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LEMONS AND TRUST: THE CONTRIBUTION OF ANAESTHESIA TO THE STUDY OF THE NEURAL SUBSTRATES OF CONCRETE AND ABSTRACT WORD PROCESSING

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To my sons,

hoping that one day they will be proud of me for this.

To my husband,

who is proud of me everyday.

To my parents and sister,

who have always been.

But especially, to me,

for never giving up.

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ABSTRACT

There is evidence that abstract and concrete words are represented and processed differently in the brain. Numerous studies suggest the activation of a bilateral network for both abstract and concrete words, with a greater involvement of posterior, sensory areas in concrete word processing, and a more focal activation of anterior regions, involved in verbal processing, for abstract words. This Ph.D. thesis aimed at investigating the different neural substrates of concrete and abstract words by studying memory priming during general anesthesia. Implicit memory tasks, in fact, seem to be immune to the concreteness effect and recent neurophysiological studies suggest that conscious and unconscious semantic activation involve similar brain areas. Experiment 1 focused on the priming effect for intraoperatively primed abstract and concrete words in patients under general intravenous (propofol) anesthesia. Considering the specific brain targets of propofol, I hypothesized a stronger priming effect for concrete than for abstract words. Implicit memory for primed words was tested with a three-letter word stem completion test, in which half of the stems referred to primes, and half were foils. Both stimulation and testing were auditory, to avoid cross-modality interference. A control group of patients, who did not receive any intraoperative stimulation, but completed both concrete and abstract word stem completion test, was also recruited. As expected, a priming effect was found for concrete words, since the number of target hits was significantly higher than the number of non target hits. This difference did not apply to abstract words. The abstract experimental group performed comparably to controls. These results support the thesis that abstract word processing relies on the activity of anterior

brain areas, as for example the inferior frontal cortex, which are suppressed by propofol. The results would also confirm that priming, investigated through word stem completion, is not a simple perceptual, pre-semantic task, but engages multiple processes, including semantic access. As suggested by electrophysiological studies, semantic access might occur at very early stages of verbal processing, thus explaining a selective intraoperative priming effect for concrete words only. To further investigate these hypotheses, a second experiment was conducted. In experiment 2 the same methodology of experiment 1 was applied, but the volatile anesthetic sevoflurane was used, which is known to lower activity in brain regions located more posteriorly than those suppressed by propofol. The most interesting finding was the presence of a priming effect also for abstract words, which would confirm data from neuroimaging studies of a greater engagement of anterior brain regions in abstract word processing. To better define the involvement of the frontal cortex in the processing of abstract words, a series of patients undergoing awake surgery for brain tumor removal was studied in experiment 3. Patients performed a lexical and a semantic decision task, together with a standard intraoperative cognitive monitoring, during direct cortical stimulation. The fundamental role of the left inferior frontal gyrus in abstract word processing was confirmed.

CHAPTER 1. CONCRETE AND ABSTRACT WORD PROCESSING

Abstract concepts are abundant in spoken language and are extremely frequent in our vocabulary but still little is known about their representation in semantic memory. Abstract words like "happiness" and "memory" are usually considered non-concrete, since they cannot be experienced by our senses, and their meaning is retrieved from association with other words and concepts. Abstract words are also usually considered to have low-imageability, because it is difficult to evoke mental images of the referent word (Macoir, 2008).

Concrete words differ from abstract words in that they refer to concepts that can be experienced with our senses, like tangible objects, places, people. Concrete words are usually considered as having high imageability because of the ease with which they evoke mental representations.

Concreteness and imageability are therefore correlated parameters (Paivio, Yuille, Madigan, 1968) but not synonymous. Although concrete words are usually also imageable, abstract material presents a high degree of variability within this dimension, and some abstract words, for example those referring to emotions, can be highly imageable (Kousta et al., 2011; Papagno, Martello, Mattavelli, 2013). Some authors suggest that rather than a dichotomy, abstractness and concreteness may be considered as a continuum between two distinct clusters of highly concrete and highly abstract concepts (Wiemer-Hastings et al., 2001; Crutch & Warrington, 2005; Macoir, 2009).

A number of studies have demonstrated a behavioural advantage of concrete over abstract word processing (Paivio, 1991). This phenomenon has been referred to as the concreteness effect, and has been accounted for by a number of proposals, of which the two most popular are the Dual Coding Theory and the Context Availability Theory (§ 1.1). The neural basis of the concreteness effect, and the possible different neural underpinnings of concrete vs. abstract word processing, have been investigated in a large number of neuropsychological, neuroimaging and electrophysiological studies (§1.2), with contrasting results. Studies on brain-damaged subjects, who consistently show better performance on abstract as compared to concrete words, have been reported too. The reversed concreteness effect (§1.3) is incompatible with both the Dual Coding Theory and the Context Availability model, and sets up the need for a comprehensive proposal, which should account for both clinical and experimental data.

1.1 THEORETICAL MODELS TO EXPLAIN THE CONCRETENESS EFFECT

The concreteness effect refers to the common observation of superior performance for concrete words compared to abstract ones, in terms of speed of processing and accuracy (Jessen et al., 2000).

Children acquire concrete words before abstract ones (Brown, 1957) and this advantage has been demonstrated also in adults in spontaneous speech, reading, writing, repetition, naming and comprehension (Papagno, Capasso & Miceli, 2009).

Among the proposals that have been put forward to account for the concreteness effect, two have been particularly influential, as already reported: the Dual Coding Theory by Paivio (1991) and the Context Availability Theory (Schwanenflugel, 1991; Schwanenflugel & Shoben, 1983). In both of these accounts, concrete word representations are assumed to be richer than abstract ones, but, as described below, the explanation is more complex.

1.1.1 Dual Coding Theory (DCT)

The DCT evolved from specific experiments on the role of imagery in memory and developed to a general theory of memory and cognition (Paivio, 1991). It represents a variant of the multiple semantic systems approach, in that it interprets concreteness effects by means of modality-specific representational and processing systems, and emphasizes the importance of the verbal/non verbal symbolic contrast.

The theory assumes an orthogonal relation between a symbolic system and a specific sensory-motor system. Verbal and non-verbal systems symbolically represent the structure and functional properties of language and the non-linguistic word, respectively, even if both classes of events come in different modalities (visual, auditory, haptic). The representational units of the two systems are assumed to be modality-specific perceptual motor analogues. They have been referred to as *logogens* (word generator) and *imagens* (image generator). Verbal and nonverbal systems are assumed to be functionally independent, in that one system can be active without the other or both can be active in parallel. This implies, for example, that verbal and nonverbal codes corresponding to the same object should have additive effects on recall (Paivio, 1991). Also, different representational units might be functionally interconnected so that activity can spread between (*referential* interconnections) and within (*associative* interconnections) systems. A schematization of DCT principal assumptions is depicted in figure 1.1.

As far as specifically concerns abstract/concrete concept processing, the DCT assumes that abstract words are represented mainly in a symbolic (verbal) system and are associated to other linguistic material, with limited (or no) connections with the nonverbal system. Concrete words are quantitatively and qualitatively different from abstract words in that they

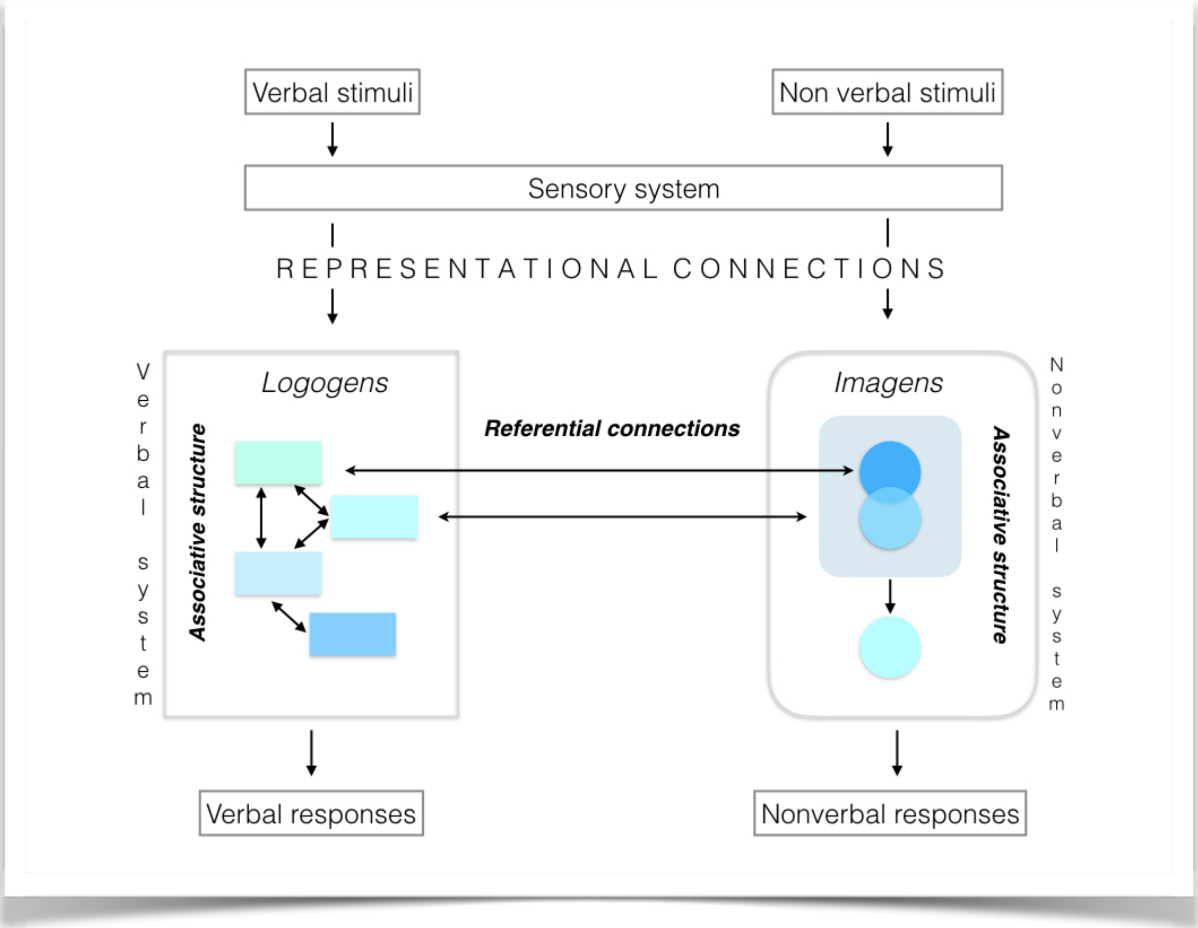

Figure 1.1. A schematic representation of the principal assumptions from Dual Coding Theory, adapted from *Clark JM, Paivio A. Dual Coding Theory and Education. Educational Psychology Review 1991; 3(3):149-210.*

are represented not only in the same symbolic system, but are also linked to the visual (non-verbal) information system. Concrete words would at first activate the verbal system and then, through referential connections, the nonverbal system. The cognitive advantage for words referring to concrete concepts is therefore attributed to the fact that all words engage associated verbal codes, but concrete words activate image-based (i.e. non-verbal) codes to a greater degree than abstract words.

DCT assumptions have been demonstrated in a large number of memory tasks, for example free recall, cued recall, recognition memory (Paivio, 1991; Paivio, 1994). These studies demonstrate a superior encoding and retrieval of concrete words (Jessen, 2000).

As mentioned, the DCT evolved from specific experiments on the role of imagery in memory, and its interpretation of concreteness effects relies particularly on the role of imagery as an integrative mechanism in associative learning and as an additive supplement to the verbal code in memory. A number of studies (e.g. Paivio, Smith & Yuille, 1968; Paivio, 1968; Paivio & Walsh, 1991) demonstrated that rated imagery value surpassed other sublexical language properties (e.g. word frequency, familiarity) as the best single predictor of word recall. They also supported the additivity of imaginal and verbal codes by concrete superiority in both cued and free recall (Paivio, 1991).

For what concerns the neural basis of semantic processing, the DCT would predict different, although overlapping, neural mechanisms for concrete and abstract concept processing (Paivio, 1991; Binder et a., 2005). One specific hypothesis is that verbally mediated system is lateralized to the language-dominant hemisphere, whereas nonverbal system engages both hemispheres (Paivio, 1986). Therefore, abstract concepts should engage mainly language areas in the left hemisphere, while concrete items should be represented bilaterally in the brain and activate not only language-dedicated networks, but also sensory-motor areas. These predictions have been endorsed by a number of behavioural studies using visual hemifield stimulation paradigms (e.g. Shibahara & Lucero-Wagoner, 2002), by clinical reports of right-brain damaged patients (Funnel et al., 2001), by electrophysiological investigations (e.g. West & Holcomb, 2000) and by some neuroimaging studies (e.g. Binder et al., 2005).

1.1.2 Context Availability Theory

Several functional imaging studies, however, failed to provide support for the right hemisphere involvement in concrete word processing as predicted by the DCT (e.g. Noppeney

& Price 2004; Fiebach & Friederici 2003; Kiehl et al., 1999; Perani et al., 1999) and concrete word advantages are not always seen in all tasks (van Hell & de Groot, 1998; Schwanenflugel & Stowe, 1989). These findings have been used to uphold the DCT competing account known as context availability theory.

In contrast to the DCT, the context availability model denies the existence of different processing systems as determinants of the concreteness effect. This theory argues that the nature of the representations and the elaboration processes of abstract and concrete words do not differ and there is a pure quantitative difference between abstract and concrete items, within a same unique semantic system. According to context availability, the most likely explanation for the concreteness effect is that concrete words are easier to associate with a context than abstract words and activate a richer semantic network. Context information can either be retrieved from (semantic) memory or be present in the stimulus environment. Concrete words would be more strictly associated than abstract words to relevant contextual information in the semantic memory.

The advantage of concrete over abstract words should disappear if abstract nouns are presented in a meaningful context with sufficient verbal information, resulting in abstract nouns being responded to as quickly as concrete ones (Schwanenflugel & Stowe, 1989). Empirical studies demonstrated that, when abstract and concrete concepts are matched with respect to the amount of contextual information (i.e. the amount of contextual information participants can generate for each word or the amount of contextual information participants are given, either in the form of several or even a single prior sentence) the concreteness effect on accuracy and reaction times (RTs) diminishes or even vanishes in a variety of tasks, including word recognition, lexical decision, naming and sentence meaningfulness judgments

(Schwanenflugel, 1991; Schwanenfugel, Harnishfeger & Stowe, 1988; van Hell & de Groot, 1998; Schwanenfugel & Shoben, 1983; Schwanenfugel & Sotwe, 1989). Hence, if words are presented in isolation, contextual information is assumed to be more readily available for concrete than for abstract words. According to this account, the processing disadvantage for abstract items stems either from the fact that abstract concepts are more weakly associated with other concepts in the semantic system and have, therefore, less contextual information available; or from the fact that semantic representations of abstract words contain less information than representations of concrete words (Schwanenfugel & Shoben, 1983). Accordingly, the processing of abstract words is assumed to entail more effort in retrieving contextual semantic information.

Also, the context availability theory, in contrast with the DCT, does not emphasize the concrete words linkage to sensory information and imagery abilities, but stresses the importance of being able to access *any* associated information when processing a concept.

With regard to the neural basis of the concreteness effect, the context availability theory does not explicitly rule out a right hemisphere involvement, but attributes the concreteness effect purely to the access of more verbal information, which implies a predominant left hemisphere processing system (Jessen, 2000). This hypothesis is in line with some neuroimaging studies, which failed to demonstrate a specific right hemisphere activation to concrete word processing (Noppeney & Price 2004; Fiebach & Friederici 2003; Kiehl et al., 1999; Perani et al., 1999).

1.1.3 Conclusion

DCT explains the concreteness effect in terms of concrete words activating two representational systems, verbal and non verbal, while abstract words would be able to access almost exclusively the verbal system and require more effort to retrieve semantic information. On the opposite, the context availability theory claims that the advantage of concrete over abstract words is purely quantitative, since both types of words engage the same verbal system, but concrete words can rely on richer semantic connections.

Even if the DCT has received more robust experimental support, neither view can claim, on the basis of experimental and clinical findings, to be the complete explanation of the concreteness effect. Nor can these theories account for what can be observed in rare clinical cases and is referred to as the reversal of the concreteness effect, which will be discussed in § 1.3.

Below, an overview of the more relevant studies in the field of cognitive neuroscience, which investigated the neural basis of the concreteness effect and the possible different brain regions that subserve abstract and concrete word processing, is reported. Also, a recap of the inferences made from these results on the functional processing of concrete and abstract concepts is provided.

1.2 CLINICAL AND EXPERIMENTAL DATA

The neural representation of concepts is a crucial issue in cognitive neuroscience. Studies on semantic memory have focused on the representation of concrete vs. abstract words following the observation of selective deficits in neurologically affected patients. These data can provide crucial insights into the modality with which different information are processed and retrieved in the brain, and are relevant in understanding language function in both healthy and clinical populations (Wang et al. 2010).

1.2.1 Neuropsychological studies

Clinical data from patients with neurodegenerative disorders, such as Alzheimer's disease (AD), generally show that patients have more difficulties with abstract than concrete words. Rissenberg and Glanzer (1987) conducted two experiments comparing young adults, healthy old adults, and AD individuals on concrete vs. abstract recall and word finding tasks. The first results indicated an overall decline in recall across the three groups with a reduction in normal aging of the memory advantage of concrete over abstract words. Demented patients did not show this attenuation. In their second experiment, word-finding ability was significantly impaired in AD patients, but not in normal aging. Also, the AD group performed worse on the abstract items.

More recently, Peters and colleagues (2009) investigated the influence of semantic knowledge on short term memory (STM) performance in healthy seniors, AD patients and young adults with an immediate serial recall task using word lists of high (concrete) or low (abstract) imageability words. They found that all participants recalled more high-imageability words than low-imageability words, but the effect of word imageability was greater in AD patients. It should however be considered that in this study there seems to be an overlapping between concreteness and imageability, which, as stated before, is not the case.

The concreteness effect is a common observation also in aphasic patients, who often show an advantage for concrete over abstract words in naming, comprehension, reading and repetition (Roll et al., 2012). In general, aphasic patients with anterior lesions are found to have greater difficulty in processing abstract words (Hagoort, 1998; Tyler, Moss, Jennings, 1995). A damage in more posterior regions has been associated with a selective impairment of word access from visual input, e.g. naming of visually presented objects and colors (Girkin & Miller, 2001; Gainotti, 2004; Coslett & Saffran, 1992; Forde, Francis, Riddoch, Rumiati & Humphreys, 1997; Luzzatti, 2003).

Franklin, Howard & Patterson report an interesting case. Studying DRB (Franklin, Howard & Patterson, 1994), a fluent aphasic patient, they found a pattern of impaired auditory comprehension for abstract but not for concrete words, in a context of preserved comprehension of all types of written words, which they called "abstract word meaning deafness". DRB showed the same disadvantage for abstract words (and for nonwords), as compared to concrete words, in repetition and writing to dictation tasks. Notably, DRB's auditory comprehension and repetition impairments were not affected by word frequency. In the light of his preserved comprehension for all written words, DRB impairment in word finding, which the authors refer to as "abstract word anomia", was further investigated (Franklin, Howard & Patterson, 1995). DRB was severely anomic in spontaneous speech, but only mildly impaired on picture naming tests. The authors explain this discrepancy in terms of DRB's specific difficulty for abstract words.

Shapiro, Shelton and Caramazza (2000) reported the case of JR, a patient suffering an anomic aphasia due to post-stroke left frontal temporal and bilateral parietal damage. JR was impaired in producing nouns relative to verbs in picture naming, sentence completion, and sentence generation tasks. He was better at both producing and comprehending concrete nouns than abstract nouns.

Recently, Roll and colleagues (2012) reported results from three subjects with left frontal brain damage suffering Broca's aphasia; they were compared to twelve control subjects on a free association to cued words test. The degree of abstractness of the generated words and semantic similarity to the cue words were measured. The authors found that word production in Broca's aphasics was characterized by a lower degree of abstractness and a lower degree of coherence in association to abstract cue words, as compared to controls. A general pattern of impaired production and comprehension for abstract words was found in Broca's aphasic patients.

Papagno, Martello & Mattavelli (2013) investigated the anatomical substrates of abstract and concrete words in a population of 22 brain-damaged patients with a single vascular lesion, either in the right or left hemisphere. In a semantic judgment similarity task, they found a significant interaction in word type per group, in that left temporal brain-damaged patients performed significantly better with concrete than abstract words. In general, their results from lesion mapping indicated that the left superior and middle temporal gyri and the insula are crucial areas in processing abstract words.

Considered together, findings from neuropsychological studies suggest at least partly different neural basis for abstract and concrete word processing, since most of neurologically impaired patients with left frontal and/or temporal damage show the concreteness effect.

