	p(unc)	x	y	z {mm}
0.005	2964	0.001	0	0	10.71	7.04	0	28	-40	27
			0.002	0.001	6.98	5.46	0	18	-6	33
			0.872	0.27	4.14	3.7	0	24	-52	28
0.095	1424	0.010	0.001	0	7.55	5.75	0	-26	-26	34
			0.052	0.01	5.68	4.73	0	-22	-44	28
			0.691	0.17	4.4	3.88	0	-26	-51	14

Table 5.4. *Corrected and uncorrected p values for the changes in eating habits scale.*

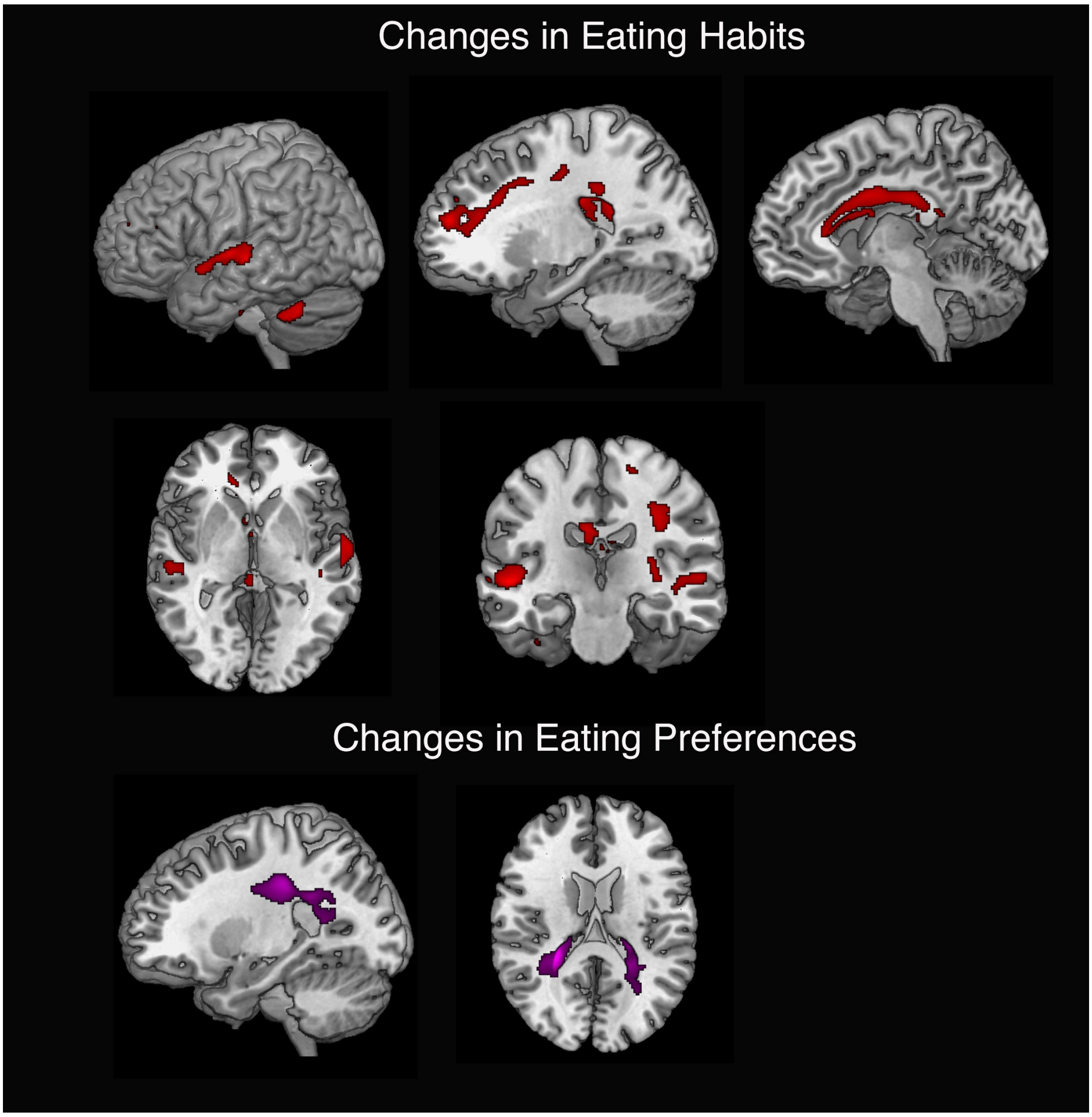


***Figure* 5.2**. *Significant clusters correlating with pathological scores at the subscales describing changes in eating habits (in red) and changes in eating preferences (in violet).*

Semantic tasks. Performance on the naming task revealed a significant cluster in the left anterior temporal lobe (*p*FWE < .001, see Appendix D6). Performance on the word-picture matching correlates with a cluster in the left temporal lobe and in the fusiform gyrus, see Appendix D7.