Concrete words are associated by definition with perceptual and motor features of the referent object (Martin, 2007). Thus, it could be speculated that the meaning of concrete words is represented in neural networks involving unimodal and heteromodal brain regions, such as the ventral-medial area of the temporal lobe, which is thought to be part of the visual association cortex (Libon et al., 2013). On the other hand, the meaning of abstract words might be more dependent on connections to other word forms, possibly involving left frontal and prefrontal regions (Roll et al., 2012; Papagno, Martello, Mattavelli, 2013). The left prefrontal ventrolateral cortex, in particular, is thought to control top-down retrieval processes of the conceptual information stored in the posterior temporal cortex and possibly in other regions (Martin, 2007). Finally, the results reported support the hypothesis of different organisation of concrete (semantic similarity) and abstract (associative organization) concepts (Papagno, Martello, Mattavelli, 2013).

1.2.3 Neuroimaging studies

Neuroimaging studies allow the predictions made from theories and clinical investigations about the functional neuroanatomy of the concreteness effect to be tested. Thus far, they have produced contrasting results, possibly because of methodological issues, such as tasks and stimuli features (Wang et al, 2010) and the lack of control of possible confounding variables (e.g. the retrieval strategies used by participants in recall tasks (Jessen et al., 2000)).

Some studies support the hypothesis of a lateralized concrete vs. abstract processing in the brain (e.g. Kiehl et al, 1999; Nopponey & Price, 2004; Binder et al., 2005). Left hemisphere activation has been found predominantly for abstract items, while concrete ones might produce a bilateral activation of several structures, almost invariably including the fusiform gyrus. Binder and colleagues (2005) for example, used event-related functional magnetic resonance imaging (fMRI) while participants identified abstract and concrete words. Relative to non-words, both abstract and concrete items activated a left-lateralized network, which included the left angular gyrus, middle and inferior temporal gyri, and the dorsal prefrontal cortex. Direct contrast between concrete and abstract words showed stronger activation by concrete words bilaterally in the angular gyrus, posterior cingulate gyrus, and the precuneus; and in the left dorsal prefrontal cortex. Conversely, greater activation by abstract words was almost entirely confined to the left hemisphere, including the inferior frontal gyrus, the premotor cortex and the dorsal temporal lobe.

On the basis of these findings and consistent with a dual-coding model, it has been speculated that the meaning of abstract concepts is largely specified by their usage in language rather than by their relations to the physical world (which is true instead for concrete, sensory-based material) and subjects might therefore generate an appropriate semantic sentential context to specify the meaning of abstract concepts (Binder, 2005). Specifically, the activation of the left inferior frontal lobe by abstract words (and nonwords) has led to the conclusion that this area is not involved in processing semantic information per se, but that it serves as a phonological working memory that holds the phonological form of abstract words while retrieving associated words. The right hemisphere preferential activation by concrete words would demonstrate the existence of a right-lateralized nonverbal system that represents primarily concrete concepts. Finally, the fact that some brain regions (like the left lateral temporal lobe) were activated by both types of words might suggest that these areas subserve a common mechanism, such as contextual access, in both concrete and abstract word processing (Binder et al., 2005).

Conversely, other studies (e.g. Perani et al., 1999; Jessen et al., 2000; Whatmough et al., 2004; Fiebach & Friederici, 2004) support a bilateral involvement for both abstract and concrete item processing.

Perani et al. (1999) used positron emission tomography (PET) to assess regional cerebral activity during visual lexical decision of concrete vs. abstract nouns. They found a selective activation of the right temporal pole, the right amygdala and the bilateral inferior frontal cortex when processing abstract words was compared to concrete words, whereas no brain areas were more active in response to concrete than abstract words.

Also Fiebach and Friederici (2004) used a lexical decision task but with fMRI. They found that abstract words activated the pars triangularis of the left inferior frontal gyrus more strongly than concrete words; specific activity for concrete words was observed in the left basal temporal cortex.

Jessen and colleagues (2000) used event-related fMRI and an explicit encoding paradigm to address the question of which cortical regions are responsible for the superior intentional encoding of concrete over abstract words. In the contrast of concrete > abstract words, they found a greater activation in the lower left parietal area, in the left inferior prefrontal gyrus, in the lower right parietal lobe and the precuneus. In the contrast of abstract > concrete words they found stronger activation in the left inferior frontal gyrus (Broca's region) and in the right lateral occipital gyrus.

A major problem with neuroimaging experiments is that a single study typically does not have enough power to reveal the neural substrates of a cognitive process, partly due to the limited sample size (Wang et al., 2010). Meta-analysis, by integrating existing data from different studies, may overcome this limit (Fiebach & Friederici, 2004; Binder et al., 2009). Wang and colleagues (2010) aimed at identifying the differences in neural representation of abstract and concrete items by combining data from nineteen neuroimaging studies on healthy subjects. These studies compared peaks of activation for abstract and concrete concepts at a whole brain level, for a total of 303 participants. Meta-analysis results indicated consistent and significant differences in the neural representation of abstract and concrete material. In particular, as depicted in figure 1.2, the comparison of abstract > concrete concepts showed a significant consistent activation among studies in the left inferior frontal gyrus and in the middle temporal gyrus. The former has been linked to verbally-mediated semantic knowledge processing and has been considered as a specialized central executive area for semantic retrieval; the latter is thought to play a role in abstract/concrete concepts different retrieval mechanisms or strategies (Wang et al., 2010).

The comparison of concrete > abstract words showed stronger activation in the left precuneus, posterior cingulate, parahippocampal gyrus, fusiform gyrus, and culmen, with a trend of left temporal, occipital and parietal regions. The activation of these areas has been interpreted as a

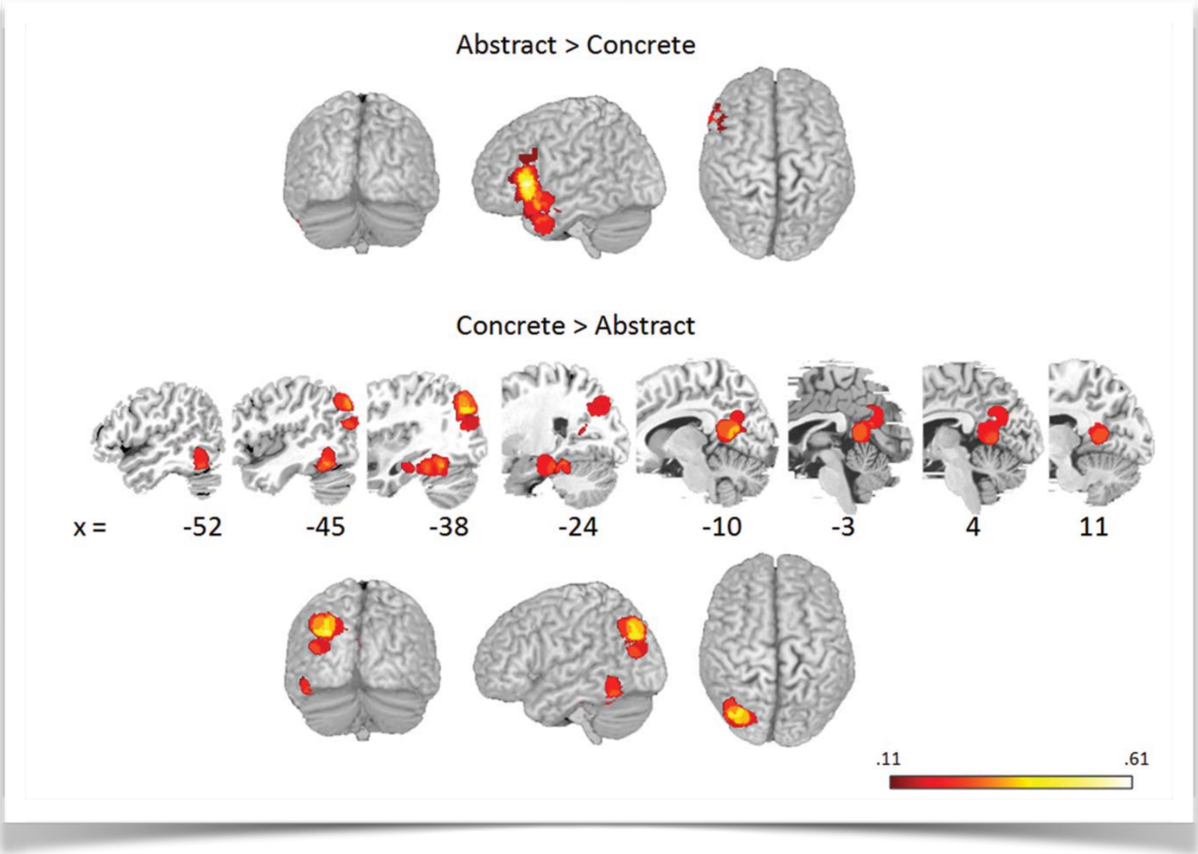

Figure 1.2. Regions surpassing the maximum activation proportion expected under the null hypothesis for abstract > concrete and concrete > abstract comparisons. *From Wang J, Conder A, Blitzer Dn, Shinkareva SV. Neural representation of abstract and concrete concepts: a meta-analysis of neuroimaging studies. Human Brain Mapping 2010; 31:1459-68.*

greater engagement of mental image generation in concrete compared to abstract word processing, since mental imagery has been correlated with activation of perceptual systems (Kosslyn et al., 2001). Findings from these neuroimaging studies suggest that mental imagery is a key component in processing of concrete compared to abstract words. Abstract concept processing seems to rely more heavily on the verbal system, while concrete concept representation involves more mental imagery than abstract concept and relies more heavily on the perceptual system (Wang et al., 2010).

1.2.2 Event-related potential (ERP) studies

Electrophysiological investigations generally demonstrate that the behavioural advantage of concrete over abstract words is also mapped in electrophysiological responses.

A number of ERP studies using different tasks (e.g. Kounions & Holcomb, 1994; Holcomb et al., 1999; West & Holcomb, 2000; Tsai et al., 2009; Renoult, Brodeur & Debruille, 2010) have found that concrete words elicit more negative ERPs than abstract words in the time window of N400 component and are differently processed in the brain.

Adorni & Mado Proverbio (2012) aimed at investigating whether the processing of abstract vs. concrete words differently affected the timing and topographical distribution of ERP components. They used the LORETA source localization technique to identify the intra-cranial generators of surface potentials reflecting lexicon-semantic processing. They tested the specific hypotheses that: 1) abstract vs. concrete words differently affect the latency, amplitude and scalp topographic distribution of ERP components; 2) concrete words are associated with higher activation in brain regions usually involved in visual object processing; 3) abstract words are (or not) associated with higher activation in the left temporal and prefrontal areas that are usually involved in verbal semantic processing; and 4) concrete words are (or not) associated with selective activation of right hemispheric regions. Their results indicate, respectively, that: 1) the semantic status (abstract vs. concrete) of words may differently affect ERP components, suggesting a dynamic interaction among the brain regions enrolled in lexico-semantic processing; 2) concrete words are associated with higher activation in brain regions usually involved in visual processing and in particular elicit greater activation of the left extrastriate visual areas (as compared to abstract words processing); 3) abstract words elicit greater activation of left temporal and prefrontal areas; and 4) there is no clear evidence for a greater involvement of the right hemisphere in concrete word processing than in abstract word processing. The authors conclude that concrete words are processed quite easily due to the activation of perceptual associations (involving more posterior, even occipital regions), while abstract words, having less access to perception-based representations, might be more dependent on word associations and on the verbal semantic system (and therefore on the activity of more anterior regions, namely the left temporal cortex and the left medial frontal gyrus) for the retrieval of their meaning. This is in clear contrast with the neuropsychological literature concerning the reversal of concreteness effect (see later).

In a recent study Barber and colleagues (2013) investigated ERP differences between concrete and abstract nouns, matched on a large number of lexical and sublexical variables, including imageability and context availability (i.e. the richness of semantic associations), in a lexical decision task. They found faster RTs for abstract than concrete words, which however still elicited larger N400 and N700 responses. These ERP components have been classically linked to the concreteness effect (Holcomb et al., 1999; West & Holcomb, 2000). In this experiment, the modulation of the N400 component has been taken as evidence of word meaning activation during lexical decision. The frontocentral distribution of the N400 concreteness effect and its amplitude variations, together with faster abstract words RTs, might reflect differences in the level of meaning activation when words are presented in isolation (like in this lexical decision task): concrete words would activate and integrate multi-modal, sensory-motor features from distributed cortical networks, while the processing of abstract words result in superficial linguistic associations that can be quickly used for response decision. Event if the authors matched words for imageability, the greater N700 elicited by concrete than by abstract words might reflect differences in the amount of intrinsic sensory-motor features that need to be integrated and manipulated to build and maintain mental representation of words. To conclude, even if abstract words, controlled for context richness and imageability, could trigger a larger number of superficial linguistic associations, brain concrete-word-potentials would indicate a greater semantic processing and integration of multimodal information for concrete than abstract concepts (Barber et al., 2013).

1.2.4 Repetitive Transcranial Magnetic Stimulation (rTMS)

The neural basis for concrete and abstract concept processing has been investigated also by means of transcranial magnetic stimulation (TMS). As known, TMS is a safe, non-invasive brain stimulation technique used to study causality in the brain-behaviour relationship and, apart from its intrinsic limitations, presents some advantages on neuroimaging (Sliwinska, Vitello & Devlin, 2014). While neuroimaging techniques can only demonstrate that a brain region is active during a given task, TMS can also be used to prove that the area is actually essential for task performance. Also, since it can be used to investigate healthy subjects, it eliminates the possible confounding effects of neurologic impairment and reorganisation processes due to brain plasticity or compensatory strategies.

Romero Lauro and colleagues (2007) investigated the role of the inferior temporal gyrus in processing abstract and concrete words, by means of rTMS. Eighteen healthy subjects performed an odd-one out paradigm, in which they were presented with noun triplets and asked to indicate which word was least related in meaning. Two sites were stimulated: left and right inferior temporal gyri, and accuracy and RTs were collected. Overall, their results indicate a significant reduction in response accuracy for abstract words when the right inferior temporal gyrus was stimulated, while concrete word processing was not affected by stimulation.

Papagno and colleagues (2009) report two experiments in which they investigated the processing of abstract vs. concrete by means of rTMS and a lexical decision paradigm in healthy subjects. They stimulated four cortical sites: left inferior frontal, bilaterally posterior-superior temporal and left posterior-inferior parietal, and measured accuracy and RTs. In their first experiment, they found interference on accuracy for abstract words when stimulation was applied over the left temporal site. Accuracy for abstract, but not for concrete, words decreased also after left frontal stimulation. A significant increase in error rate was found for concrete words when stimulation was applied over the right temporal site. The second experiment was designed to address two specific issues: 1) the role of the left inferior frontal gyrus in abstract vs concrete word processing, and 2) the role of the left parietal region in the processing of concrete words, with particular respect for living items. They found a significant reduction in accuracy for abstract words during frontal stimulation, and no effect of parietal stimulation on concrete living item processing. Their results indicate that the posterior part of the left temporal superior gyrus and the left frontal inferior gyrus play a role in abstract item storage; the right temporal cortex instead might be involved in concrete item storage. Consistent with previous studies, this one is in line with the hypothesis that not only concrete, but also abstract concepts are processed by a bilateral network, but the involved regions differ from each other (Papagno et al., 2009).

1.2.5 Conclusion

To sum up, the substantial corpus of studies reported above demonstrate the existence of different neural substrates dedicated to concrete and abstract concepts processing, partly modulated by specific task and stimuli properties. Functional neuroimaging and neuropsychological studies provide some evidence that these systems are subserved not only by common neural pathways (e.g. middle and inferior left temporal gyri; Binder et al., 2005), but also by dedicated networks (e.g. inferior frontal gyrus and middle temporal gyrus for abstract words, and posterior cingulate, precuneus, fusiform gyrus and parahippocampal gyrus for concrete items). Data also suggest an anterior/posterior dissociation in abstract/concrete processing in the brain, possibly due to the different sensory-motor content and imageability of various items (Roll et al., 2012). The issue of a possible hemispheric lateralization of abstract vs. concrete processing, in terms of abstract concepts activating predominantly left regions and concrete concepts engaging a bilateral network, is still under discussion. Most recent findings, however, would point out the engagement of a diffuse bilateral network both for abstract and concrete items processing.

These findings make a single "concreteness effect" theory unlikely, and rather suggest a combination of models. Superior encoding of concrete words may results either from greater verbal context information, reflected by the activation of left (e.g. parietal and frontal) associative areas, and by the additional activation of a nonverbal, imagery based system, in the temporal and parietal lobes (Jessen et al., 2000). However, new theoretical proposals should account also for the (rare) performance of brain-damaged patients who show a reversal of the concreteness effect, with a clear advantage for abstract over concrete word processing.

1.3 THE REVERSAL OF THE CONCRETENESS EFFECT CHALLENGES CLASSICAL THEORIES

The two main models that were put forward to explain the concreteness effect cannot account for the opposite pattern, the reversal of the concreteness effect, that is, the processing advantage for abstract over concrete concepts.

The reversal of the concreteness effect has been reported in a few, mostly single patient studies (e.g. Warrington, 1975; Warrington, 1981; Warrington & Shallice, 1984; Sirigu et al., 1991; Breedin et al., 1994; Marshall et al., 1996; Bachoud-Lévi & Dupoux, 2003; Macoir, 2008; Papagno et al., 2009). Typically, patients who show a reversal of the concreteness effect suffer from temporal atrophy (resulting in a semantic dementia, SD), or herpes simplex encephalitis, which usually affects temporal lobes bilaterally (Papagno et al., 2009).

Breedin and colleagues (1994) reported the case of a patient, DM, who had a progressive semantic loss due to atrophic changes in his temporal lobes, particularly on the left. Her semantic impairment predominantly involved object terms and showed an advantage for abstract words on a wide range of tasks, e.g. producing definitions and synonymy judgments. To account for this, the authors suggested that abstract and concrete concepts are qualitatively distinguished by the manner in which they are acquired, and by the relative weight of sensory-perceptual features in their representation. Sensory experience is supposed to be a key factor in the acquisition of concrete concepts, while abstract concepts could be acquired in the context of language, without direct perceptual input. Since concrete words rely on sensory-motor features more than abstract words, loss of such features causes a disproportionate damage to concrete entities and a reversed concreteness effect. The perceptual components of semantic representations could be therefore associated with structures in the inferior temporal lobe(s) (Breedin et al., 1994).

The same explanation has been proposed by Macoir (2009) and by Yi and colleagues (2007). The latter, studied 41 participants with neurodegenerative diseases known to impair semantic memory, including 29 patients with probable AD and 12 patients with SD. Patients underwent a multiple-choice naming-to-description task. SD patients were found to have particular difficulty in recognizing the meaning of verbs with respect to nouns, and of motion verbs with respect to cognition verbs. Also, some SD participants were found to have relative difficulty with concrete nouns. Since SD affects preferentially the association cortex in the left inferior temporal lobe, which is thought to play a role in mental imagery and visual-spatial knowledge (Wang et al., 2010), a degraded visual-perceptual feature knowledge may be the cause for SD patients' greater difficulty with motion, than cognition, verbs and with concrete, than abstract, nouns.

A similar pattern of impairment for "concrete" verbs was found by Bonner and his group (2005). In their study, patients with SD had a significantly greater difficulty with concrete verbs in a two-alternative, forced-choice test that measured lexical semantic associative knowledge. SD patients were found to have a significant cortical thinning in the anterior and infero-lateral portions of the temporal lobes, which, as already mentioned, are thought to be important for storing and processing visual features for word meaning (Bonner et al., 2005). Also, patients' poor performance with concrete relative to abstract verbs correlated with right anterior temporal lobe atrophy, which would indicate again that this area might contribute to the storing and processing of visual semantic features. These results would confirm that degraded visual feature knowledge, partly contributes to the impaired comprehension of concrete items in SD patients.

An alternative explanation to the reversed concreteness effect has been suggested by Crutch and Warrington (2005). They reported a series of experiments with a patient, AZ, who became globally aphasic following a left middle cerebral artery hemorrhage with left parietal, temporal and posterior frontal involvement. In tasks where AZ was asked to indicate, among four possibilities, the written word that corresponded to the stimulus pronounced by the examiner, they found that semantically associated abstract words (e.g. fight, punch, violent, struggle) reliably interfered with one another significantly more than semantically coordinate abstract words (e.g. boil, heat, cook, fry). Concrete words showed the reverse pattern. The authors interpret these results in terms of abstract and concrete conceptual knowledge relying upon qualitatively different representations. They argued that concrete and abstract word representations might be fundamentally different in their architecture: concrete words primary behaviour might be categorical, whereas abstract concepts would be represented in an associative neural network. A reversed concreteness effect might therefore arise from a selective damage to categorical information, which affects selectively concrete words processing.

However, none of these explanations can account for the pattern of performance found by Papagno and colleagues (2009), who explicitly tested these hypotheses with MC, a patient with semantic dementia due to selective atrophy of the left anterior temporal lobe. The experimental assessment tested performance on concrete nouns, and in particular on proper names (celebrities and landmarks), living and inanimate entities and knowledge of visual features; and performance on abstract vs. concrete words (word fluency, synonymy task, word-definition verification task).

MC's performance on concrete nouns revealed a significant poorer functioning with living (conspecifics and animals) than with non-living things. However, on a verbal semantic questionnaire, MC responded with significantly greater accuracy to questions relying on visual properties (e.g. butterfly: does it have transparent wings, colored wings, no wings?) than to questions relying on conceptual knowledge (e.g. butterfly: does it jump, fly or run?). This pattern contradicts the account proposed by Breedin and colleagues (1994) and by other authors, since in MC loss of visuoperceptual features seems not to be a prerequisite for the reversed concreteness effect. Also, results obtained by MC in abstract/concrete words tests clearly documented a more accurate performance on abstract than on concrete words, with a pattern opposite to which Crutch & Warrington's proposal would predict. Results from Papagno and colleagues further stress the role of temporal lobes in semantic representations and concur with previous findings, both from clinical case reports and neuroimaging studies (e.g. Nopponey et al., 2004), suggesting the importance of the right temporal lobe (and possibly the left prefrontal cortex) in the representation of abstract concepts (Papagno et al., 2009).

Considered together, the evidence for the existence of a reversed concreteness effect challenges classical models on semantic cognitive organisation, which have been mostly built on concrete concept studies. Data from concreteness effect and its reversal should be merged with neurophysiological and neuroimaging evidences in a comprehensive proposal, which should account for both the neural and cognitive mechanisms supporting semantic knowledge.

CHAPTER 2. RETENTION WITHOUT REMEMBERING. IMPLICIT MEMORY AND ANAESTHESIA

"In truth it no longer represents our past to us, but it acts it; and if it still deserves the name of memory, it is not because it conserves bygone images, but because it prolongs their useful effect into the present moment."
Henri Bergson, philosopher, 1910.

Processing differences between abstract and concrete words have been mainly studied through explicit memory paradigms, i.e. using tasks in which an intentional retrieval was requested (Paivio, 1991). A restricted number of studies (e.g. Roediger, 1987; Hamilton & Rajaram, 2001; ter Doest & Semin, 2005) investigated abstract vs concrete word processing in implicit memory, i.e. in the absence of conscious recall (§2.1.3). The classic implicit (nondeclarative) - explicit (declarative) dissociation of memory systems has been first observed in amnesic patients, who generally show impaired explicit memory but relatively intact implicit memory (e.g. Milner, 1962; Schacter 1987; Squire 1987; Chun & Phelps, 1999), and then investigated in several behavioral and neuroimaging studies, in animals and humans (e.g. Squire & Zola-Morgan, 1983; Schacter, 1992; Buckner et al., 1995; Paller et al., 2003; Schott et al., 2005). These studies generally support the classical taxonomic categorization of memory systems and conclude for the existence of specific neural substrates for implicit memory (§ 2.1.1). Neuroimaging studies on specific implicit memory phenomena, such as priming, even if they are not conclusive, also suggest specific brain activation patterns using different tasks (e.g. word stem completion) (§ 2.1.2). Increasing interest has been given to the issue of implicit memory in medical research, and in particular in anaestheiological research, due to the fact that both explicit and implicit recall may have severe psychological effects on patients (e.g. post-traumatic stress disorder) if referred to episodes occurred during a general anaesthesia. In this chapter, basic knowledge of anaesthesia and of cognitive functioning during anaesthesia is given and the phenomenon of implicit memory formation during general anaesthesia is discussed (§ 2.2). The synthesis of the scientific literature introduces the rationale for the experimental studies that will be presented later (§ 2.3).

2.1 IMPLICIT MEMORY, PRIMING AND WORD STEM COMPLETION

2.1.1 Introduction to the taxonomy and the neural basis of implicit memory

The idea that memory is not a single faculty of the mind is not itself new. Since the early 19th century, philosophers and psychologists questioned about the existence of different types of memory, referring to them as memory/habit (Bergson, 1910) rather than explicit/implicit recognition (McDougall, 1923). The "modern" experimental era arguably began with the observation that amnesic patients, who were severely impaired in explicit memory tasks, performed unexpectedly well (comparable to healthy controls) on implicit learning and retention tasks (e.g. Milner, 1962; Jacoby & Witherspoon, 1982). Since then, different learning and memory tasks have been investigated, both in humans and animals, and taxonomies of memory have been proposed to guide research questions. A widely accepted taxonomy, which incorporates an accurate classification of memory by placing the work within a biological framework is depicted in figure 2.1. Briefly, explicit (or declarative) memory refers to the capacity for conscious recollection about facts (semantic memory) and events (episodic memory) and is representational in nature, since it supports the encoding of information in terms of relationships among multiple items and events (Squire, 2004). Explicit memory is thought to be dependent on structures in the medial temporal lobe and midline diencephalon (Squire, 2004). In contrast, implicit (or nondeclarative) memory is expressed through a change in performance rather than recollection (Squire, 2004). Implicit forms of memory are revealed through reactivation of the systems within which the learning originally occurred (Schacter, 1992, Squire, 2004). For the purpose of the present work, I will focus on what is referred to as *priming,* the type of implicit memory that is often spared in amnesia (Voss & Paller, 2008). It refers to the enhanced recognition or recollection of

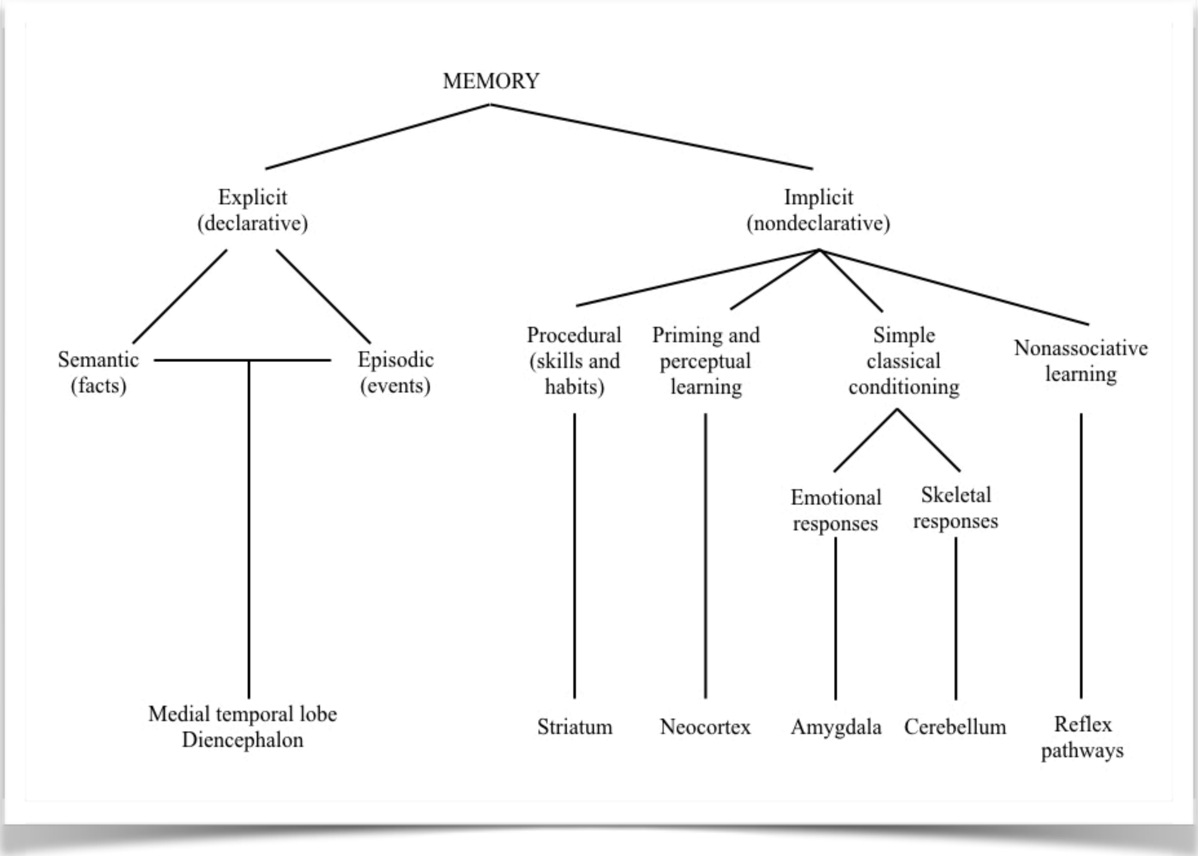

Figure 2.1 A taxonomy of long-term memory systems. The brain structures that are thought to be especially important for each form of explicit and implicit memory are listed. Adapted from *Squire LR. Memory systems of the brain: a brief history and current perspective. Neurobiology of Learning and Memory 2004; 82:171-7.*

perceptual objects from reduced cues as a consequence of a specific prior exposure to an object (Tulving and Schacter, 1990). Priming is considered a form of implicit memory since it can occur independently from any conscious or explicit recollection of a previous encounter with that stimulus (Schacter, 1992). Specific measures of priming comprise faster or more accurate behavioral responses on specialized tests. The most common priming tests are *perceptual priming tests*. They are thought to reflect facilitated or more fluent perceptual processing of the physical features of repeated items (Voss & Paller, 2008). Conversely, *conceptual priming* can occur when concepts are repeated, and the behavioral effect here is thought to reflect facilitated access to meaning (Voss & Paller, 2008). Classical priming tests are the so-called "data-driven" tests, including word-stem completion, word fragment completion, masked priming, repetition priming of visual objects (Henson, 2003). They are considered "indirect" memory tasks (Richardson-Klavehn and Bjork, 1988), since no reference is made to the prior encoding. A typical instruction of an implicit memory task is to complete the test (e.g. a word stem or a word fragment) with the first word that comes to mind (Squire, 2004). Since different types of memory can work in parallel even in well constructed implicit tasks (Squire, 2004), a major problem in studying priming is to develop experimental paradigms that simultaneously consider and differentiate the contribution of explicit and implicit memory, and of perceptual and conceptual priming (see, for example, the process dissociation procedure, Jacoby, 1991).

Studies on the neural basis of priming are not clear-cut, due to methodological differences and to the problem of implicit and explicit memory contamination mentioned above. However, a common result is the involvement of the neocortex in priming (see also figure 2.1). Specifically, neuroimaging studies suggest that priming, compared to baseline or explicit memory tasks, is associated with hemodynamic response decrease in occipital (extrastriate), inferior temporal, and prefrontal cortices and in the fusyform gyrus (Schacter et al., 1996; Schacter & Buckner, 1998; Henson, 2003; Schott et al., 2005). The reduced activity in these brain regions has been referred to as *repetition suppression* (in analogy with the neural phenomenon of "response suppression", for details see for example Desimone, 1996) and has been ascribed to a perceptual learning process that occurs when the same stimulus is repeatedly processed (Paller et al., 2003). Electrophysiological studies found specific ERP correlates of implicit memory in parietal (Rugg et al., 1998) and frontal sites (Paller, 2003). Neuropsychological investigations are in line with neuroimaging and ERP results. For example, Heindel and colleagues (1999) studied the performance on a motor learning task and on a lexical priming task in AD and Huntington's disease (HD) patients. They found a clear double dissociation between AD and HD patients, since AD patients were impaired on the lexical priming task, but intact on motor skill learning, while the opposite pattern was observed in HD patients. The authors therefore argued that lexical priming might depend upon the integrity of neocortical association areas damaged in AD (Heindel et al., 1999).

Together, the findings reported above support the taxonomy of memory and the existence of implicit memory systems specifically represented in cortical brain regions.

2.1.2 Neural basis of priming investigated through word stem completion

There is a very large number of behavioral, neuroimaging and electrophysiological studies on priming that used different tasks to investigate the possible neural basis of priming (for a comprehensive review, see Henson, 2003). However, every task is likely to involve a number of different cognitive steps from the stimulus to the response. For example, word stem completion, in which the subject has to complete a word stem with the first word that comes to mind, is likely to include orthographic, phonological, lexical and semantic access, each of which might be facilitated to some extent by prior exposure to the prime (Weldon, 1991; Henson, 2003). These processing differences are reflected in brain activations. For this reason, and because a word stem completion test was used in the experiments (see later), in this section I will focus on the results from studies that used word stem completion to investigate the neural basis of priming.

The word stem completion paradigm is usually considered as an example of perceptual priming, even if, as mentioned above, it should be better considered in terms of multiple processes (Weldon, 1991; Henson, 2003). The task is normally divided into study and test phases, with the study phase serving to prime a set of words. Priming is indexed by the probability of completing a word stem with a word from the study phase.

Squire et al. (1992) report results from one of the earliest imaging studies investigating visual priming with PET. Participants completed three-letter stems with the first word that came to mind in a baseline and a priming condition. They found that 70% of stems that corresponded to a studied (primed) word were completed with that word in the priming condition, compared with a baseline rate of 7%. Comparing priming vs. baseline condition, they found a significant reduction in blood flow in the right occipital cortex and a significant greater activity in the medial temporal region. Buckner et al. (1995; 2000) replicated these results using similar tasks, finding a decreased activity in the occipital cortex bilaterally and also in the posterior temporal cortex. These occipitotemporal deactivations have been attributed to more efficient perceptual processing, which would increase the possibility that a stem is completed with a primed word (Squire et al., 1992; Buckner et al., 1995). The medial temporal activation in

Squire et al.'s study may have reflected contamination of the implicit task by explicit memory (Buckner et al., 1995).

Badgaiyan et al. (1999) investigated the neural activations of priming within and across modalities, using either auditory primes and auditory stems or visual primes and auditory stems, in a PET study. They found a behavioral priming effect for both experimental conditions (within and across modalities), without significant differences: the percentage of stems completed with studied words were 54% in the within-modality condition, 48% in the cross-modality condition; 20% in the baseline condition. In the within-modality condition, they found a pattern of bilateral occipitotemporal repetition suppression similar to the one found by Squire (1992) and Buckner (1995; 2000). They also found repetition suppression in the precuneus, the right angular gyrus and the medial anterior frontal cortex. In their visual/ auditory cross-modality condition, they found repetition suppression in the left angular gyrus and an increased response in the anterior frontal cortex, particularly on the right, for primed vs. unprimed stimuli.

Complementary findings were reported by Schacter et al. (1999) when comparing within- and cross-modality priming with visual, rather than auditory stems. Again, an advantage for within-modality priming was accompanied by an occipitotemporal repetition suppression, which was not seen in the across-modality condition. They also confirmed the repetition suppression in the left angular gyrus and the stronger activation in the anterior frontal cortex for primed vs. unprimed words in the cross-modality condition.

Data from Badgaiyan's and Schacter's studies are inconsistent with a purely visual interpretation of occipitotemporal priming effects. They would rather suggests a more complex, modality-independent role of the occipitotemporal regions, the deactivation of which would not reflect form-specific visual processes, but may operate at a more abstract level (e.g. orthographic or lexical; Henson, 2003). The repetition suppression found in the right angular gyrus has been attributed to priming of lexical representations, which can mediate across-modality priming (Weldon, 1991). Finally, the activation of the anterior frontal cortex, accordingly to imaging studies that have associated this region with episodic retrieval (e.g. Tulving et al., 1994), was attributed to involuntary explicit memory, i.e. conscious memory, subsequent to completion of the stem, that the word was studied. This hypothesis has been further supported by the results from a further study (Badgaiyan et al., 2001).

One major problem with the word-stem completion studies described above is that they conform to a "blocked" design, as is normally necessary for PET. This means that primed and unprimed trials are presented in different blocks, rather than being randomly intermixed. Therefore differences in the participant's strategies or "mental state", particularly if the participants detect this blocking, may have biased the results (Verfaellie et al., 2001). The use of event-related techniques in fMRI allows random intermixing test stimuli. Of particular interest is an event-related fMRI study of word-stem completion by Thiel et al. (2001). The primary aim of this study was to investigate the neural basis of repetition priming with a pharmacological paradigm. Since cholinergic blockade is believed to impair explicit memory, but not implicit memory (Schifano and Curran, 1994), while GABAergic modulation is believed to impair implicit memory (Vidailhet et al., 1999), they tested the effects of the administration of a cholinergic blocker (scopolamine), a GABAergic modulator (lorezapam), or a placebo, to different groups of participants, on priming. They found that both drugs reduced the amount of priming in visual word-stem completion. The imaging data from the placebo group showed the classical repetition suppression in several of the regions identified by the blocked studies described above, as well as in inferior and posterior regions of left frontal cortex (see also Buckner et al., 2000). Repetition suppression in three of these regions, namely left occipitotemporal cortex and the two left frontal regions, was reduced or abolished in the scopolamine and lorezapam groups relative to the placebo group. Therefore event-related methods like the one just described, seem to support the common findings of previous blocked studies.

In conclusion, several imaging studies on variants of the word-stem completion task agree on distinct processes operating in occipitotemporal, left angular gyrus, left inferior frontal and right anterior frontal cortices. The occipitotemporal process appears independent from the perceptual (visual or auditory) modality, but is engaged only when the modality is the same for primes and stems. The left angular gyrus process may relate to an implicit, amodal lexical process, given that it occurs across modalities. Finally, the right anterior frontal activations may relate to explicit memory processes, rather than priming, either voluntary or unintended.

2.1.3 The concreteness effect in implicit memory

As previously discussed, the concreteness effect is a robust phenomenon, generalizing over different tasks, stimulus types, languages and memory tests (ter Doest & Semin, 2005). However, the effect has been mainly studied through explicit memory paradigms. Only a restricted number of studies focused on the possible differences in abstract vs. concrete processing in implicit memory. Even if these studies are behavioural and do not directly investigate the neural basis of abstract vs. concrete word processing in implicit tasks, they are of particular interest considering the topic of the present work.

Roediger and Weldon (1987) were the first to point out that, if we consider memory processes as involving the broad stages of encoding, storage and retrieval, theories (e.g. the dual-coding theory) explaining the superior retention of information encoded imaginally have emphasized encoding and storage processes as the loci of the concreteness effect. In their experiments, manipulating the retrieval condition, Roediger and Weldon found the usual picture superiority effect in explicit (or conceptually-driven[1]) memory tasks, in which recall was cued by words that were associatively related (e.g. semantically) to the studied items. Pictures were also remembered better than words in an implicit picture fragment completion tests. However, words surpassed pictures when retention was measured through a word fragment completion test. The authors thus concluded that the retrieval task is critical in producing the "standard" picture superiority effect; and that, whilst conceptually-driven tests generally result in better retention for pictures than words, the opposite is true for data-driven tests, depending on the physical match between study and test stimuli (Roediger & Weldon, 1987). The authors extended their conclusions to other "imagery" effects, such as the superiority of concrete over abstract word processing. To account for their results, they proposed an interpretation, called "transfer appropriate processing framework", in which the emphasis is on matching processes or procedures between encoding and retrieval (Roediger & Weldon, 1987; Kolers & Roediger, 1984). The transfer appropriate processing framework has been supported by a number of subsequent studies, in different memory tasks (e.g. Blaxton 1989; Nyberg & Nilsson, 1995; Wippich & Mecklenbrauker, 1995).

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[1] *Conceptually-driven* tasks (e.g free recall) require subjects to produce their own retrieval cues. Differently, as mentioned earlier, *data-driven* tasks (e.g. word stem completion) provide the subject with relevant perceptual stimulus information in the test phase (Paivio, 1991).

More recently, Hamilton and Rajaram (2001) have systematically considered the concreteness effect in the retrieval contexts other than explicit conceptual memory tests. Accordingly with their predictions based on the transfer appropriate processing framework and on Paivio's dual coding theory (Paivio, 1991), they found a concreteness effect on two conceptual explicit tasks (namely, free recall and explicit general knowledge test), but not on a perceptual implicit test (implicit word fragment completion test). Also, they failed to demonstrate a predicted concreteness effect in the conceptual implicit tasks (implicit general knowledge) or in the perceptual explicit test (explicit word fragment test). Therefore these results would indicate that conceptual processing for concrete words is weaker than that found for imaging the words. To explain these effects of images and concrete words on memory, the authors suggested that the extent of conceptual processing involved for different items may vary along a *continuum* such that abstract words, concrete words and imagery span the continuum from lesser to greater degree of conceptual processing.

Ter Doest & Semin (2005) also examined the effects of retrieval contexts on the concreteness effect. They conducted two experiments evaluating intentional memory for concrete and abstract words (verbs and nouns) in three retrieval contexts: free recall, explicit word stem completion test (both explicit memory tests) and implicit word stem completion test. Like Roediger and Weldon (1987), they found that the concreteness effect was modulated by the study condition, since they found a concreteness effect in the explicit, but not implicit, memory tasks.