Semantic tasks and APEHQ – Conjunction analyses. Then, we explored where the local grey matter concentration correlates with performance on the semantic task and the pathological scores at the APEHQ. In order to do so, we ran two separate analyses, one for the naming and a second for the word-picture matching task. We correlated the naming scores and the score on the five subscales of the APEHQ with the local grey matter concentration, in order to investigate which regions contribute to *both* semantic deficits in naming and abnormal eating behaviours. We found a significant correlation for naming together with changes in eating habits, with large clusters in the temporal lobe bilaterally, specifically in the anterior temporal portion; in addition, a cluster emerged in the right fusiform gyrus (see Figure 5.3 and Table 5.5).

Naming+Preferences> ALL

Cluster			Peak					Coordinates		
p(FWE-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-c	T	equivZ	p(unc)	x	y	z{mm}
0.00	7347	0	0	0	4.94	6.35	0	-34	-4	-18
			0.001	0.005	4.18	5.63	0	-30	4	-20
			0.001	0.005	4.150	5.59	0	-46	-2	-30
0.00	4136	0	0.016	0.019	3.650	5.08	0	46	-4	-12
			0.025	0.026	3.550	4.97	0	36	-3	-22
			0.230	0.186	3.040	4.41	0	44	15	-18

Table 5.5. *Corrected and uncorrected p values for naming performance + changes in eating habits.*

The correlation analysis between the scores on the APEHQ and word-picture matching task and the local grey matter concentration returned a cluster in the left anterior temporal lobe with the *changes in eating habits* subscale ($p < .001$ uncorrected). In addition, we found a peak ($p < .001$ uncorrected) in the right temporal lobe for word-picture matching and the *changes in eating preferences* subscale, consistently with what emerged in the previous analysis, for the same subscale and the naming task (see Table and Figure D8 in Appendix D). No results were found in the conjunction analysis with word-picture matching accuracy and the scores at other subscales (swallowing, appetite, oral behaviours).