Considered together, these findings would suggest that the explicit or implicit nature of memory test instructions could generate a key retrieval condition for the concreteness effect, which may be limited to intentionally guided retrieval (ter Doest & Semin, 2005).

To conclude, considering that: 1. implicit memory tests are thought to involve not only perceptual, but also conceptual (i.e. semantic) processes; 2. implicit memory tests seem to be immune to the concreteness effect; 3. recent neurophysiological studies suggest that conscious and unconscious semantic activation involve similar brain areas (even if with distinct, qualitatively different time courses, Kiefer & Spitzer, 2000); it is possible to speculate that studies aimed at investigating the neural basis of abstract vs. concrete word processing could benefit from the use of implicit memory paradigms.

2.2 MEMORY AND ANAESTHESIA

A study that became famous in anaestheiological literature sounds more like a story. In 1965, doctor Bernard Levinson, a psychiatrist and anaesthestist, dosed 10 dental patients with thiopentone, nitrous oxide and ether in order to perform an unusual experiment. Mid-way through the operation, he staged a mock crisis in which he exclaimed: "Just a moment! I don't like the patient's color. Much too blue. I'm going to give a little more oxygen…There, that' better now. You can carry on with the operation". Thereafter, surgery continued and all patients had an uneventful recovery. However, under hypnosis one month later, four of the patients repeated verbatim Levinson's statement, and another four had some recall for intraoperative events (Levinson, 1965).

This study is in many ways methodologically flawed. However, the startling findings provided a starting point for research into psychological aspects of anaesthesia. This research really took off when psychologists provided appropriate tools and frameworks for studying implicit memory (e.g. Andrade & Deeprose, 2006). The main message from this research is that the boundaries are blurred, with loss of consciousness involving gradual changes in sensation, cognition and memory rather than a sudden switch from awake to asleep.

Levinson's experiment deals with the key aim of anaesthesia to prevent the experience of surgery (Sanders et al., 2012), that is to prevent intraoperative awareness. Awareness is defined as "post-operative recall of intra-operative events" (Lesile, 2007). This postoperative recall can be either conscious, or unconscious (Andrade, 1995). Intraoperative memory formation can produce features of post-traumatic stress disorder (PTSD) postoperatively in up to 70% of patients (Leslie et al., 2010).

Large studies in which data were collected prospectively have reported incidence of awareness of around 1 or 2 in 1000 in routine patients under general anaesthesia (GA) (e.g. Sebel et al., 2004), which is even more frequent (almost 1% of incidence) in high-risk settings (e.g. cardiac surgery, Phillips et al., 1993). Studies unequivocally demonstrate that the incidence of awareness without explicit recall is significantly and consistently higher than the incidence of awareness with recall (Sanders et al., 2012). Thus, there has been growing interest for the issue of memory formation during GA and a fair number of studies are now available which investigated the phenomenon of implicit memory and priming during GA (Andrade & Deeprose, 2007).

Before discussing these studies, it could be useful to give some basic knowledge on anaesthesia and on cognitive functioning during anaesthesia. The concepts of amnesia, hypnosis and consciousness are closely tied, but discussing consciousness goes beyond the scope of this work.

2.3.1 Basics of anaesthesia and introduction to cognitive activity during anaesthesia

The first public demonstration of GA was in 1846 by a Boston dentist named William Morton at the Massachusetts General Hospital. Dr. Morton gave an ether anaesthetic for the removal of a neck tumor by surgeon John Collins Warren. Since then, anaesthesia evolved to the multidisciplinary medical specialty that we know today, comprising critical care medicine, pain management and, of course, anaestheiology. This consists in a medical intervention which does not itself offer any particular medical benefit and instead enables the performance of other medical (e.g. surgical) interventions (Satwik & Naveed, 2015).

Anaesthestists often talk about sending patients ‘off to sleep’, but sleep is not an accurate analogy for anaesthesia, even if they seem to share some mechanisms (Franks, 2008). EEG studies demonstrate that general anaesthesia does not have the same electroencephalic signature, architecture or sleep stages of natural somnolence (Schwartz, 2010). Unlike sleep, unconsciousness resulting from anaesthesia is a state artificially created, and, by definition, there is no response to very strong stimulation.

Generally it is held that there are three common endpoints of general anaesthesia:

1. analgesia (loss of sensation, to prevent physiological shock);
2. muscle paralysis (to allow for surgical access);
3. hypnosis (unconsciousness or oblivion).

Often at least three different drugs are responsible for these components, and thus they are relatively independent. It is possible, for example, to deliver sufficient muscle relaxant to produce effective paralysis, with insufficient hypnotic, leaving the patient conscious but unable to move.

The effect of the hypnotic component of the anaesthetic cocktail, that is the anaesthetic proper, is determined by the balance between the dose of anaesthetic and the level of surgical stimulation and psychological arousal. Just as it may be difficult sleeping in a noisy environment, so more anaesthetic will be necessary to keep someone unconscious during an invasive surgical procedure than during a minor superficial procedure. The patient's cognitive state lies on a continuum of cognitive activity from consciousness to complete oblivion, encompassing complete recall, conscious memories (near-miss awareness, dreams, possible awareness), unconscious memories (basic and complex) and complete oblivion (Lesile, 2007). This will also vary during an operation, and a difficulty for the anaesthestist is to determine how close the patient is to moving into the 'wakeful' end of the continuum before it is time to do so. The reason why anaesthestists just do not continually give an overdose of anaesthetic is that there are dangers of increased medical morbidity and (rarely) mortality (Gunther et al., 2008).

The idea of a continuum of consciousness is supported by studies of the effects of sedative or sub-anaesthestic doses of anaesthetic drugs. These studies have found a progressive, sequential but dissociative loss of sensation. Hearing, for example, is commonly the last sense to be affected and electrophysiological studies have shown that limited sense of hearing can continue despite even deep anaesthesia (Koelsch et al., 2006). Importantly, long-term encoding of memories is impaired before language and working memory functions (Andrade, 1994, 1996).

Studies using postoperative interviewing may underestimate the true incidence of consciousness during anaesthesia. This is because explicit memory, as assessed using retrospective recall, does not necessarily correlate with consciousness at the time of learning:

there can be full consciousness with explicit memory, full consciousness with no explicit memory but with implicit memory, unconsciousness with no explicit memory but with implicit memory, or unconsciousness with no explicit or detectable implicit memory (Wang et al., 2012). A synthesis of the possible intraoperative cognitive states (which also consider the postoperative period) is given in table 2.1. Many low-dose anaesthesia studies have demonstrated that anaesthetic drugs commonly obliterate explicit recall, giving rise to

		Postoperative state		
Intraoperative state		**Immediate**	**Late (> 1 month)**	**Descriptor**
Unconscious	no signs; no response to command	no recall	no recall	adequate anaesthesia
Unconscious; word stimuli presented	no signs; no response to command	no explicit recall, implicit memory of word stimuli	no explicit recall; implicit memory for word stimuli	adequate anaesthesia with implicit memory
Conscious	signs/response to command	no recall	no recall or emotional sequelae	intraoperative wakefulness with obliterated explicit and implicit memory
Conscious; word stimuli presented	signs/response to command	no explicit recall, implicit memory of word stimuli	no explicit recall; implicit memory for word stimuli but no emotional sequelae	intraoperative wakefulness with subsequent implicit memory
Conscious	signs/response to command	no recall	PTSD/nightmares but no explicit recall	intraoperative wakefulness with implicit emotional memory
Conscious	signs/response to command	explicit recall with or without pain	explicit recall but no emotional sequelae	Awareness but resilient patient
Conscious	signs/response to command	explicit recall with distress and/or pain	PTSD/nightmares with explicit recall	Awareness with emotional sequelae

Table 2.1. Classification of intraoperative cognitive states and postoperative cognitive and emotional states. Adapted from *Wang M, Messina AG, Russell IF. The topography of awareness: a classification of intra-operative cognitive states. Anaesthesia 2012; 67: 1189-1201.*

amnesia, despite the fact that the patient was conscious and communicative during the period the drugs were active (see review by Andrade, 1996). This is particularly common in the case of conscious sedation during unpleasant investigative procedures such as endoscopy. Many people have complete amnesia for such procedures and imagine they

have been unconscious when clearly they have not (Woodruff & Wang, 2004). So, it is possible to be wakeful during general anaesthesia and have no postoperative recall for this episode. A useful distinction of concepts relevant to anaesthesia is the one among consciousness, connectedness and responsiveness (Sanders et al., 2012). Consciousness here is intended as subjective experience, be it pure darkness or intraoperative sensations. Connectedness describes the connection of consciousness to the external world allowing experience of external stimuli. Responsiveness is the complexity of our behavioral interactions with the outside world. Consciousness can be disconnected, like when we dream; or connected, like during wakefulness, where experiences can be triggered by environmental stimuli. Awareness during anaesthesia can be considered a state of environmentally connected consciousness, usually in an unresponsive patient that cannot therefore communicate his/her state (Sanders et al., 2012).

The major focus of the research on assessing depth of anaesthesia has been EEG measures of brain function. There is evidence that these measures can help reduce awareness during anaesthesia (Myles et al., 2004), but at best they provide a probabilistic indication of a patient's state of consciousness. In other words, they tell us that the majority of patients will be unconscious at a particular EEG index reading. Most anaesthestists believe that they can detect consciousness because of changes in heart rate, blood pressure, tear secretion and sweating. However, there is now abundant empirical evidence that this is untrue (Moerman et al.,1993). The isolated forearm technique provides a simple yet highly effective method for determining consciousness during anaesthesia (Russell, 1993; Russell & Wang, 1997, 2001). Before muscle relaxants are administered, a tourniquet is applied to one arm using a cuff, ensuring the patient is capable of moving the hand during surgery despite the presence of muscle relaxant in the rest of the body. The patient is then asked to squeeze the anaesthestist's fingers at regular intervals. In early studies of the isolated forearm technique, Russell (1989) found that 44 per cent of patients receiving a commonly used anaesthestic could respond sensibly to command at some point during the operation. However, on recovery almost all patients had complete amnesia for the surgical period. The isolated forearm technique is not used routinely in clinical practice, and usually clinicians are either not aware of the technique or resistant to adopting it. Instead the use of electrophysiological measures like the Bispectral Index Monitor (BIS), even if not routinary throughout Europe, is spreading thanks to emerging evidence of its efficacy in preventing intraoperative awareness and anaesthestic overdose (e.g. Sieber et al., 2010). BIS is a patient monitor that quantifies the depth of the hypnotic component of anaesthesia using electroencephalogram recorded over the forehead. Through a mathematical algorithm, it computes a number ranging from 0 to 100, with 0 meaning cerebral death, and 100 wakefulness. This number is displayed on the monitor and, together with the EEG trace, helps the anaesthestist to titrate the anaesthestic drug. A BIS range of 40-60 is generally accepted to represent the ideal anaesthestic depth where explicit recall is extremely unlikely (Bowdle, 2006).

Anaesthesia, and hypnosis, can be induced through two different classes of anaesthestics: inhalational or intravenous. Examples of inhalational drugs are sevoflurane and isoflurane. They are usually delivered using minimum alveolar concentration (MAC) as units of measure, which indicate the concentration of a vapour in the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (painful) stimulus (Miller & Pardo, 2011).

Among intravenous anaesthetics, one of the most commonly used is propofol. This anaesthetic is administered as part of an anaesthesia maintenance technique called total intravenous anaesthesia, using either manually-programmed infusion pumps or computer-controlled infusion pumps in a process called target controlled infusion (TCI) (Miller & Pardo, 2011).

All general anaesthetics by definition cause a reversible and safe loss of consciousness (LOC). For any given anaesthetic, the concentration at which LOC is reached is well defined and varies between drugs. For example, propofol is known to cause LOC at much lower doses than sevoflurane (Katoh et al., 2000). Very briefly, anaesthetics are thought to exert their effects by binding to specific protein targets. Although over the years a large number of different ion channels, receptors, enzymes and other proteins have been investigated as putative anaesthetic targets (e.g Rudolph & Antkowiak, 2004), there is strong evidence for a direct involvement in anaesthetic action for only a handful of them. Namely, they are gamma-aminobutyric acid (GABA) type A receptors, two-pore domain K^+ (2PK) channels and N-methyl-D-aspartate (NMDA) receptors. GABA receptors are found throughout the central nervous system and are members of a superfamily that also includes receptors for acetylcholine, glycine and serotonin. Almost all general anaesthetics have been found to directly activate $GABA_A$ receptors in the absence of GABA. 2PK channels are thought to provide "background" modulation of neuronal excitability and there is growing evidence that some members of this channel family can be directly activated by volatile general anaesthetics (Patel et al., 1999). NMDA receptors are known to mediate the slow components of synaptic transmission and might be an important target for some anaesthetics (Flohr et al., 1998).

From a functional point of view, it has been demonstrated (e.g. Heinke & Koelsch, 2005) that some brain regions (and the cognitive processes mediated by those regions) seem to be more sensitive to specific anaesthetics than others, in a dose-dependent manner. Inhibition of activity in multimodal association cortices (parietal and prefrontal) by low dose anaesthetics (i.e. to achieve sedation, not GA) produces amnesia and attention deficits, whereas activity in unimodal cortices and in the thalamus remains largely unaffected by low doses of anaesthetics. Activity in the midbrain reticular formation, thalamus, and unimodal cortices appears to be suppressed only by anaesthetic concentrations causing LOC. Besides these regional suppressive effects, anaesthetics impair functional connections between neurons in distributed cortical and thalamocortical networks (Heinke & Koelsch, 2005).

In detail, PET studies have demonstrated that most anaesthetics cause a global reduction in cerebral blood flow (rCBF) when LOC is reached, although the extent of this reduction is variable (Fiset et al., 1999; Alkire et al., 2000). As said, pattern across the brain is not uniform, and certain regions are consistently more deactivated than others. A common finding in all of the human imaging studies is that the thalamus is deactivated during GA (Kaisti et al., 2003), which support the assumption that the disruption of thalamocortical connectivity, and thus of information transfer from the periphery to the cortex, might be an essential common feature of anaesthetic action (Fiset et al., 1999; Alkire et al., 2000). Apart from common mechanisms, the major changes in rCBF resulting from propofol administration at doses that induce LOC, were found in the precuneus, the posterior cingulate cortex, the cuneus and the frontoparietal cortex (Kaisti et al., 2003). Administration of sevoflurane at concentrations that induce LOC resulted in decrease activity in the precuneus, posterior cingulate cortex, cuneus, frontoparietal cortex and cerebellum (Kaisti et al., 2003). These deactivations are bilateral, since anaesthestics equally affects both hemispheres (Franks, 2008). A map of the brain regions commonly found to be deactivated by propofol and sevoflurane at doses that cause LOC is depicted in figure 2.2.

Anaesthestics therefore are thought to produce changes in the patient's behavioral and cognitive state by interacting with brain activity via at least two mechanisms: the dose-dependent global and regionally specific suppression of neuronal activity and the disruption of functional interactivity within distributed neural networks.

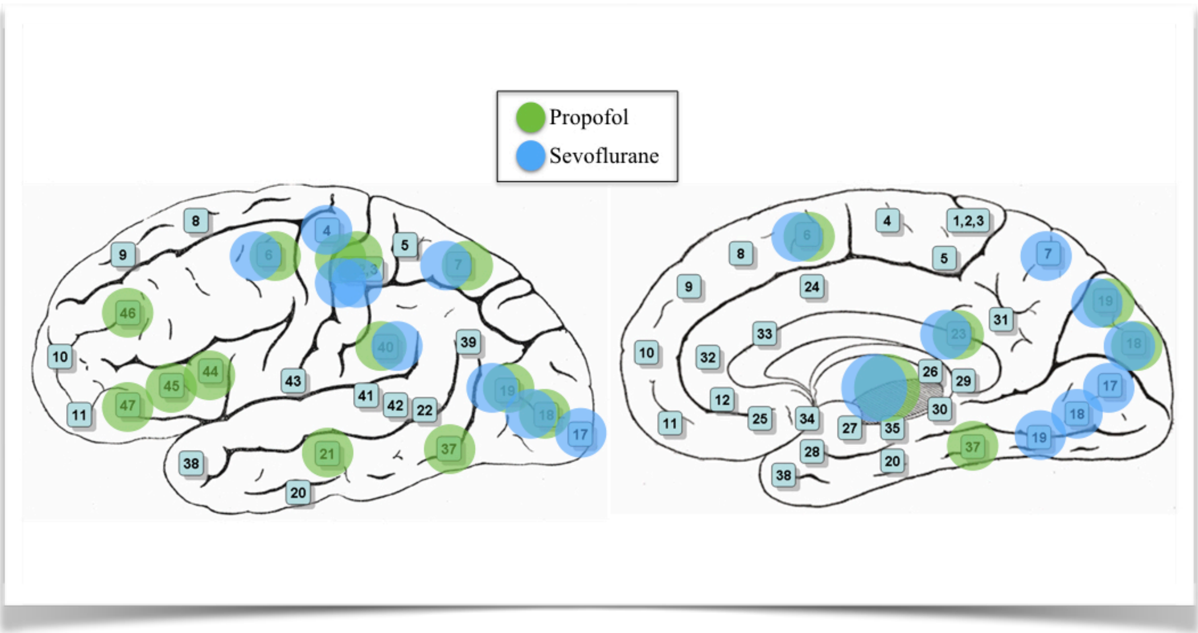

Figure 2.2. A schematic lateral (left) and medial (right) map of brain regions commonly found to be deactivated by propofol (green circles) and sevoflurane (blue circles) at doses that cause unconsciousness. Broadmann's areas, where available (see the thalamus), are indicated. Note that sevoflurane causes activity suppression also in the cerebellum.

2.3.2 Unconscious memory formation during anaesthesia

Given that both explicit and implicit recall seem possible under GA, and considering the possible psychological effects of both, a line of research has been dedicated to understand the extent to which the human brain continues to process auditory information during GA. Importantly, these studies share the use of specific and careful measures of memory and of awareness or anaesthetic depth to rule out periods of consciousness during surgery, since lack of explicit recall on recovery does not guarantee lack of awareness during surgery (Andrade & Deeprose, 2007).

Tracing the distinction mentioned earlier between perceptual and conceptual priming, studies on implicit memory formation during GA can be divided into these two categories.

Studies on implicit perceptual priming have shown contrasting results. For example Lubke et al. (1999) investigated the dependence of priming on the depth of anaesthesia, measured using the bisprectral index. To ensure a wide range in anaesthetic depth, they tested patients undergoing surgery for trauma anaesthestized with volatile anaesthestic. Measure of priming was obtained with a word stem completion test with process dissociation procedure (PDP; Jacoby et al., 1991). This procedure consists of two test conditions. In the inclusion condition, patients are asked to use the stem to recall a word from the list presented during anaesthesia, and to use that word to complete the stem. Failing recall, they complete the stem with the first word that comes to mind. In this condition implicit and explicit memory are thought to work together to boost performance. In the exclusion condition, participants use the stem to recall a presented word and then avoid using that word to complete the stem. Here, explicit memory acts in opposition to implicit memory. Thus, the relative contributions of explicit and implicit memory can be estimated. Lubke and colleagues found that hits (i.e. the completion of a stem with a word presented intraoperatively) increased with increasing BIS values and exceeded responses from a distractor list at BIS values less than 60. At BIS values less than 40, no priming effect was detected. They found evidence of priming occurring during adequate anaesthesia, defined as BIS values between 40 and 60, and evidence that priming increased as the anaesthestic became lighter.

However, subsequent findings from the same researchers failed in reporting evidence of priming during GA. Kerssens et al. (2005) used both intravenous (propofol) or volatile (nitrus oxide and isoflurane) anaesthestics in BIS monitored patients, and again evaluated priming with a word stem completion task with PDP. They reported that 98% of primed words were played within a BIS range of 40-60. The lack of memory priming under these conditions would suggest that fluctuations in anaesthestic depth might be necessary for learning to occur. However, two studies, in which anaesthesia was deliberately light, still found no evidence for implicit memory (Lubke et al, 2000; Kerssens et al., 2002). It has been claimed therefore that a problem with the PDP is that the relative complexity of the task instructions can lead to considerable variation in strategies for completing the task (Andrade & Deeprose, 2007). Trying to recall words from a period of unconsciousness is a difficult and unrewarding task, so patients may generate a suitable response and then check whether it seems familiar. This strategy leads to a bias against responding with any familiar words in the exclusion condition of PDP (Stapleton & Andrade, 2000). The relative complexity of the PDP could make it less sensitive than simpler tests and could possibly be the cause of such a variability among results (Andrade & Deeprose, 2007).