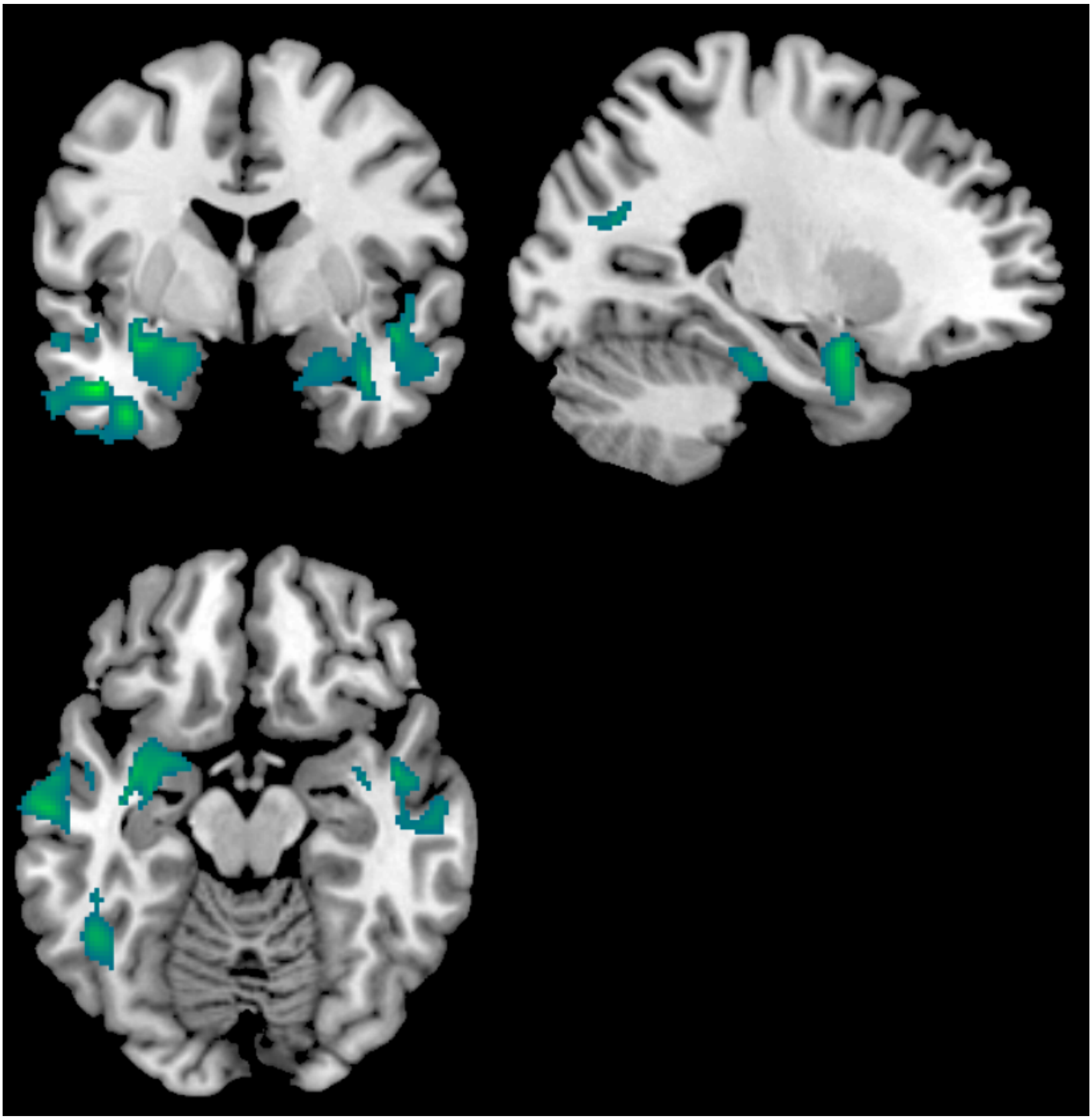


Figure 5.3. *Depicted in cyan, significant clusters correlating with naming performance and APEHQ's changes in eating habits subscale together.*

5.4 Discussion

This study provides evidence that there is a link between semantic deficits and specific eating disorders in dementia, both behaviourally and anatomically. The first main result is that semantic deficits in recognizing food items significantly predict both changes in eating habits and preferences, evaluated with the APEHQ in patients with FTD. Interestingly, these results were not observed with the subscale of *appetite*, which describes behaviours such as hyperphagia. Anatomically, we observed that both food naming and changes in eating habits, correlated with atrophy in the anterior portion of the left temporal lobe, known to be the site of semantic memory (e.g., Mummery et al., 2000). The same pattern of results emerged when we considered word-picture matching scores, strongly supporting the hypothesis that a semantic deficit for food may be responsible for those specific eating behaviours. In addition, the anatomical analysis exploring the neural correlates of *changes in eating habits* revealed a correlation with a cluster in the right fusiform gyrus, which has been found to be involved in pathological sweet tooth in patients with dementia (e.g., Withwell et al., 2007) and recognition of palatable foods in healthy participants (e.g. Simmons et al., 2005; see also van der Laan et al., 2011 for a meta-analysis).

Consistently with a recent VBM study assessing abnormal eating behaviour in dementia (Ahmed et al., 2015), the present results show that a significant atrophy on both sides of the temporal lobe, even if more pronounced on the left, is associated with semantic deficits and eating abnormalities together. These results are also in accordance with the pattern of progression that characterizes SD: patients that show an early impairment only in naming tasks, begin to show lower performance also on the word-picture matching task, as the atrophy extends to the right temporal lobe (see Lambon-Ralph et al., 2001 for an extensive discussion). Based on our findings, we can suggest that the eating abnormalities progress, as well as semantic deficits, together with this pattern of atrophy.

Overall, by showing that the semantic degradation accounts for specific eating alterations, such as changes in eating habits and in eating preferences, our results are in accordance with clinical observations (Thompson, 2016; Mendez, 2007) and the proposed hypothesis that different mechanisms may explain different eating disorders in FTD patients (Aiello et al., 2016). Related to our findings is also a recent study (Funayama et al., 2017) in which the relationship between semantic deficits and eating disorders associated to neurodegeneration was investigated. In particular the authors assessed the ability to use everyday objects in patients with pica, an eating disorder consisting in a strong change in eating behaviour leading to eat non-foods (DSM V, American Psychiatric Association, 2013). They found that patients with pica were those with a greater temporal lobe atrophy and failing when required to use some everyday objects (e.g. nail clippers, scissors, comb, hammer, toothbrush, but also kitchen utensils, such as a fork, a spoon, a knife, a cup). This result suggests that the temporal lobe is likely to be a critical structure for specific abnormal eating behaviour in dementia. However, differently from what described in their study, we found that the semantic disorder responsible for changes in eating habits and preferences was stronger food, rather than generalised.

The second interesting result is the association between the scores on the APEHQ subscales of *changes in eating preferences* and eating *habits* and local grey matter concentration in brain regions not involved in semantic processing such as the insular cortex, which is the primary gustatory cortex and is known to have a role in food processing (for a meta-analysis see van der Laan et al., 2011), the posterior cingulate cortex, involved in visual processing of foods with a high caloric content in obese participants (Rothemund et al., 2007) and the caudate nucleus, known to regulate eating behaviour (Farooqi et al., 2003) and to be involved in the processing of high calorie foods (e.g. Page et al., 2011, Killgore et al., 2003).

Finally, we found an interesting pattern of association between semantic deficits and eating behaviours in AD patients, that is, a significant correlating between naming and word-picture matching accuracy for food and *swallowing* and *oral behaviours* scores, which are sometimes reported in these patients (see Abdelhamid et al., 2016; Ikeda et al., 2002; Priefer and Robbins, 1997; Volicer et al., 1989). One could speculate that the semantic deficit could represent a more general cognitive impairment in these patients, which may in turn be responsible for these eating alterations. Indeed, patients with AD in a moderate stage of the disease, as those enrolled in this study, frequently report a worse anomia, together with the ability to swallow and with other oral behaviours. However, since this result has not previously described in the literature, it opens interesting possibilities that need to be further investigated.

In conclusion, this study demonstrates that a semantic memory degradation, i.e. low scores of patients on both naming and word-picture matching tasks, is critical for the emergence of abnormal eating behaviours, in particular meaningful modifications in eating habits and preferences, such as an extremely restrict diet, the rejection of specific type of foods or the increased preference for sweet foods and stocking up on desserts. These results could translate well to improve eating abnormalities, for instance, by implementing the use of pictures of food items in rehabilitation strategies for semantic impairment that have proven useful, such as the rehersal of the appropriate nouns paired with a picture (Graham et al. 2001), or word-picture matching (Savage, Ballard, Piguet & Hodges, 2013).

Chapter 6

General discussion

In my thesis I have described four different studies investigating semantic memory for food. In Study 1 (Chapter 2), I have tested in patients with different types of dementia (Alheimer's, svPPA, bvFTD) the prediction derived from the SFH as to whether natural food and living things, and transformed food and nonliving things share neural correlates. The results confirm and extend this prediction, as I showed that living things and natural food recognition depends upon the integrity of shared brain regions, and that the same can be said for transformed food and nonliving things. In Study 2 (Chapter 3), I have explored the extent to which experience in terms of life-long eating habits might affect semantic memory about food, by showing a relationship between the frequency with which specific foods were eaten and their naming and recognition accuracy. Specifically, centenarians named and recognized natural food better than transformed, whereas younger elderly adults showed the opposite patter. In Study 3 (Chapter 4), I have studied whether and how the distinction between natural and transformed food, observed in semantic memory, extends to episodic memory as well. The results showed in that transformed foods are better memorized than natural food, an advantage that is present even in centenarians and in patients with PPA, but not in Alzheimer patients. This finding suggests that transformed food is more resilient to episodic memory decline and further supports the view that semantic and episodic memory undergo different decline processes. This is also in line with the proposal that palatable foods, such as transformed foods, might activate the hippocampus thus facilitating episodic recollection (Stevenson & Francis, 2017). The aim of the final Study 4 (Chapter 5) was to establish a link between semantic deficits and abnormal eating behaviours in patients with dementia. I found that changes in eating habits and preferences in patients with dementia are predicted by their semantic impairment for food stimuli. This study for the first time demonstrated that sematic degradation and these specific abnormal eating behaviours are correlated, and that the temporal lobe plays a critical role in this process. In the following I will now discuss these results in turn and how they relate to the models of semantic memory that I have described in Chapter 1.

6.1 *Towards a comprehensive model of semantic memory: Sensory-functional knowledge of natural and transformed items*

In Chapter 2, I described a VBM study involving patients suffering from different neurodegenerative disorders and showing semantic deficits when performing tasks tapping lexical-semantic processes. The main findings of Study 1 are that i) the recognition of natural and transformed food is supported by different brain regions, and that ii) these regions appear to belong to two different networks, one coding sensory properties (e.g., visual, olfactory, gustatory), the other functional properties (e.g. functional, motor).

For what concerns the structural connectivity, the results highlighted a set of cortical regions and white matter tracts involved in semantic processing. In particular, bilateral OFC, FG, and LOC, connected by the uncinated fasciculus, are associated with sensory knowledge, while IFG, STG, MTG, and posterior parietal cortex, connected by the arcuate fasciculus and the inferior longitudinal fasciculus, are associated with functional knowledge. These results suggest that the sensory information (e.g. gustatory, in the OFC) may be conveyed to the ATL trough the uncinate, where it is integrated with the visual information from LOC (supposedly conveyed by the IFOF), and then to the frontal cortex through the uncinate or the arcuate fasciculus, where a decision on how and whether act upon the object is likely to be made (see Figure G1).