Two studies using a simple word-stem completion test in patients anaesthestized with intravenous (midazolam) or volatile (sevoflurane or desflurane) anaesthestics, found evidence that memory priming only occurred during very light anaesthesia (Smith et al., 1998; Dobrunz et al., 2007). Loveman et al. (2001) found no evidence of priming using a simple word stem completion test, in patients anaesthestized with propofol and even when patients, whose forearm was isolated, squeezed the experimenter's hand. Conversely, Deeprose et al. (2005) did find a priming effect in patients undergoing general propofol anaesthesia, and with a mean BIS = 42.

Considered together, studies on perceptual priming during general anaesthesia suggest that perceptual priming can occur during periods of light (BIS > 60) or adequate (BIS between 40 and 60) anaesthesia, particularly if there is surgical stimulation (e.g. Lubke et al., 1999; Stonell et al., 2006; Deeprose et al., 2004). The variability between positive and negative results can be due to methodological differences, and in particular to the use of complex task instructions, which do not fit the specific experimental setting.

Studies on conceptual priming tested whether sufficient memory function persists during anaesthesia, so that presenting intraoperative stimuli could activate related knowledge in memory. These studies typically used stimuli that are considerably more complex than the lists of single words used in perceptual priming studies. Some authors for example (Schwender et al., 1994; Struys et al., 1998; Ghoneim et al., 2000; Aceto et al., 2003) played a story during anaesthesia and surgery and asked patients, at recovery, to make free associations. Schwender and colleagues (1994) played the story of Robinson Crusoe during EEG-monitored cardiac surgery in patients anaesthestized with either volatile or intravenous anaesthetics. At recovery, patients were asked to freely associate the word "Friday". Associating "Robinson Crusoe" to "Friday" was interpreted as evidence of priming. Half of the patients, who showed auditory evoked potential data comparable to those of awake patients, associated “Robinson Crusoe” to “Friday”. Among patients whose early cortical auditory response was strongly suppressed (which would indicate deep anaesthesia), only one out of ten made the expected association. Subsequent studies (Struys et al., 1998; Ghoneim et al., 2000; Aceto et al., 2003) used similar methodology, with different stories. Again, priming was found to correlated with latency of the early auditory cortical response (Ghoneim et al., 2000; Aceto et al., 2003), in that only patients who showed latencies in auditory evoked potentials similar to those found in awake patients, showed a priming effect. Also, priming effect seems to be stronger in patients anaesthestized with an opioid regimen, consisting of high levels of analgesia and less anaesthesia (Ghoneim et al., 2000). This pattern of results would suggest that intraoperative priming could occur only when anaesthesia in very light (as indicated by auditory evoked potentials) or during undetected periods of recovered consciousness (likely to occur in opioid regimen anaesthestized patients).

Other studies investigating intraoperative conceptual priming used a category generation task (Van Hoof et al., 1995; Russel & Wang, 1997; Russel & Wang, 2001; Andrade et al., 2001). During anaesthesia, patients were played lists of category exemplars (i.e. birds and vegetables) and were asked on recovery to generate examples of those categories. None of these studies found evidence of intraoperative priming.

An interesting study by Münte and colleagues (2003) used increased reading speed as a measure of implicit memory. Patients were played one of four short stories before surgery with light EEG-monitored anaesthesia and another story during surgery with deep anaesthesia. On recovery, no patients had explicit recall for the stories, tested using a structured interview and a free recall task. Priming was measured by asking patients to read passages from the presented or control stories. Increased reading speed was found only for passages presented during light to moderate anaesthesia, before surgery.

Together, findings from studies on conceptual intraoperative priming would suggest that priming occurs only during very light anaesthesia and probably results from conscious encoding of the stimulus material.

2.3 CONCLUSION

The reviewed literature illustrates a point well known to psychologists – that being conscious and being able to remember being conscious are not the same thing. It raises some important questions for cognitive sciences. Although we know a lot about explicit and implicit memory, both from a behavioral and a neuro-functional point of view, there remain questions about how conscious we need to be, and which brain processes need to operate, to encode memories of different sorts of stimuli. This interdisciplinary research shows the usefulness of cognitive neuroscience and psychology for providing a framework for understanding and tackling clinical problems and the usefulness of anaesthesia as an experimental field to investigate cognitive processes. However, if one considers studies on intraoperative priming in the light of the literature discussed in the first part of the chapter on implicit memory and priming in general, and on priming studied through word-stem completion in particular, methodological pitfalls become evident. The experimental studies that will be presented afterwards aimed at filling this methodological gap and at providing reliable results on intraoperative priming for different types of stimuli. Also, since the focus was specifically on abstract vs. concrete words, these studies aimed at contributing to the definition of the neural basis of abstract and concrete words processing.

CHAPTER 3. EXPERIMENT 1: Auditory priming for concrete, but not for abstract words during general intravenous anaesthesia.

3.1 INTRODUCTION

How concepts are represented in the brain is a central issue in cognitive neuroscience. A large number of studies focused on the possible different neural substrates of abstract vs. concrete words, with contrasting results, partly due to methodological differences. However, common results suggest that abstract and concrete word processing is subserved not only by common neural pathways, but also by dedicated networks. Most of neurologically impaired patients with left frontal and/or temporal damage show a behavioral advantage for concrete over abstract words (i.e. the concreteness effect) (e.g. Shelton & Caramazza, 2000; Roll et al., 2012; Papagno et al., 2013). Neuroimaging and TMS results, even if not clear-cut, would indicate that both abstract and concrete words activate a bilateral distributed network, with the involved regions differing from each other (Papagno et al., 2009). Abstract words seem to involve the left inferior frontal gyrus and the middle and superior temporal gyrus to a greater degree than concrete words (Wang et al., 2010; Papagno et al., 2009), while concrete words cause stronger activation in the left precuneus, posterior cingulate, parahippocampal gyrus, fusiform gyrus, and culmen (Wang et al., 2010). These results have been interpreted in terms of abstract concept processing relying more heavily on the verbal system, and concrete concept representation involving more mental imagery and relying more on the perceptual system than abstract concepts (Wang et al., 2010). Also, data suggest anterior/posterior dissociation in abstract/concrete processing in the brain, possibly due to the different sensory-motor content and imageability of various items (Roll et al., 2012).

Differences between abstract and concrete word processing have been studied mainly through explicit memory paradigm, in which the concreteness effect showed to be a robust phenomenon (Paivio, 1991). However, a limited number of studies focused on the behavioral differences in abstract vs. concrete processing using implicit memory tasks, such as the word stem completion, which is thought to involve both perceptual and conceptual (i.e. semantic) processes (Henson, 2003). These studies generally found that the explicit or implicit nature of memory test instructions could generate a key retrieval condition for the concreteness effect, which may be limited to intentionally guided retrieval (ter Doest & Semin, 2005). Implicit memory tests seem therefore to be immune to the concreteness effect. Also, recent neurophysiological studies indicate that conscious and unconscious semantic activation involve similar brain areas, even if with distinct, qualitatively different time courses (Kiefer & Spitzer, 2000). Studies aimed at investigating the neural basis of abstract vs. concrete word processing could therefore benefit from the use of implicit memory paradigms.

Research in the field of anaesthesiology got interested in implicit memory processes following the observation that patients undergoing general anaesthesia could form memories of intraoperative events, and develop symptoms of post-traumatic stress disorder even if these memories were implicit (Leslie et al., 2010). Studies on priming during anaesthesia suggest that perceptual priming (e.g. word stem completion) can occur during periods of light or adequate anaesthesia, particularly if there is surgical stimulation (e.g. Lubke et al., 1999; Stonell et al., 2006; Deeprose et al., 2004) and that the variability between results can be due to methodological differences. Conceptual priming studies typically used stimuli that are considerably more complex than lists of single words used in perceptual priming studies. Studies on conceptual priming conclude that priming occurs only during very light anaesthesia and probably results from conscious encoding of the stimulus material (Aceto et al., 2003; Russel & Wang, 2001; Andrade et al., 2001).

These studies, however, are very heterogeneous and present some methodological pitfalls. First of all, they do not systematically take into consideration the effect that different anaesthetic drugs may have on the brain and, therefore, on implicit memory. The mechanisms through which anaesthetics, an extremely complex group of drugs, act and cause reversible loss of consciousness have been a long standing mystery. Recent work has highlighted a relative small number of important molecular targets and suggests that the thalamus and the neural networks that regulate its activity are crucial to understand how anaesthetics work (Franks, 2008). Functional human brain imaging studies revealed a functional dissociation between unimodal and polymodal cortices, since the latter tend to be more affected by anaesthetics than the primary and secondary sensory cortices (Alkire et al, 2008). It has also been demonstrated that different anaesthetics act through different mechanisms involving different cerebral areas. For example propofol, an intravenous anaesthetic largely used nowadays in clinical practice, enhances selectively the GABA receptors function, deactivating or disconnecting frontal areas and posterior multimodal areas, and modulating the activity in the precuneus, the posterior cingulate cortex, the cuneus and the frontoparietal cortex (Franks, 2008). One can therefore speculate that, considering the specific anaesthetic drug used, intraoperative priming effect would be different.

Secondly, studies on priming under general anaesthesia only considered the difference between perceptual and conceptual priming and not any possible difference among the stimuli

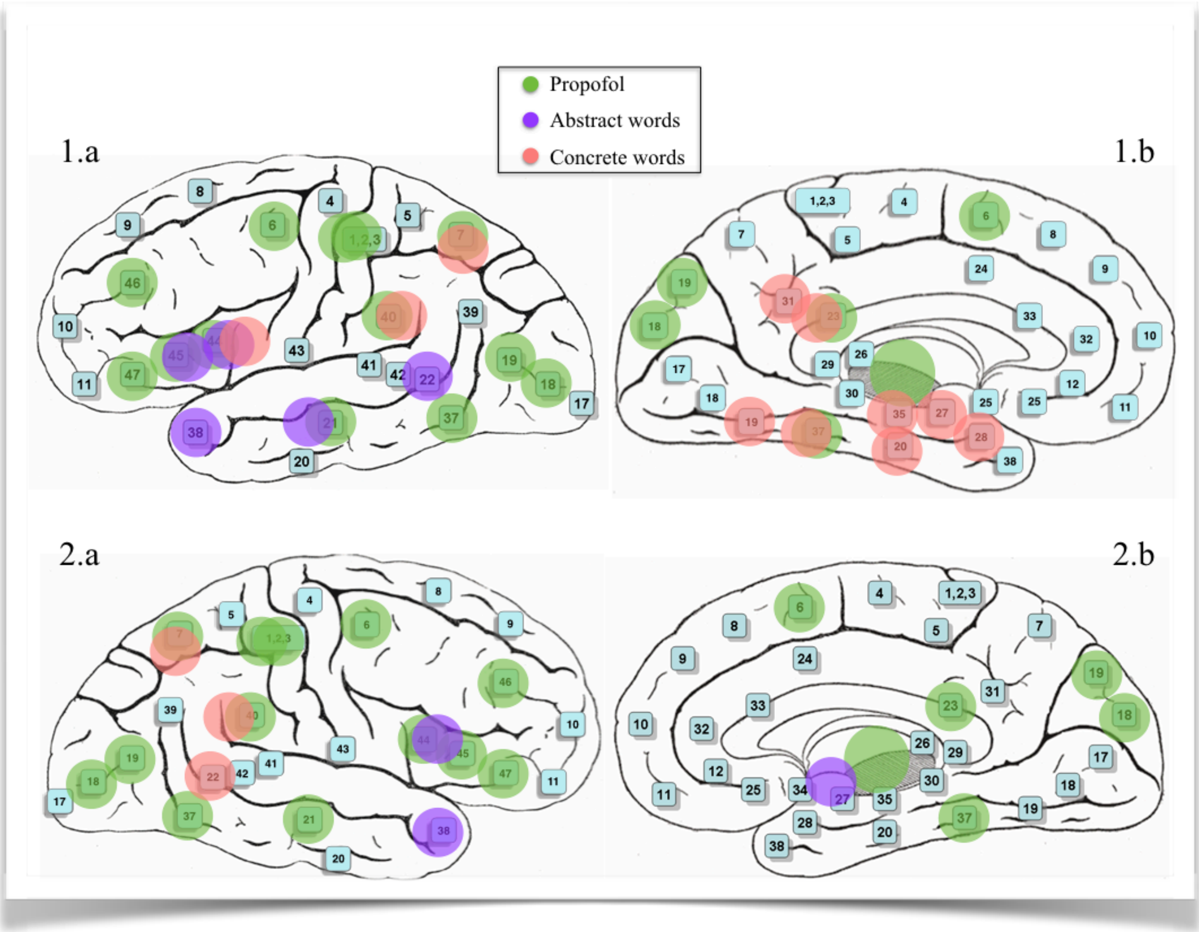

Figure 3.1. A schematic left lateral (1.a), left medial (1.b), right lateral (2.a) and right medial (2.b) map of brain regions commonly found to be deactivated by propofol (green circles) and of regions whose activity is greater for abstract than concrete word processing (purple circles) or vice versa (pink circles). Broadmann's areas, where available (see the thalamus, 1.b and 2.b., and the amygdala, 2.b), are indicated. Note that greater activation to concrete than abstract words has been found also in the culmen. This map was obtained merging results from the neuroimaging and TMS studies discussed in § 1.2.3, § 1.2.4 and § 2.3.1.

used. Indeed, the possible difference in neural substrate between concrete and abstract word processing has been already discussed (see chapter 1).

Therefore, this study aimed at filling the methodological and knowledge gap on perceptual memory priming during general anaesthesia and at examining the anatomical basis for abstract vs. concrete word processing.

Considering the heterogeneous literature on priming under general anaesthesia and the contrasting results from neuroimaging studies on abstract vs. concrete word processing, in the present study particular attention was given in controlling for possible confounding factors, namely the type and modality of anaesthesia, duration of stimulation, and the more relevant linguistic variables, namely semantic category, word length, frequency. A careful control of the depth of anaesthesia allows excluding with high reliability the contribution of explicit memory to the performance on the implicit test, which is a major concern in classical implicit memory paradigms (e.g. Jacoby, 1991; Squire, 2004).

Priming effect for auditory-presented concrete and abstract words was assessed in patients undergoing back surgery under propofol general anaesthesia, monitored for depth of anaesthesia, by means of a simple word stem completion test. Considering the results from the literature on abstract vs. concrete word processing and on propofol neuronal targets (see figure 3.1), which have been discussed in the previous chapters, the presence of a priming effect, also with adequate levels of anaesthesia, and a difference in the priming effect between abstract and concrete nouns, in favour of the latter, were expected.

3.2 METHODS

The study was approved by the local Ethics Committee of the Neurologic Institute Carlo Besta and all patients gave written informed consent before participating in the study.

3.2.1 Sample

The study was performed on two experimental groups, one for concrete and one for abstract nouns. Based on the literature, and according to Cohen's categorization (Cohen, 1992), a large effect size (ES ≥ 0,8) of the difference between the priming effect of the concrete group and the priming effect of the abstract group was hypothesized. Therefore, considering a power ($1-\beta$) = 0,80 and α = 0,05, a total sample size of 52 (26 for each group) was calculated. In addition, a control group of 15 patients, who completed both concrete and abstract postoperative testing, without any intraoperative stimulation, was included.

All participants were patients undergoing general propofol BIS-guided anaesthesia (see § 3.2.2) for back surgery at the Neurologic Institute Carlo Besta of Milano. Participants were randomly assigned to the experimental condition (concrete or abstract). A between-subjects design instead of a within-subjects one was adopted to avoid false negative data resulting from the difficulty of the task (i.e. a single, too long list of words). The inclusion criteria were the following: (1) to have an ASA physical status classification[2] I or II (healthy person or mild systemic disease), (2) to be older than 18 and younger than 65 years old, (3) to be Italian native speaker, (4) to be right-handed (Edinburgh Handedness Inventory score above 75%; Oldfield, 1971), (5) not to suffer memory deficits, hearing impairment or any other medical/psychiatric condition that could have affected memory performance or hearing.

3.2.2. Anaesthetic plan

All patients underwent intravenous general anaesthesia. Anaesthesia was induced with propofol target control infusion (TCI) exclusively, until the patient reached loss of consciousness (LOC), clinically identified by a lack of response to verbal command or mild

[2] The ASA physical status classification system is a system for assessing the fitness of patients before surgery. In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system; a sixth category was later added. These are: I. healthy person; II. mild systemic disease; III. severe systemic disease; IV. severe systemic disease that is a constant threat to life; V. a moribund person who is not expected to survive without the operation; VI. a declared brain-dead person whose organs are being removed for donor purposes (Fitz-Henri, 2011).

prodding. Anaesthesia was maintained with propofol TCI and remifentanil as analgesic drug. Depth of anaesthesia was monitored during the entire procedure (from induction of anaesthesia until recovery of consciousness) with the Bispectral Index Monitoring (BIS), in order to maintain adequate levels of unconsciousness (40<BIS<60). Muscle relaxants (i.e. cisatracurium 0,15 mg/kg) were administered for airway securing purposes only and not during the entire surgical session. After the surgical procedure has ended, patients were taken to the recovery room, where they remained until complete recovery of consciousness and absence of pain. Before discharge from the recovery room, patients were tested for immediate postoperative explicit recall (see § 3.2.4).

3.2.3 Stimuli and stimulation procedure

A simple word stem completion test was chosen to investigate the priming effect. This choice depended from a number of reasons. For example, previous studies on priming during general anaesthesia (Andrade & Deeprose, 2007) demonstrated the sensitivity of this task in testing implicit memory. Indeed, conceptual priming (e.g. listening to a story while unconscious) is thought to request a level of information processing which is not possible under general anaesthesia (Alkire et al., 2008). A process dissociation procedure (Jacoby, 1991) was not applied because instructions are too difficult leading to false negatives (Andrade & Deeprose, 2007).

A total of 80 words (40 abstract and 40 concrete) were randomly selected from a pre-existing database (see Papagno et al., 2009), matched for length (p=.235) and frequency (p=0.91). It was verified that these parameters were balanced also between target and non target words within and between the same category, so that abstract target and abstract non target words had similar length (p=.558) and frequency (p=.214), and the same applied for concrete target and non target words (length: p=.664; frequency of use: p=.917); abstract target and concrete target words were balanced both for length (p=.281) and frequency (p=.378), and abstract non target and concrete non target words also had comparable length (p=.521) and frequency (p=.153). Norms were taken from a comprehensive online database of Italian words, CoLFIS (Corpus e Lessico di Frequenza dell'Italiano Scritto) (Bertinetto et al., 2005). The reference corpus consists of excerpts from newspapers, magazines and books, including textbooks and books relating to professional interests, and comprises more than 3 millions lexical occurrences.

Imageability was rated by 30 independent subjects who did not participate in the experimental study. The rating was based on a 5-point scale ranging from 1 to 5 using standardized instructions (Adorni & Mado Proverbio, 2012). Concrete words were significantly more imageable than abstract words (p=.000). See Appendix 1 for the complete list of stimuli.

Forty nouns were used for intraoperative stimulation (20 abstract and 20 concrete) and 40 were used as foils in the postoperative testing. Both abstract and concrete word lists lasted approximately 30 seconds, and lists were repeated continuously from the beginning to the conclusion of surgical procedure. Words were recorded by the examiner at a sample rate of 44.1 kHz and 16 bit sample size using a laptop microphone and a free, open source audio software for multi-track recording and editing, Audacity® (ver. 2.1.2, http://www.audacityteam.org). Word sequences were randomized for every list repetition. Words were presented auditory using EPrime software (Psychology Software Tools, Pittsburgh, PA) installed on a laptop computer, connected to noise-insulated in-ear headphones.

3.2.4 Testing

Patients were tested for explicit memory immediately and 24 h after surgery and for implicit memory 24 h after surgery. Explicit memory was tested through explicit recall and the structured Brice interview. This is a tool commonly used in clinical practice, which consists of 5 questions aimed at evaluating voluntary and explicit recall of episodes happened just before induction of anaesthesia, at recovery and between these two time points (Brice et al., 1970).

Implicit memory was assessed using a three-letter word stem completion test, which comprised the 20 words presented intra-operatively and 20 non-target foils, of the same category (concrete or abstract) of the target words. Stems were built editing the recorded words used for intraoperative stimulation. This was to ensure the identical sound of word-stems and nouns in all section of the study. Both primes and stems were presented auditory to avoid inter-sensory interference (Henson, 2003). Each stem could be completed to form only one of the words presented during the study phase. Also, word stems were screened using the online version of the Italian dictionary Olivetti (http://dizionario-italiano.it) to investigate stem facility (ter Doest & Semin, 2005). For every stem, more than 30 possible completions were found, with the exception of "noia" (bore - abstract list), whose stem, noi-, has 16 possible completions; and "cuoco" (cook - concrete list), whose stem, cuo-, has 26 possible completions. Stem sequence was randomized for every patient. Control patients, as mentioned, completed both the abstract and the concrete word stem completion tests, in a random order, without any previous stimulation.