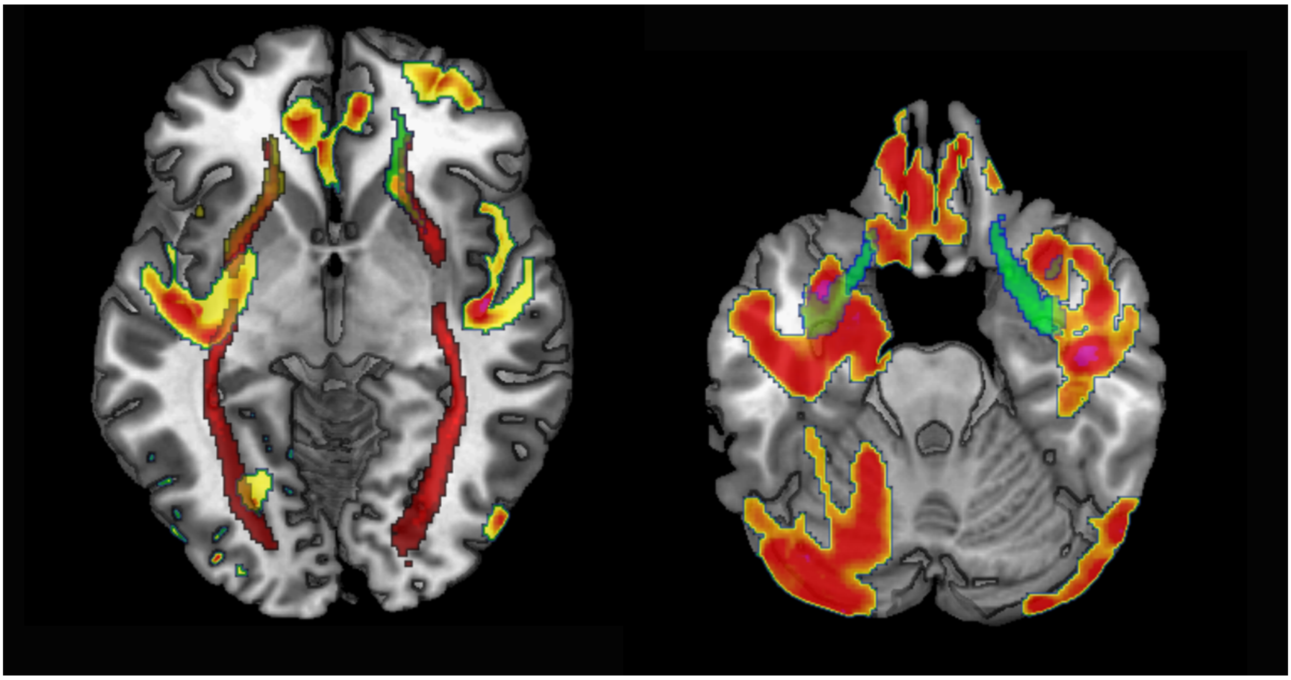


Figure G1*. The sensory network. The regions shown in the hotmap are those found associated with sensory knowledge, such as the cerebellum, LOC, FG bilaterally and OFC. In green, the uncinate fasciculus, and, in red, the IFOF. These white matter tracts connect the regions found involved for sensory knowledge to the temporal and the frontal cortices, providing all the connections necessary for perceptual information to be integrated in the temporal lobe and conveyed to frontal regions.*

Similarly, functional information from the IFG, the STG and the PPC may be conveyed to the temporal lobe through the different segments of the arcuate fasciculus. Indeed, this white matter tract has been found connect the superior and middle temporal lobe, and the inferior frontal and precentral gyrus, among the others (see Catani et al., 2005) (see Figure G2). In addition, the arcuate fasciculus has been implicated in tool use (see Rilling et al., 2008) This information should, then, be relayed to the frontal cortex through the uncinate fasciculus (see Vigneau et al., 2006). Overall, these results provided new evidence in support of current models of semantic memory, in particular the SFH. Indeed, as outlined in Chapters 1-2, the SFH holds that semantic knowledge for living things depends upon the integrity of a sensory subsystem, whereas that for nonliving things is proposed to depend upon a functional subsystem. In this view, it has been proposed (see Rumiati & Foroni, 2016) that natural foods should be processed as living things and transformed foods as nonliving things. My results show that food breaks down in natural and transformed, and that this distinction depends upon a sensory/functional organization of semantic knowledge. Indeed, we found that the integrity of a set of regions that are implicated in sensory processing, such as the visual cortices, are critical for an accurate recognition of both natural foods and living things. Likewise, atrophy in brain regions that process information about functions is correlated to a pathological recognition performance on transformed foods and nonliving things, consistently with the predictions derived from the SFH.

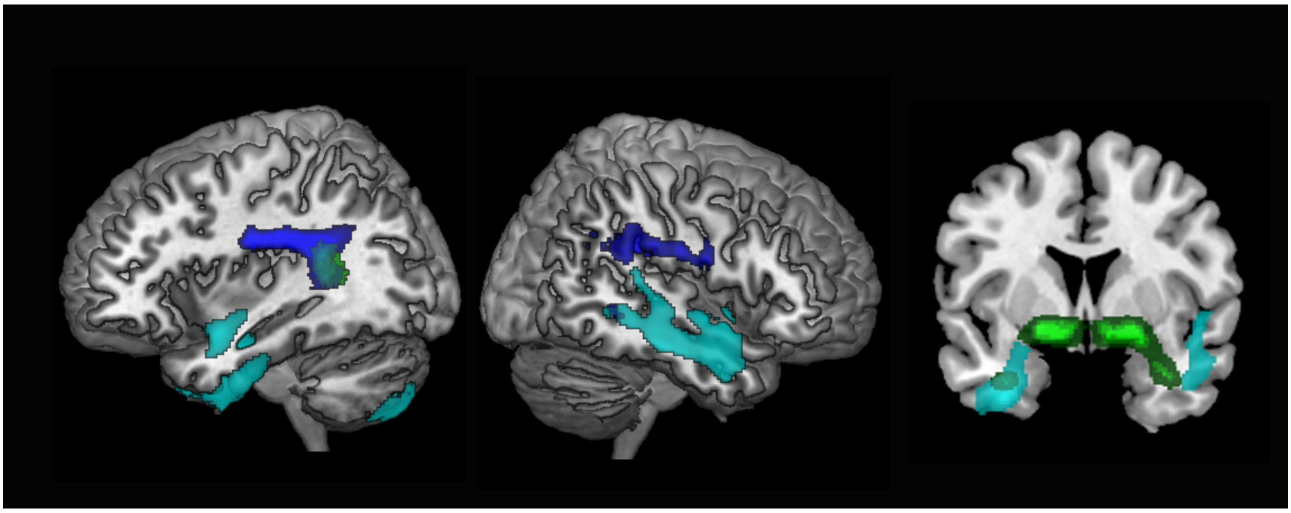


Figure G2. *The functional network. In cyan, the grey matter regions identified with the VBM analyses. In blue, the arcuate fasciculus, in dark green the posterior segment and in light green the anterior commissure, some of the white matter tracts connecting the regions of this putative functional network.*

At the same time these results are also in partial accord with Martin's model (GRAPES). Based on this model, one should expect i) that semantic memory is organized in a property-specific manner, and ii) that this information is organized in regions that overlap with those that process that type of information. I show that, to some extent, there is a property-specificity in the organization of semantic memory. However, there are two main dissimilarities between Martin's model and our findings. First there is not a clear pattern of overlap between regions that respond to a specific type of information, and regions that seem to recognize that object. For instance, transformed foods are recognized by the IFG and pMTG, among the others, that is regions that are not responsible for tasting or visual processing. Second, the set of regions that are implicated in object recognition and that are property-tuned, are strongly clustered along the sensory/functional distinction.

My results are not all easily explained with the DDSH (Mahon and Caramazza, 2011), in that I show that semantic knowledge is not domain-specific, but rather modality-specific. This emerges from the result that natural food and living things share several brain regions that are crucial for their recognition, as that transformed food has a similar patter when associated to nonliving things. I think that semantic knowledge is domain general but modality specific. However, there is a result that is consistent with the DDSH. This theory proposes that there are innate patterns of connectivity between the ventral cortex and other brain regions, that mediate object recognition, and that are these innate patterns that drive the specialization in semantic categories. I also argued that connectivity plays a critical role in semantic categorization, but with connectivity patterns being organized, as I clarified above, according to the modality of processing rather than to the domain (see Figures G1, G2 and G3 for details).

In addition, one of the results of Study 1 is that the ATLs' integrity correlated only when we considered the overall semantic performance, regardless of the type of category investigated (see A9 in Appendix A), while other regions were found specifically associated to sensory processing, such as the LOC and the ITC. This result is in line with a recent model emphasizing the role of the ATLs as a semantic hub, as the C^3 model (Chen, Lambon Ralph and Rogers, 2017). As described in Chapter 1, this theory has gathered aspects drawn from different theories and is modelled based on disorders entailing semantic deficits (HSE, svPPA, TPT and VA, see Chapter1) and expecting, on the basis of the type of lesion, a specific pattern of impairment. It shares several relevant similarities with the SFH: for instance, that sensory features are considered crucial for recognizing living things in svPPA (see Hoffman et al., 2012; Lambon Ralph et al., 2003), a result that we have also found (Chapter 2), whereas shape is not (Hoffman et al., 2012). However, this theory diverges from the SFH in that it proposes the ATLs as a cross-modal hub communicating with modality-specific spokes (Chen, Lambon Ralph and Rogers, 2017). Our results converge with their view that ATLs may be critical in integrating semantic information. We speculate that, when encountering an object, the initial information, that could be either sensory or functional, based on the type of knowledge is more relevant for recognizing that object, is processed by regions that we have found to be associated with recognition of natural entities (LOC, ITC, among the others) or of artificial entities (IGF, pMTG, STG). Then, this information is eventually integrated in the ventral ATLs, that have been proposed to be cross-modal hub (e.g. Chen, Ralph, and Rogers, 2017; Jackson et al., 2015; Binder et al., 2011; Patterson et al., 2007). In our view, the 'visual spoke' described in the C^3 model (see Hoffman et al., 2012) might be one of the components of the sensory subsystem/network. Finally, the semantic information about the object is likely to be conveyed to the frontal cortex through, e.g., the arcuate fasciculus, allowing individuals to name the object (see Catani and Mesulam, 2008), or through the uncinate fasciculus to the OFC, where the information is evaluated and a decision is made (e.g. Bechara et al, 2000). See Figure G3 for a proposal of a model of how semantic memory may be organized.