3.2.5 Scoring

Response coding was very strict: a stimulus word was scored as correctly retrieved only if the participant had told the very same word heard intraoperatively. Inflectional variants of the same word (e.g. plural instead of single), synonyms of the target word or longer words formed from the target word were not coded as correct retrieval. This could be considered a limitation of the study, since it could have underpowered the results. However, a strict criterion seemed necessary in the light of the heterogeneous methodology found in the literature and therefore the need of a simple, clear and rigorous methodology. The strict coding rules were also intended to limit false positive due to perceptually driven retrieval processes, since both stimulation and postoperative testing were administered aurally.

The number of target and non target hits was re-calculated as a proportion of the total target or non target stimuli. An implicit memory score was obtained by subtracting the non-target hits from the target hints, divided for the total number of target words (i.e. 20). The implicit memory score could therefore range from +1 to -1.

3.2.6 Aims

A primary aim of this study was to verify the existence of memory priming during adequate general anaesthesia. In the light of the anaesthetic plan used, differences in priming effect between concrete and abstract nouns were expected, in favour of the former. Should this difference be confirmed, conclusions on the hypothesized neural basis for abstract and concrete word processing could be drawn.

3.2.7 Statistical analysis

Data were analysed using SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to test normality of the distribution of the single variables. Demographic characteristics between groups were compared using a Kruskal–Wallis one-way analysis of variance. Anaesthesiologic characteristics of the two experimental groups were compared by means of an independent Student T test (duration and depth of anaesthesia) and of a Mann-Whitney U test (anaesthetic dosage). For within group analysis (i.e. the comparison between target and non target hits) a Wilcoxon signed rank test was used. Between group differences were analysed with a Kruskall-Wallis one-way analysis of variance, and Mann-Whitney U tests for post hoc analysis, for the variables target hits e non target hits; with a one-way ANOVA and Tukey's post hoc analysis for the implicit memory score. Cohen's d or r, respectively for normally and non normally distributed variables, were calculated to estimate effect size (Fritz et al., 2011). All tests were two-tailed, and the significance level was set at $p < .05$.

3.3 RESULTS

Data from 57 participants (26 females), 22 in the abstract words priming group, 21 in the concrete words priming group, and 15 controls (5 females), were included in the analysis. Ten were removed from the study for the following reasons: one turned out to be hearing impaired during the postoperative testing, even if hearing loss was not reported in the medical history and was not evident preoperatively; two patients refused the postoperative testing; one patient had postoperative complications due to previously unknown clinical conditions, and was transferred to the Intensive Care Unit; intraoperative stimulation of one patient was accidentally stopped during the surgical procedure; four patients developed postoperative

	Concrete	Abstract	Control	Total	*p value*
Age	54 (25-63)	61 (24-65)	46 (27-53)	53 (24-65)	.200
Education	13 (8-18)	13 (8-18)	13 (13-18)	13 (13-18)	.785
Duration (min)	83 ± 23	75 ± 19	-	80 ± 21	.481
Depth of anesthesia (BIS)	43 ± 5	37 ± 8	-	40 ± 7	.144
Anesthetic dosage (µg/ml)	2 (1,7-3,5)	1,9 (1,4-2)	-	2 (1,4-3,5)	.121

Table 3.1. Demographic and anaesthesiological characteristics of concrete and abstract experimental groups and demographic characteristics of control group. Data are expressed as median (min-max) or as mean ± standard deviation (sd), depending on the distribution of the variable.

cognitive complications (namely postoperative delirium) during hospitalization and could not complete the experiment.

No significant differences were found between groups for age and education, between the two experimental groups for surgery/stimulation duration, depth of anaesthesia and anaesthetic drug delivery (see Table 3.1).

No patient reported having heard words intraoperatively on the explicit recall test and no patient had explicit memory for intraoperative events, both at recovery of consciousness and after 24 h.

The proportion of target hits was significantly greater than the proportion of non target hits for the concrete experimental group (p=.018). This difference does not apply to the abstract experimental group (p=.202), nor to the control group, both for abstract (p=.197) and for concrete words (p=.180).

The Kruskall-Wallis one-way analysis of variance revealed a significant difference between groups only for the proportion of target hits (p= .001), and not for the proportion of non target

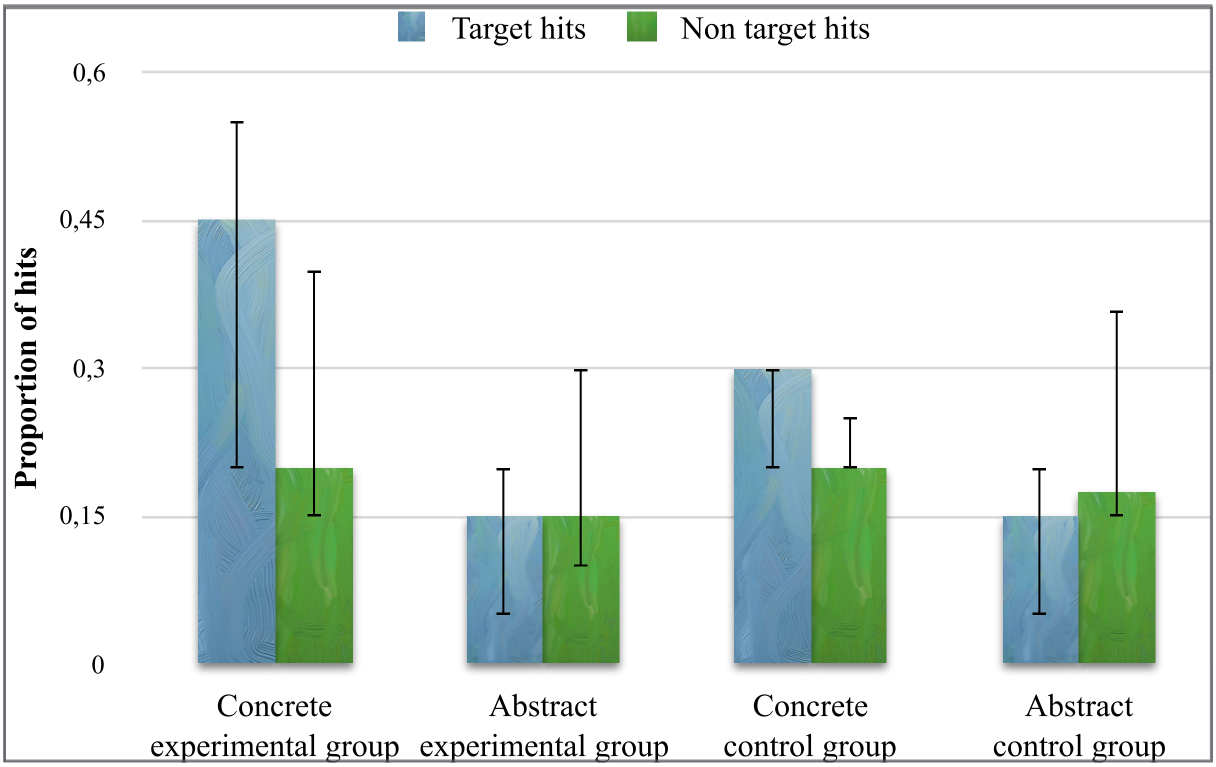

Figure 3.2. Proportion of target and non target hits per group. Data are expressed as median and min-max (error bars).

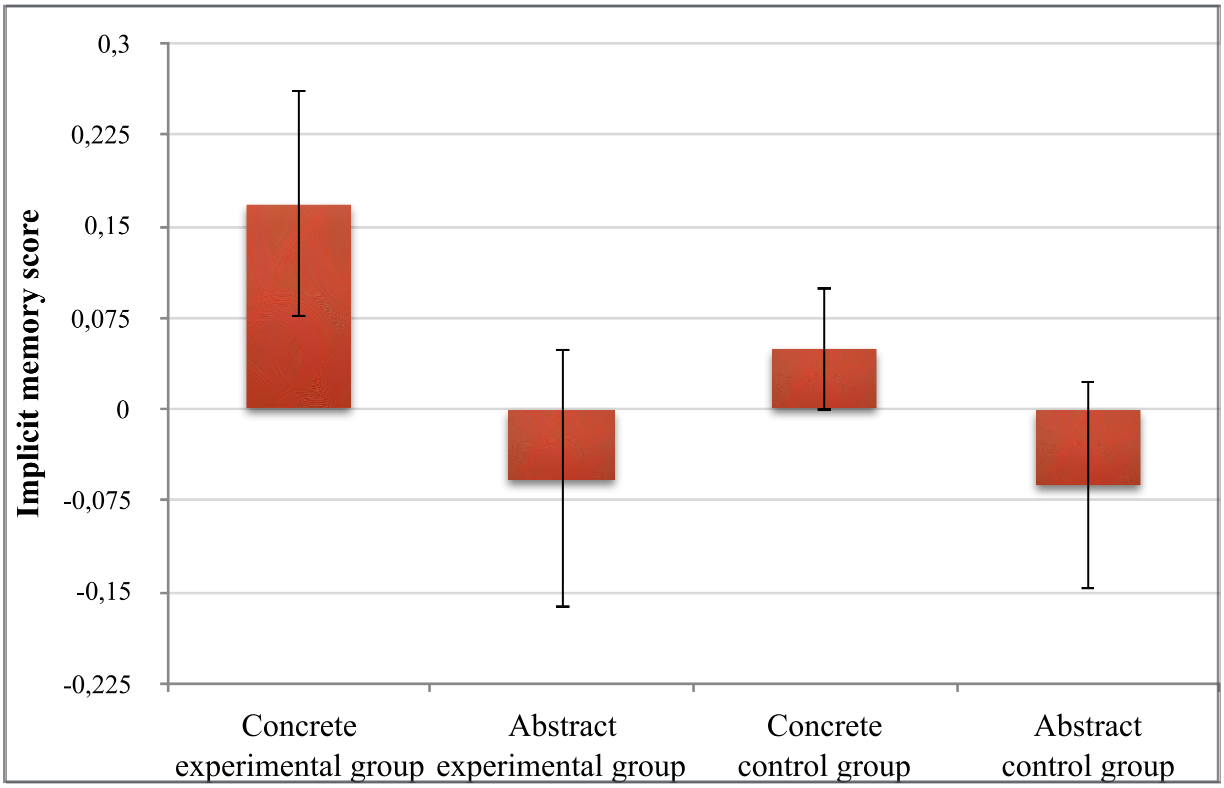

Figure 3.3. Implicit memory score per group. Data are expressed as mean ± standard deviation (error bars).

hits (*p*=.386). The post-hoc analysis indicated a significantly greater proportion of target hits for the concrete experimental group (median 0,45; min-max 0,2-0,55) than for the abstract experimental group (0,15; 0,05-0,2; *p*=.001; Cohen's *r*=0,81), and for the experimental concrete group than for the concrete control group (0,3; 0,2-0,3; *p*=.048; Cohen's *r*=0,59) (see figure 3.2). The comparison of the implicit memory score showed a significant difference between groups (F= 9,406; *p*=.001). Post-hoc analysis indicated that this difference applied for the abstract experimental group (mean ± sd: -0,571 ± 0,106) vs. the concrete experimental group (0,169 ± 0,092; *p*=.001; Cohen's *d*=7,5) and for the concrete experimental group vs. the abstract control group (-0,06 ± 0,04; *p*=.004; Cohen's *d*=2,5) (see figure 3.3).

3.4 DISCUSSION

This experiment aimed at investigating the neural basis of concrete and abstract word processing through intraoperative perceptual priming.

A priming effect was found, in that the rate of target hits was significantly higher than the rate of non target hits in the concrete experimental group, and its implicit memory score clearly exceeded zero. The level of general anaesthesia was adequate in all patients, as confirmed by the intraoperative depth of anaesthesia monitoring. Also, patients did not receive neuromuscular blocking drug during surgical procedure, and were therefore free to move if they became conscious, but this was never the case. No patient had a positive score in the explicit recall test or at the structured interview. Therefore, it is possible to exclude that the priming effect was not, at least partly, due to the contribution of explicit memory.

This result is in line with previous studies that demonstrate that simple perceptual priming is possible even in patients undergoing GA with adequate levels of depth of sedation. Deeprose et al. found a memory priming effect for words heard during propofol GA in two consecutive studies (Deeprose et al., 2004; Deeprose et al., 2005). They tested implicit memory through a word stem completion test and found comparable priming effect size in both studies (0,40 and 0,39 respectively) and similar implicit memory score (0,07 ± 0,18; 0,08 ± 0,19). They suggested that their results provide evidence of unconscious priming. In the present experiment the implicit memory score for the concrete experimental group was greater than the one found by Deeprose et al., since it reached 0,169 ± 0,092 (mean ± sd). This result further supports the hypothesis that unconscious priming exists and that patients undergoing general propofol anaesthesia are still able of low-level information processing and implicit memory formation. The fact that the priming effect found here is greater than that of Deeprose et al. is not surprising, since the methodology of this study was specifically designed to maximize the priming effect, including the distinction made between concrete and abstract words.

The phenomenon of intraoperative priming can be explained by the fact that anaesthesia leaves intact low-level auditory cortices that subserve initial processing of stimuli; moreover, the processes involved in perceptual implicit memory tests, such as the word stem completion task, rely upon the same neural networks (Gabrieli, 1998). A number of studies investigating intraoperative priming failed in finding evidences of this phenomenon. However, as discussed earlier, this could be due to the type of memory test used. Conceptual tests, such as category generation and word association task, in fact, demand high-level processing of stimuli and priming of links between stimuli, probably in frontal and temporal association areas and information flow to these areas is disrupted by anaesthesia (Angel, 1993).

The priming effect was observed only for the group listening to the concrete word list intraoperatively. A significant difference between target and non-target hits was found only in this group. The implicit memory score of the concrete experimental group was significantly higher than the implicit score of the other three groups, who performed similarly, with scores around (even under) zero. To my knowledge, no previous studies investigated intraoperative memory priming with a specific focus on the category of the stimuli. The priming effect for concrete words found in this suggests at least two issues.

First, for what concerns the neural basis of abstract and concrete word processing, this result confirms that abstract and concrete words are processed by at least partly different neural networks. In particular, referring to figure 3.1, propofol suppresses all the cortical regions supposed to be involved in abstract word processing, with the exception of the posterior and the anterior superior temporal gyrus (namely, Brodmann's areas 22 and 38). On the other hand, the majority of those areas considered crucial for concrete word processing (e.g. the anterior temporal pole, the precuneus and the cuneus) are spared by the anaesthetic. One could argue that the difference in the priming effect between abstract and concrete words is due to the higher degree of imageability of concrete vs. abstract words. Concrete words evoke mental images more easily than abstract words, and this feature has been classically considered the main responsible for the concreteness effect, both by behavioural and by neuroimaging studies (Paivio, 1991; Wang, 2010; Roll et al., 2012). However, implicit memory tasks do not seem to be subjected to the concreteness effect (ter Doest & Semin, 2005). Considering the neural target of propofol and the finding of a selective intraoperative priming for concrete words only, this study would therefore support neuroimaging studies showing a greater involvement of posterior, sensory cortical regions in the processing of concrete words, probably due to the significant "perceptual" component in the representation of concrete concepts. It is noteworthy that, even if the limbic system is known not to be affected by general anaesthetics and that affective words may have a potentially arousing effect (Kousta et al., 2011; Adorni & Mado Proverbio, 2012; Vigliocco et al., 2014), a priming effect for abstract words was not observed in this experiment, even if the abstract list included emotional words (e.g. anxiety, fear, surprise).

Second, the result of a selective unconscious priming for concrete words would support the finding of neurophysiological studies (e.g. Kiefer & Spitzer, 2000; Adorni & Mado Proverbio, 2012), suggesting that semantic access begins at very early stages of verbal processing. These studies, in fact, suggest that abstract and concrete words are discriminated as early as 350 ms post-stimulus, and that the brain regions responsible for conscious and unconscious semantic processing are the same, differentiated only qualitatively by the time course: semantic brain activation decays fast within 200 ms for unconsciously perceived words, but increases with time for consciously perceived words.

This is in contrast to what classically hypothesized by Schacter in his perceptual representation system (PRS) theory (Schacter, 1992). The author stated that priming reflects the operation of a PRS that can function independently from the episodic memory. PRS would refer to a class of domain-specific subsystems, based in cortical regions, that process and represent information about the form and the structure, but not the meaning and other associative properties, of words and objects. Each of the subsystems differs from the others in several ways, but all share common features: they operate at a pre-semantic level, and they are involved in non-conscious expressions of memory for previous experiences. Also Schott et al. (2005) argued that word stem completion priming involves perceptual and lexical processing, but not conceptual processing. Based on the present results and neurophysiological studies, it is likely instead that priming is a complex multiprocess phenomenon, which includes not only phonological and lexical, but also an early conceptual processing (Henson, 2003).

This study presents some limitations. First, a potential a-priori advantage for concrete words was not investigated in the experimental group, in order to avoid any learning bias. However, the control group, who did not receive any intraoperative stimulation, did not show any advantage for concrete or abstract words, therefore supporting the view that the implicit memory score truly represents a measure of implicit memory. Also, even if stem facility was investigated in terms of numbers of possible different completions, no specific analysis was carried on the sublexical properties of such alternative completions (e.g. semantic neighborhood density, frequency of use, length, imageability). The strict coding rules were applied to partly limit false positives deriving from this limitation.

Lastly, due to the specific nature of this experiment and of the implicit memory test, it was not possible to collect response reaction times, which usually provide interesting information.

A part from these limitations, this experiment is the first study on intraoperative priming to specifically consider the possible effect of the anaesthetic drug used on cortical targets and, therefore, on implicit memory formation. In addition, since the primary aim was to investigate the neural substrates of concrete and abstract word processing, the category of the primed stimuli was an independent variable and its effect on the implicit memory test was considered. Finally, as already mentioned, studying priming during general anaesthesia, if the depth of sedation is carefully and continuously monitored, allows to exclude the contribution of explicit memory on the implicit test performance and to guarantee that any priming effect observed is a true implicit memory phenomenon.

To conclude, in this study the neural basis of abstract and concrete word processing were studied through intraoperative perceptual priming and a simple word stem completion test. The result of a selective priming effect for concrete words would support the hypothesis that concrete words are processed in posterior cortical areas, strictly linked to sensory systems, which are not suppressed by the general anaesthetic propofol. Semantic access, as demonstrated also by electrophysiological studies, seems to occur at very early stages of verbal processing.

Further studies on intraoperative priming should consider the use of different anaesthetic drugs on concrete and abstract words priming effect.

CHAPTER 4. EXPERIMENT 2. Auditory priming for abstract words under general inhalational anaesthesia.

4.1. INTRODUCTION

In Experiment 1, intraoperative memory priming for concrete and abstract words was investigated in patients undergoing general intravenous (propofol) anaesthesia. Consistently to the study hypothesis, a selective priming effect for concrete words was found. This result supports: (1) the existence of unconscious priming; (2) the hypothesis that priming is a multi-process phenomenon, involving phonological and lexical processing and early automatic activation of conceptual codes (Binder et al., 2005); (3) the conclusion that concrete words are processed in posterior cortical areas, strictly linked to sensory systems, whose activity is only partly modulated by propofol. Abstract word processing is thought to rely on the activity of anterior brain regions associated to verbal processing, namely middle and inferior temporal gyri and inferior frontal gyrus (Binder et al., 2005; Papagno et al., 2009; Wang et al., 2010). Since propofol is known to modulate the activity of these cortical regions (Franks, 2008), and a priming effect for abstract words was not found, results from experiment 1 would support conclusions from previous neuroimaging studies. However, every anesthetic has different and specific neuronal targets (Alkire et al., 2008), and the hypothesis of experiment 1 should be tested considering also other drugs. For example, as discussed in chapter 2, sevoflurane is a volatile anaesthetic known to modulate neuronal activity in brain areas more posterior than those suppressed by propofol, namely in the precuneus, posterior cingulate cortex, cuneus, frontoparietal cortex and cerebellum (Franks et al., 2008). Among these, the precuneus, the posterior cingulate cortex, the inferior parietal lobule, and the cerebellum are brain regions thought to be involved in concrete word processing. Therefore, considering together the neural substrates of abstract and concrete word processing and brain areas suppressed by sevoflurane (see figure 4.1), it is assumable that studying intraoperative priming in patients undergoing general sevoflurane anaesthesia would produce different results from experiment 1. Specifically, an advantage for abstract words on the implicit memory test was expected. Experiment 2 constitutes a methodological replication of experiment 1, with the noteworthy difference of the type of anaesthetic agent used.