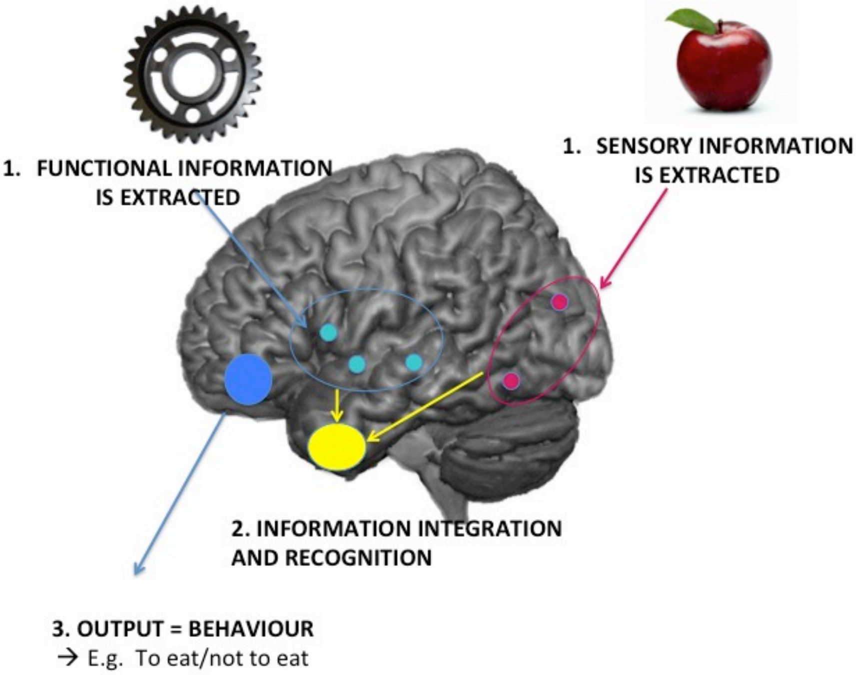


Figure G3. *A proposal for a comprehensive model of semantic memory. When we encounter an object, based on its most efficiently descriptive features, that are sensory vs. functional (the sensory and functional regions depicted are representative of a part of the set of regions found), we recognize it by integrating this information with the contents stored in our semantic memory in the ATL. From here, possibly trough the uncinate fasciculus, information is conveyed to the frontal cortex, where a decision is made. In the figure, for instance, whether to eat or not to eat an object. It is to note that shape is not a distinctive feature, as already suggested by the SFH and confirmed by the study of Hoffman et al., 2012. This model can be easily applied to natural and transformed food: for instance, if we are weak and we feel a great need of energy, a food with higher caloric content shall be chosen over a food with less calories.*

We argue that our data on natural and transformed food are sensible also from an evolutionary viewpoint. We speculate that we have evolved by relying on our senses to discriminate safe foods from those that are dangerous because rotten or poisonous (Becker et al., 2016). Therefore, natural food being represented in a set of sensory regions accords well with this hypothesis. Moreover, when the *homo erectus* discovered fire and began to cook (see Wobber, Hare & Wrangham, 2008 for a broad discussion), it was no longer necessary to use our senses to confirm that cooked foods were not dangerous, since cooking drastically reduced the possibility of infections (Aiello & Wheeler, 1995; Tauxe, 2001). Moreover, cooked food was largely favoured because of its greater energetic value (Wrangham, 1999; Carmody and Warangham, 2009), which may be described as a functional property.

Another relevant point emerging from our anatomical analyses and that may be related to evolution, is the involvement of the precentral gyrus in semantically processing natural food. This region is not only a primary sensory area, but is also the site of the somatic motor and sensory homunculus (Penfield & Boldrey, 1937). Recently Catani (2017) revised Penfield's data and showed that, in this brain region there are co-localization of sensory maps representing different body parts, rather than a full segregation and critically between the hand region and mouth region. One may speculate that this is linked to the fact that hand-to-mouth movement are necessary to bring food to our mouth and that, initially, this movement was more likely to be associate to natural foods.