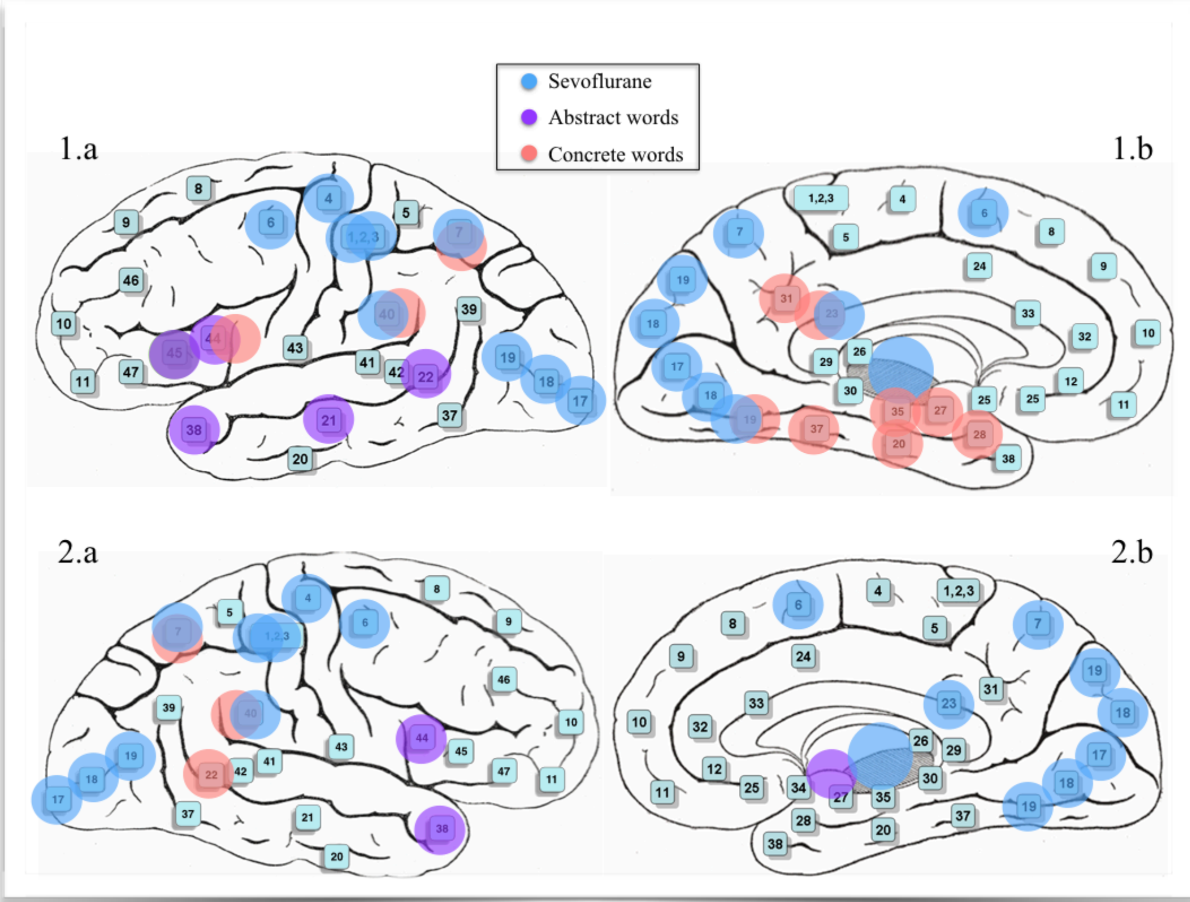

Figure 4.1. A schematic left lateral (1.a), left medial (1.b), right lateral (2.a) and right medial (2.b) map of brain regions commonly found to be deactivated by sevoflurane (blue circles) and of regions whose activity is greater for abstract than concrete word processing (purple circles) or vice versa (pink circles). Broadmann's areas, where available (see the thalamus, 1.b and 2.b., and the amygdala, 2.b), are indicated. Note that greater activation to concrete than abstract words has been found also in the culmen, and that sevoflurane causes activity suppression also in the cerebellum.. This map was obtained merging results from the neuroimaging and TMS studies discussed in § 1.2.3, § 1.2.4 and § 2.3.1.

4.2 METHODS

The study was approved by the local Ethics Committee of the Neurologic Institute Carlo Besta and all patients gave written informed consent before participating in the study.

4.2.1 Sample

As in experiment 1, the study was performed on two experimental groups, one for concrete and one for abstract nouns. The sample size was calculated based on the results of the primary outcome (i.e. the implicit memory score) obtained from experiment 1. Considering the very large effect size Cohen's d = 7,5 of the difference in the priming effect between the two experimental groups, the size of the sample was very small. Therefore, despite the sample size calculation, 14 patients were included in the study, 7 for each experimental group (concrete and abstract). Seven additional patients were included as control group. All participants were patients undergoing general sevoflurane anaesthesia (see § 4.2.2) for back surgery at the Neurologic Institute Carlo Besta of Milan.

For further details on sample characteristics (e.g. inclusion criteria), please refer to § 3.2.1.

4.2.2 Anaesthetic plan

All patients underwent general inhalation anaesthesia. Loss of consciousness was induced with a single bolus of opioid (propofol 2mg/kg) and infusion of fentanyl as analgesic drug. Anaesthesia was then maintained with sevoflurane at MAC > 1% (see § 2.3.1) or at the concentration needed to keep BIS values between 40 and 60, and remifentanyl (infusion 0,1-0,3 μg/kg/hr) or fentanyl (boluses of 50 μg each) as analgesic drug. Muscle relaxants (i.e. cisatracurium 0,15 mg/kg) were administered for airway securing purposes only and not during the entire surgical session. After the surgical procedure, patients were taken to the recovery room, where they remained until complete recovery of consciousness and absence of pain. Before discharge from the recovery room, patients were tested for immediate postoperative explicit recall.

4.2.3 Stimuli and stimulation procedure

Please refer to §3.2.3.

4.2.4 Testing

Please refer to § 3.2.4.

4.2.5 Scoring

Please refer to § 3.2.5

4.2.6 Aims

The primary aim of this experiment was, as in experiment 1, to investigate the neural substrate of abstract and concrete word processing through an implicit memory paradigm. In detail, considering the results from experiment 1, a priming effect was expected. Furthermore, in the light of the specific anaesthetic plan used, a difference in the priming effect size was hypothesized between the two experimental groups, with an advantage for the “abstract” group.

4.2.7 Statistical analysis

Data were analysed using SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to test normality of the distribution of the single variables.

Demographic characteristics between groups were compared using a one-way ANOVA and Tukey's post hoc analysis (age) and a Kruskall-Wallis one-way analysis of variance (education). Anaesthesiologic characteristics of the two experimental groups were compared by means of an independent Student T test (duration and depth of anaesthesia) and a Mann-Whitney U test (anaesthetic dosage). For within group analysis (i.e. the comparison between target and non target hits), a Wilcoxon signed rank-test was used. Between-group differences were analysed with a one-way ANOVA and Tukey's post hoc analysis for non target hits; with a Kruskall-Wallis one-way analysis of variance, and Mann-Whitney U tests for post hoc analysis, for target hits and the implicit memory score. Cohen's *d* or *r*, respectively for normally and non normally distributed variables, were calculated to estimate effect size (Fritz et al., 2011). All tests were two-tailed, and the significance level was set at $p < .05$.

4.3 RESULTS

Data from 14 patients (7 females), 7 for each experimental group, and 18 controls (8 females), were included in the analysis. There were no dropouts. No significant differences were found between groups for age and education and between the two experimental groups for surgery/stimulation duration, depth of anaesthesia and anaesthetic drug delivery (see Table 4.1). None of the patients obtained a positive score at the explicit recall test or reported explicit memory for intraoperative events. Also, no patients showed sign of recovery of consciousness (e.g. movements) intraoperatively.

The proportion of target hits was significantly higher than the proportion of non target hits for the abstract experimental group (median, min-max; target hits: 0,3, 0,2-0,5; non target hits: 0,175, 0,1-0,35; p=.027); the difference did not apply for the concrete experimental group

	Concrete	Abstract	Control	Total	*p value*
Age	39,6 ± 15	52,8 ± 5,2	46,1 ± 9,7	46,1 ± 10,2	.249
Education	14 (12-16)	13 (8-17)	15 (11-21)	13,5 (8-21)	.235
Duration (min)	55,4 ± 21,3	66,6 ± 14,5	-	61 ± 18,1	.359
Depth of anesthesia (BIS)	42,2 ± 5,4	44,9 ± 3,5	-	43,5 ± 4,5	.376
Anesthetic dosage (MAC)	1,6 (0,8-2)	1,5 (1,5-1,8)	-	1,5 (0,8-2)	.841

Table 4.1. Demographic and anaesthesiological characteristics of concrete and abstract experimental groups and demographic characteristics of control group. Data are expressed as median (min-max) or as mean ± sd, depending on the distribution of the variable.

(target hits: 0,5, 0,2-0,55; non target hits: 0,4, 0,15-0,5; *p*=.233) and for the concrete control group (target hits: 0,25, 0,1-0,65; non target hits: 0,25, 0,1-0,35; *p*=.120). The rate of abstract non target hits was significantly higher than the rate of abstract target hits in the control group (target hits: 0,15, 0,05-0,25; non target hits: 0,2, 0,05-0,4; *p*=.017).

A significant difference was found in the proportion of target hits between groups (*p*=.000); the post-hoc analysis specified that the difference applied for the abstract experimental vs. the abstract control group (*p*=.001; Cohen's *r*=0,66), for the concrete experimental vs. concrete control group (*p*=.019; Cohen's *r*=0,47), and for the concrete control vs. the abstract control group (*p*=.000; Cohen's *r*=0,59). Also, a significant difference between groups was found for the proportion of non target hits ((F=6,327; *p*=.001), and specifically between the abstract experimental and the concrete experimental group (*p*=.01; Cohen's *d*=1,48) and between the concrete experimental and the concrete control group (*p*=.009; Cohen's *d*=1,35) (see

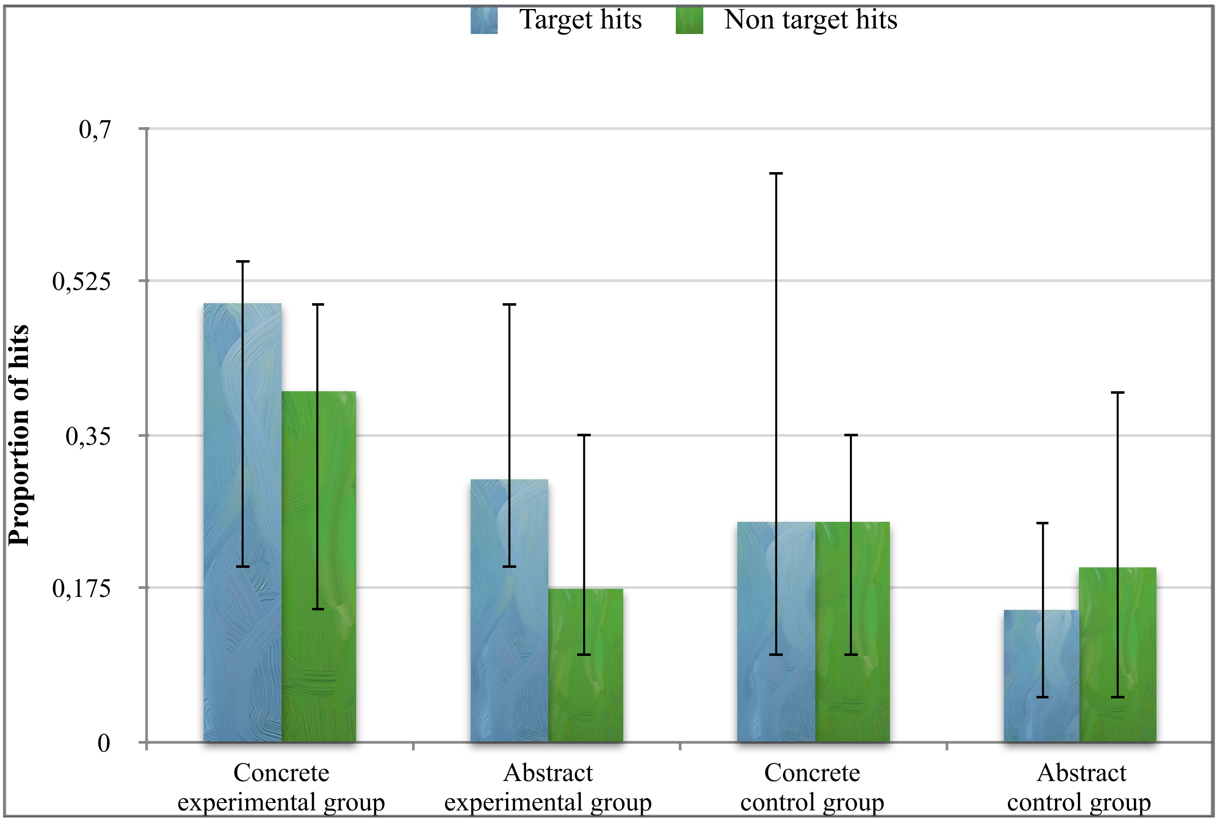

Figure 4.2. Proportion of target and non target hits per group. Data are expressed as median and min-max (error bars).

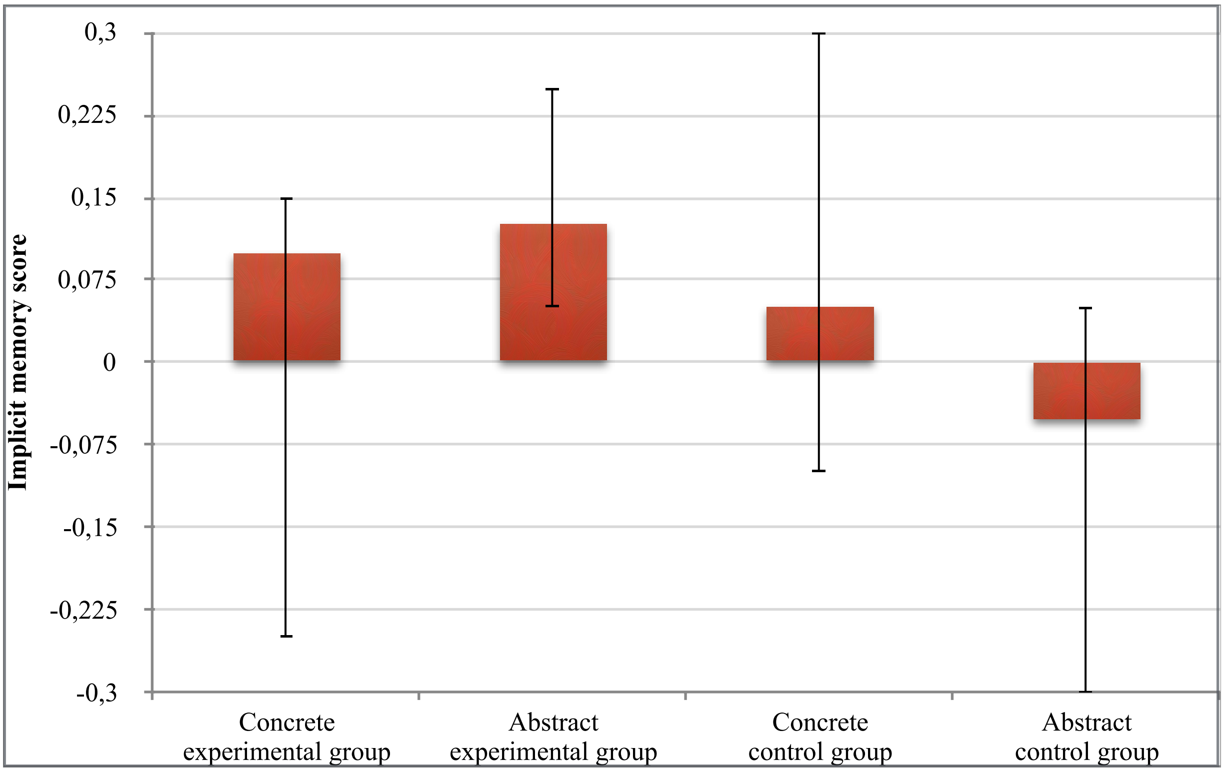

Figure 4.3. Implicit memory score per group. Data are expressed as median and min-max (error bars).

Appendix 2 and figure 4.2).

The Kruskall-Wallis one-way analysis of variance showed a significant difference between groups in the implicit memory score (p=.001). The subsequent post hoc Mann-Whitney U test revealed that the implicit memory score of the abstract experimental group (0,125, 0,05-0,25) was significantly higher than the implicit memory score of the abstract control group (-0,05, -0,3-0.05; p=.000; Cohen's r=0.72); and that the implicit memory score of the control group in the concrete word stem completion test (0,05; -0,1-0,3) was significantly higher than the implicit score in the abstract stem completion test (-0,05; -0,3-0,05; p=.006; Cohen's r=0,47) (see figure 4.3).

4.4 DISCUSSION

Based on the results obtained in experiment 1, this second study aimed at further investigating the neural basis of abstract and concrete word processing, in patients with a different type of anaesthesia, which acts on other cerebral regions. The existence of unconscious priming for intraoperatively heard words was further confirmed, since in both the concrete and the abstract experimental group the rate of target hits was higher than the proportion of non target hits (and the difference reached statistical significance in the case of the abstract experimental group), being the implicit memory score clearly above chance level. This study therefore strengthens the conclusions previously drawn on perceptual priming, namely that it occurs also with adequate levels of depth of anaesthesia and that it relies on the activity of primary perceptual cortices, only partly modulated by the action of general anaesthetics (Franks, 2008). The magnitude of the priming effect was comparable to that found in experiment 1, and again greater than what found in previous studies on intraoperative perceptual priming (e.g. Andrade & Deeprose 2007; Deeprose et al., 2005), probably because of the methodological issues already discussed (see § 4.4).

The finding of a priming effect also for concrete words refutes the study hypothesis that, considering the neuronal targets of sevoflurane, this effect would not be observed. As already mentioned, among the cortical regions that are thought to be involved in concrete word processing, sevoflurane suppresses activity in parietal (precuneus, inferior parietal lobule) and occipital cortices, and in the cerebellum (culmen). The activation of these areas has been linked to the engagement of mental imagery in concrete word processing, since mental imagery is supposed to require the activation of perceptual systems (Kosslyn et al., 2001). For this reason a priming effect for concrete words was not expected. Indeed, concrete words are more imageable than abstract ones. The finding of a priming effect for concrete words during sevoflurane general anaesthesia would suggest that concreteness and imageability are two distinct dimensions: indeed, a priming effect was found also for concrete words, even if concrete words could not take advantage of imageability; however, priming effect was smaller for concrete than abstract words. One could speculate that in experiment 1 the absence of priming for abstract words and the presence of priming for concrete words were due to the different degree of imageability. However, results from the present study suggest that the specificities of abstract and concrete word processing are purely “linguistic”, that is they appear also in the absence of the advantage of imageability.

Yet, since the difference between target and non target hits in the concrete experimental group, and the difference of the implicit score between concrete experimental and concrete control group, did not reach significance, these conclusions must be considered cautiously and deserve further confirmation.

As hypothesized, a priming effect for abstract words was found and was greater, even if not significantly, than the priming effect for concrete words. This result seems to support the hypothesis that abstract word processing relies mainly on the activity of anterior brain regions (i.e. temporal and frontal cortices), which are not suppressed by sevoflurane, but are modulated by propofol (see experiment 1). To explain the result of a priming effect for both abstract and concrete words, it is assumable that, consistently with some neuroimaging studies (e.g. Binder et al., 2005; Wang et al., 2010), abstract and concrete words are processed by specific brain regions, but also share some common networks. According to the present results, these common pathways may be represented by the temporal lobe (middle and inferior gyri; Binder et al., 2005), which could provide contextual access both for concrete as well as for abstract words.

As in the case of experiment 1, this study has some limitations. First, a potential a-priori advantage for abstract or concrete words was not investigated, even if this was made to avoid any learning bias. Also, even if the sample size was defined a-priori, based on the effect size obtained in experiment 1, the number of participants is not large. Finally, the abstract word list included emotional words, and one cannot exclude that this somehow influenced the performance of the abstract experimental group.

Nevertheless, this study applied the same strict methodology of experiment 1 and considered the effect of important possible confounding variables, namely the type of anaesthetic, the duration of the stimulation, the depth of sedation, the category of the stimuli and some of their sublexical properties. Also, the results obtained are in line with previous findings from neuroimaging studies (Binder et al., 2005; Papagno et al., 2009; Wang et al., 2010).