6.2 Semantic memory for food: modulated by experience

In Study 2 I have shown that semantic memory is modulated by experience. In particular, I explored the extent to which the degree of experience or exposure to a specific type of stimulus may explain an advantage in recognizing items belonging to a specific category. Indeed, we found that, in centenarians, both naming and word-picture matching scores for transformed food were significantly lower than those with natural food; however in younger elderly adults, the pattern of results was reversed. Interestingly, our participants' performance was affected by life-long eating habits, with centenarians having eaten significantly less frequently transformed food with respect to natural food and to the younger elderly participants. These results suggest that experience can be as important as much as concepts that may be hard wired in our brain, such as a preference for cooked foods, as it has been proposed (see Foroni & Rumiait, 2017; Rumiati & Foroni, 2016;

Coricelli et al., submitted, see also the previous section). Moreover, they are also consistent with the C^3 model and, to a certain extent, with the DDSH, as it suggests that experience and learning are of crucial importance in the organization of semantic memory (see Chapter 1, and Chen, Lambon Ralph & Rogers, 2017, for a broader discussion).

6.3 Episodic memory for food

In Study 3 I demonstrated that PPA patients and centenarians display a greater number of false alarms for natural food with respect to transformed food. This result is in line with other studies (Rumiati et al., 2016; Study 1) showing that transformed food recognition seems to be more resilient to brain damaged. This result may mean that transformed food concepts are more strongly hardwired in our brains with respect to those related to natural foods and there may be specific neural mechanisms for their recognition, in virtue of their relevance for survival (see Caramazza & Shelton, 1998). Transformed food may be more salient due to its higher calorie content (Rumiati et al., 2016), a feature that makes it an extremely relevant type of item. Stevenson and Francis (2017) have recently proposed that palatable food items, such as those used in my studies, may activate the hippocampus, thus eliciting episodic recollection. This could be due to the strong hedonic value associated with this type of stimuli.

In addition, Study 3 is the first study investigating the animacy effect in patients with dementia. It has been proposed that living things may be more resilient to brain damage due to its evolutionary meaning in episodic memory (Nairne et al., 2016). Indeed, we observed that PPA patients show the animacy effect, whereas centenarians do not, a result consistent with a previous study testing this effect in elderly adults (Bugaiska et al., 2016). This suggests that, only when a cognitive degeneration is present, there is an advantage for the living category, with respect to nonliving things. Taken together, these results suggest that both living things and transformed food, are more protected from the decline affecting episodic memory, possibly in virtue of their greater biological relevance.

6.4 *Semantic deficits for food pathologically affect eating behaviour*

Finally, I have explored how the degradation of semantic memory may affect eating behaviour. Specifically, in Chapter 5, I have described how this semantic impairment may result in the development of aberrant eating behaviours. Indeed, our analyses suggest that the degradation of semantic memory may play a causal role in the development of changes in eating habits and changes in eating preferences, as it was observed in single cases studies (Mendez et al., 2007; Thompson et al., 2016). Importantly, we also showed that both semantic memory and changes in eating habits and preferences seem to depend upon the integrity of the temporal lobe.

These results open the way for implementing food stimuli in rehabilitation therapies for semantic deficits. It has been shown that rehabilitation can minimizing lexical-semantic deficits (e.g. Senaha et al., 2010) and improve them (Rokel & Anderson, 2012; Rokel, Rochon & Leonard, 2006). An interesting and fruitful relearning therapy that has recently been proposed (Cognitive enrichment therapy, COEN, Suarez-Gonzales et al., 2014) suggests that if the concept to be relearned is associated to related concepts, the improvement of the semantic deficits may generalize to other object concepts. In this view, one could associate a food concept, such as an apple, to apple vinegar, apple pie, apple juice, inasmuch we are highly exposed to objects associated to food, as most of them pertain to everyday life and may be easily encountered in the homes of patients as well. An interesting and ecological approach, for instance, has been applied by Bier and colleagues (2011) to patient EC; a 68-year old woman with svPPA who progressively stopped cooking because she had a deficit in the recognition of food. The therapy consisted in the patient cooking, assisted by a software showing the steps to be completed and the items to be used, with their picture, their name and a description, allowing also to relearn those concepts (Groussard et al., 2010). The study shows that, across five months of therapy, the number of minutes spent by the patient consulting the software in order to successfully complete her recipe was dramatically reduced, leading her to complete 17 out of the 19 steps on her own. Moreover, EC was able to cook 9 different recipes during the five months of therapy. Importantly, she was also able to generate more attributes about the objects she had to use for the recipe if compared to the beginning of the therapy. This study shows the importance of introducing also the relearning of food concepts in rehabilitation therapies, since the impact of this loss of knowledge on patients' and their caregivers' everyday life is extremely meaningful (Bier et al., 2013).

Another interesting possibility to be explored, given the frequent association of the right hemisphere with behavioural impairments in patients with FTD, is the relationship between semantic deficits and eating disorders in svPPA patients with an initially right-lateralized atrophy of the temporal lobe. It would be interesting to test whether putative eating disorders are similar to those observed in our patients, or whether there are different behavioural disorders, such as delusions (see Chan et al., 2009), and also whether these disorders are related to semantic memory performance.

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