To conclude, results from experiment 1 and 2 provide evidence for the existence of intraoperative unconscious priming and could stimulate further research on the relationship between consciousness and memory, even if any consideration on this topic goes beyond the aim of this work. The primary objective of this thesis was to investigate the neural basis of abstract and concrete word processing through an implicit word stem completion paradigm. Results would support the conclusion that abstract and concrete word processing is subserved in part by common networks (possibly in the temporal lobe), and in part by specific brain regions. Concrete words, because of their "perceptual" content and involvement of mental imagery, might rely on the activity of posterior brain areas, for example posterior temporal, parietal and occipital cortices, which are not (or only partly) suppressed by propofol. Sevoflurane modulates the activity of these areas. A priming effect for concrete words, however, was found, indicating that the perceptual and imagery content of concrete words is important for their advantage over abstract words, but is not essential in their processing.

Anaesthesia provides a fruitful field of research, since it allows to exclude the contribution of (involuntary) explicit memory on the implicit task and to avoid false positive results caused by a concreteness effect. Unfortunately, since anaesthetics equally affect both hemispheres, no conclusions can be drawn on possible lateralized effect of concrete vs. abstract word processing.

Based on the results from these experiments, and from the substantial corpus of literature on the neural basis of abstract and concrete word processing, future studies should try to better define the diverse contribution of specific brain networks to the different stages of abstract and concrete word processing.

CHAPTER 5. EXPERIMENT 3. Investigating the role of the inferior frontal cortex in abstract and concrete word processing through direct electrical stimulation (DES) in awake surgery.

5.1 INTRODUCTION

Results from experiments 1 and 2 lead to the conclusion, consistent with neuroimaging and neuropsychological literature, that concrete and abstract word processing is subserved partly by common regions (possibly in the temporal lobe) and partly by specific network. In particular, in experiment 1, patients anaesthetized with propofol did not show a priming effect for abstract, but only for concrete words. In experiment 2, patients under general inhalational anaesthesia showed a priming effect for abstract words, which was stronger than for concrete words. It was, therefore, concluded that abstract word processing relies on the activity of anterior brain areas, classically linked to verbal processing, such as the inferior frontal gyrus; and that concrete word processing, due to their "perceptual" content, is strictly linked to the activity of posterior, sensory brain regions.

Results from neuroimaging studies on the possible neural substrates of abstract and concrete word processing have been already discussed in chapter 1. Here, I briefly remind that a number of studies, using different techniques (PET, fMRI, rTMS) and mainly a lexical decision task, support the involvement of the (left) inferior frontal gyrus in the processing of abstract words (e.g. Perani et al., 1999; Fiebach & Friederici, 2004; Binder et al., 2005; Papagno et al., 2009; Wang et al, 2010; Kumar et al., 2016). The activation of this area has been interpreted in terms of abstract words requiring verbally-mediated semantic knowledge processing (Wang et al., 2010) or as serving as a phonological working memory that holds the phonological form of abstract words while retrieving associated words (Binder et al., 2005). However, this result is not univocal, since other studies found a greater involvement of the same region for concrete than for abstract word processing (e.g. Jessen et al., 2000).

Over the past few decades, awake surgery and awake craniotomy have seen a growing role in brain tumor surgery. Based upon the surgical location and indication, including redundant regions, eloquent areas, deep brain stimulation, and epilepsy foci, some patients will benefit from this surgical procedure, allowing neurocognitive testing and neurophysiological monitoring during the intra-operative period, which are otherwise prevented under general anesthesia (GA) (Dreier et al., 2009). The possibility to analyze eloquent brain areas makes awake surgery a powerful method for reducing the risks of tumor resection over motor but in particular cognitive functions (Brown et al., 2013). The primary goal of awake surgery is therefore to provide maximum tumor resection with minimal postoperative neurological deficit (Brown et al., 2013). However, inadequate analgesia during craniotomy and prolonged sedation interfering with brain mapping can be major drawbacks of this technique. As far as intraoperative complications are concerned, the incidence of intraoperative seizures during awake surgery is not unusual, ranging from 0% to 24% in the literature (Conte et al., 2008).

For obvious reasons, awake surgery constitutes an interesting filed of research for neurosciences (e.g. Giussani et al., 2008).

Therefore, to further test the hypothesis of the involvement of the left inferior frontal cortex in the processing of abstract and concrete words, a series of patients undergoing direct cortical stimulation (DCS) for brain mapping during awake surgery for brain tumor removal, was studied.

A lexical decision and a semantic judgment task were added to the standard neuropsychological assessment, and accuracy was recorded as dependent variable. An effect of DCS on the accuracy of both tasks was expected. Also, it was hypothesized that this effect would be larger for abstract than for concrete words.

5.2 METHODS

5.2.1 Patients

A total of 8 patients with left frontal lesion were included. Two were excluded from the study since they were converted to general anaesthesia before intraoperative assessment due to unmanageable anxiety and panic attack. Demographic and clinical characteristics of the six included patients are summarized in table 5.1.

All patients were right handed (Oldfield, 1971) and hemispheric lateralization for linguistic function was verified through verb generation and verbal fluencies tasks during preoperative fMRI.

All patients underwent brain tumor removal with local anaesthesia and *awake-awake* procedure with cortical and subcortical motor and speech mapping, at the Neurologic Institute Carlo Besta of Milan.

5.2.2 Neuropsychological assessment

All patients on the pre-admission visit underwent a clinical examination routine, including MRI, fMRI, a fiber tractography (DTI-FT) (when requested by the surgeon), and were assessed, based on indications from previous studies (Papagno et al., 2012) with the following tests: verbal fluency on phonemic and semantic clue (Novelli et al., 1986), picture naming of objects (Sartori et al., 1988, 1992), picture naming of people (Bizzozero et al., 2007), verbal learning (Rey Auditory verbal learning test; Carlesimo et al., 1996), Weigl sorting test (Spinnler & Tognoni, 1987) and the trail making task, A and B (Giovagnoli et al., 1996). Based on the lesion localization, specific tests are usually added to this basic evaluation. Therefore, since all patients recruited in this experiment had a lesion in a speech eloquent area, the battery was integrated with the following: naming by description (Novelli et al., 1986), sentence-picture matching (Cecchetto et al., 2012), Token test (Spinnler & Tognoni, 1987), words and nonwords repetition test (Ciurli et al., 1996). For the specific purpose of this study, a lexical decision (abstract words, concrete words, nonwords) and a semantic judgment (abstract vs. concrete words) task were administered. Thirty abstract words, 30 concrete words and 30 nonwords were used in these tasks. Abstract and concrete words were selected from those used in experiment 1 and 2, in order to have similar frequency of use (*p*=.092), length (*p*=.946). Frequency and length were taken from the online Italian words database CoLFIS (Bertinetto et al., 2005). For each word, a corresponding nonword was created with a pseudoword generation program (http://www.psychology.nottingham.ac.uk/staff/wvh/internal/research/pseudo/). The complete list of stimuli is reported in appendix 3.

The same stimuli were used for lexical decision and semantic judgment task. Both in the preoperative and in the intraoperative assessment, the lexical decision test was administered at the beginning of the examination and the semantic judgment task was given at the end, in order to avoid any possible memory effect. Also, the lexical decision task was always administered before the semantic judgment task to avoid that a deeper processing of the semantic meaning of words could affect responses on the subsequent test. In fact, in a semantic judgment task subjects need to overtly process the meaning of the stimuli, while in a lexical decision task the meaning of the stimuli is only implicitly assessed (Ruffet et al., 2009). During intraoperative mapping, a shortened version of both tasks, including 10 abstract words, 10 concrete words and, in the case of lexical decision, 10 nonwords, was used.

Since there were objective difficulties in collecting reaction times during intraoperative stimulation and mapping, attention was focused only on accuracy, and patients were asked to respond as accurately, as possible, and not as fast. The response modality was "yes/no" in both tasks, being the question in lexical decision "Is this a real word?", and in the semantic judgment "Is this a concrete word?".

Finally, abstract words are thought to be held in working memory in phonological form to a greater degree than concrete words (Wang et al., 2010; Binder et al., 2005), Therefore, to avoid intraoperative errors due to working memory difficulties and to balance the contribution of phonological processing between concrete and abstract words, stimuli were read by the experimenter and simultaneously visually presented, until the patient responded. Stimuli were printed with black ink in the centre of an A5 card, in 100-point Times New Roman font.

The intraoperative testing is usually tailored on each patient, based on the preoperative performance using a conservative criteria, namely selecting those items which were responded correctly in the preoperative assessment. This was done for two main reasons: (1) to preserve the preoperative cognitive functioning; (2) not to misattribute baseline errors to stimulation testing. An intraoperative cognitive baseline was also performed, to ascertain that errors detected during stimulation were not caused by the items being too difficult.

Note that patients 1 and 2 performed only the lexical decision task only. Since no relevant effects of DCS on accuracy were observed, the semantic judgment task was introduced. Indeed, both abstract and concrete words involve similar processes and activations if compared to nonwords (Binder et al., 2005), and a lexical decision task alone could not be sensitive enough to differentiate between concrete and abstract word processing in the setting of intraoperative awake brain mapping.

When stimulation produced a blocking, the patient was asked to move the tongue from side to side while stimulating to assess a negative motor effect. Speech arrests reported later are net of negative motor effects.

Patients were re-evaluated after surgery, before discharge, and at 3 months follow-up. Postoperative data are not included since they are not relevant for the purpose of the experiment.

5.2.3 Anaesthesiological, surgical and neurophysiological procedures

After being admitted to the surgery room, all patients underwent a scalp block (i.e. local anesthesia of the nerves of the scalp) with local anaesthetics ropivacaine 2 mg/kg and received analgesic and anxiolytic drugs (dexmedetomidine 0,3-1 μg/kg/h).

In order to maximize lesion excision while preserving cognitive (and motor) functions, a neuronavigation system was used (Stealth Station S7 Surgical Navigation System,Medtronic Inc., Louisville, CO, USA) with electromagnetic tracking system, on which patients' preoperative exams were implemented.

Stimulation for language mapping was delivered directly over the cortical surface through a bipolar stimulator with 1-mm electrodes separated by 5 mm, delivering biphasic square wave pulses of 1 msec at 60 Hz (figure 5.1). Current amplitude started from 1mA and was progressively increased by 1mA. Current amplitude never exceeded 6mA, in order to avoid intraoperative seizures. Apart from clinical observation, electroencephalogram, electrocorticography and electromyography (NIM Eclipse, Medtronic Inc., Louisville, CO, USA) were applied to monitor for possible afterdischarges.

Stimulation sites were saved during surgery with the neuronavigator, and subsequently handled in order to be represented on a standard brain atlas (Montreal Neurological Institute (MNI) ICBM152).

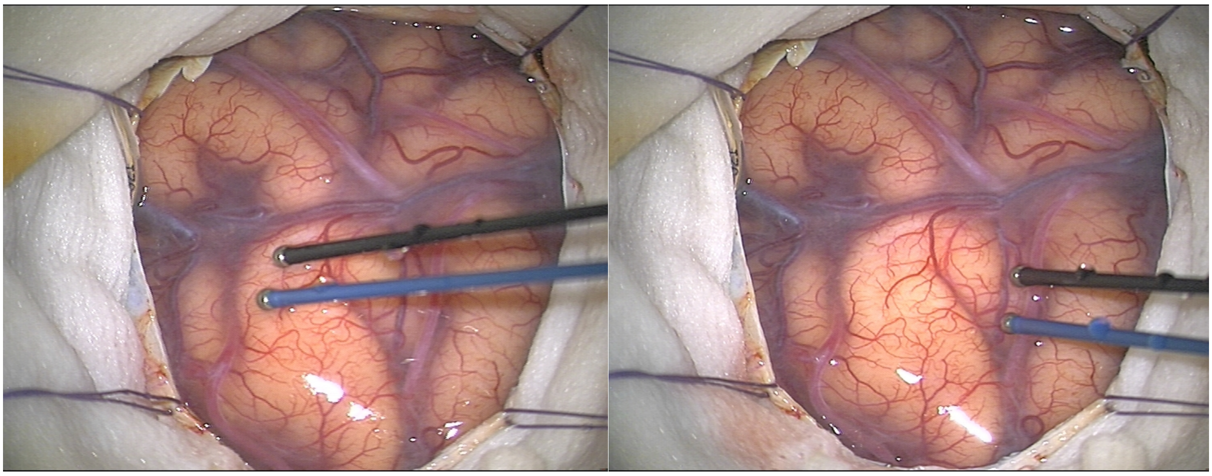

Figure 5.1. Example of DCS over middle frontal gyrus.

5.2.4 Statistical analysis

Due to the limited sample size, only a chi squared analysis on the semantic judgment task was performed, to test the association between the stimulation site (categorised according to Brodmann's: 4, 6, 9, 44, 45[3]; Garey, 2006) and the error type (abstract words error; concrete words error; both words error; correct answer). Cramer's Phi was also calculated to estimate effect size.

The test was two tailed and the significance level was set at $p < .05$.

Other data were assessed qualitatively.

[3] BA 38 was stimulated only in the case of MT and was not relevant for the purpose of the study. It was therefore excluded from the analysis.

5.3 RESULTS

A synthesis of patients' demographic and clinical data is provided in table 5.1. Patients (3 females) had a mean (± sd) age of 38,6 ± 16,3 and 13 ± 3,2 years of education.

An overview on patients' preoperative neuropsychological performance is reported in table 5.2. Intra-operative performance in the lexical decision and in the semantic judgment task is reported as percentage of correct responses per stimulation site in tables 5.3-5.8. Stimulation sites are shown in figures 5.3-5.8.

All patients were able to perform the intraoperative baseline without errors.

A total of 127 stimulations were analyzed. The chi square test revealed a significant association between the stimulation site and the error type in the semantic judgment task

Patient	Gender	Age	Education	Lesion site (left)	lesion dimension (mm)	Debut	Diagnosis
MDG	M	19	13	F3 perisylvian	11,6x7	partial seizure	cavernoma
SDA	M	30	8	F3, Fa inferior	54,2x30,3	generalized seizure	oligodendroglioma grade II
AC	F	67	13	F3 frontal opercular cortex	9,7x6,8	occasional discovery (secondary to lung adenocarcinoma)	radionecrosis
MT	F	44	13	F2, F3, insula	64x47	headache	pervasive astrocytoma grade II
GI	F	33	18	Fa inferior, F3 posterior	49,5x28	headache	chronic inflammatory process of the small vessels
CDR	M	39	13	Fa, F3 posterior	49,8x30,5	partial seizure	oligodendroglioma IDH-mutant grade II

Table 5.1. Patients' demographic and clinical characteristics. *F 2, 3, a: middle, inferior and pre-central frontal gyri.*

Patient	L_D	S_J	VF_P	VF_S	N_P	N_O	N_D	S_P	TOK	W_R	NW_R	R_I	R_D	WEIGL	TMTA	TMTB
cut-off	-	-	≥17	≥25	≥53	(64)	≥33,5	≥70,5	≥26,5	(40)	(40)	≥28,53	≥4,69	≥8	≥ 94	≥ 283
MDG	100	-	21	44	53	64	37,5	90	33,5	40	40	42,1	7,5	10,25	49	135
SDA	100	-	27	41	64	64	33,5	80	35,5	40	40	32,1	6,9	10	37	100
AC	100	96,7	45	51	74,23	64	37,5	100	34,5	40	40	47,3	7,6	11,25	42	103
MT*	100	83,3	14	35	49	62	36,5	90	33,5	40	40	27,1	4,5	11,6	48	83
GI	100	93,3	33	43	67	64	37,5	100	33,5	40	40	41,5	11,5	12,25	37	79
CDR	100	96,7	29	41	71	64	36,5	100	33,5	40	40	38,8	7,1	12,25	36	88

Table 5.2. Patients' preoperative neuropsychological evaluation. Cut-offs are reported, when available. Pathological scores are in light grey. * MT, because of insular involvement, was the only patient to perform also the Ekman test for facial expression recognition (Ekman, 1999). MT score at the Ekman test was within normal range. *L_D: lexical decision; S_J: semantic judgement; VF_P: verbal fluency on phonemic cue; VF_S: verbal fluency on semantic cue; N_P: picture naming of famous people; N_O: picture naming of objects; N_D: naming on description; S_P: sentence-picture matching; TOK: token test; W_R: word repetition; NW_R: nonword repetition; R_I: Rey Auditory Verbal Learning Test, immediate recall; R_D: Rey Auditory Verbal Learning Test, delayed recall; Weigl: Weigl Sorting Test; TMTA: Trail Making Test, part A; TMTB: Trail Making Test, part B.*

(Pearson's chi square=31,613, *p*=.011), with Cramer's phi=.503, indicating a large effect size (Cohen, 1988).

As can be seen in figure 5.2, no errors were detected during BA 4 and BA 9 stimulation. Excluding speech arrests, on a total of 17 errors detected, 12 (70,6%) concerned abstract words, 2 (11,8%) concrete words and 3 (17,6%) both word types. The highest number of total errors was found in BA 44 (N=13), during 36 stimulations. In detail, 10 were abstract word errors (77% of total errors detected over BA 44; 83,3% of the total abstract word errors observed), 1 was a concrete word error (1% of total errors detected over BA 44%; 50% of the total concrete word errors observed), and 2 were errors on both word types (15,4% of total errors detected over BA 44; 66,7 % of the total of both word type errors). On BA 6 were observed the remaining 2 (16,7%) errors regarding abstract words. In the lexical decision task only five errors were recorded, 3 on abstract and 2 on concrete words. This result was considered irrelevant.

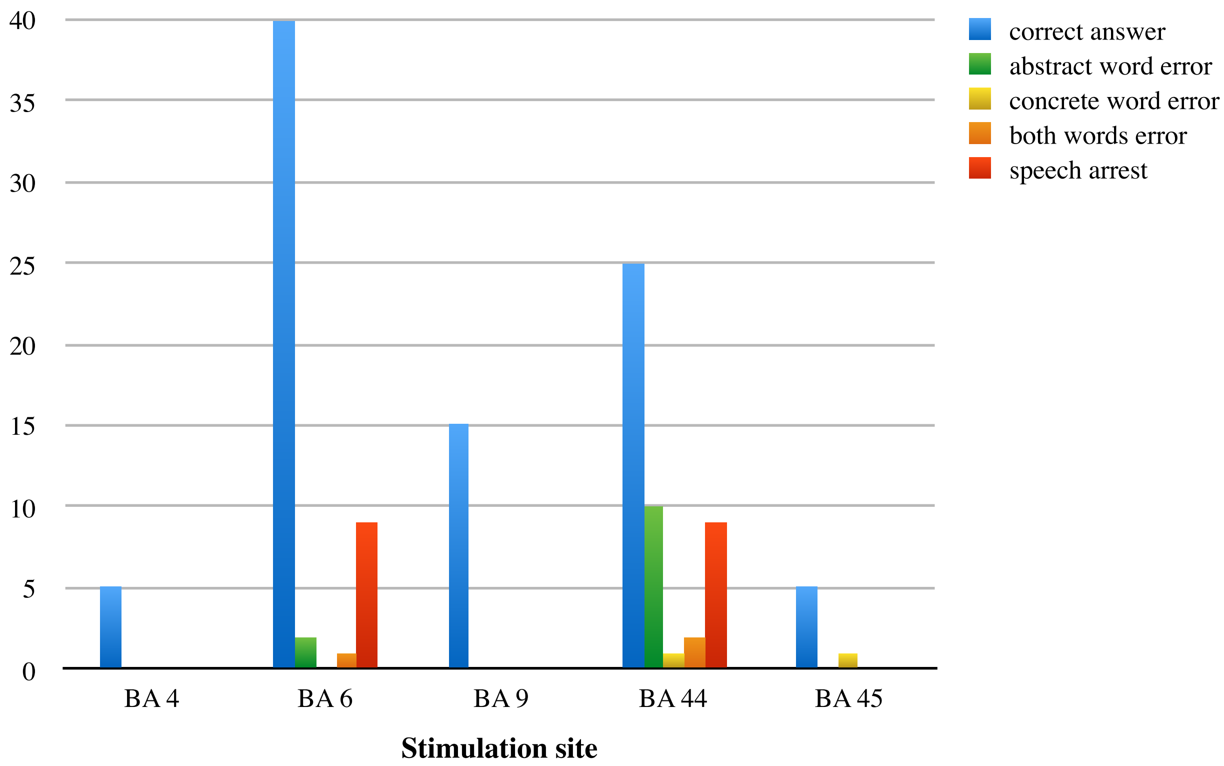

Figure 5.2. Number of errors and correct answers per stimulation site.

MDG	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lexical decision	Abstract words accuracy	100	100	100	-	-	100	100	100	-	-	100	-	100	100	100	100	100
	Concrete words accuracy	100	100	100	-	-	100	100	100	-	-	100	-	100	100	100	100	100
	Speech arrest	no	no	no	yes	yes	no	no	no	yes	yes	no	yes	no	no	no	no	no

Table 5.3. MDG's intraoperative performance per stimulation site.

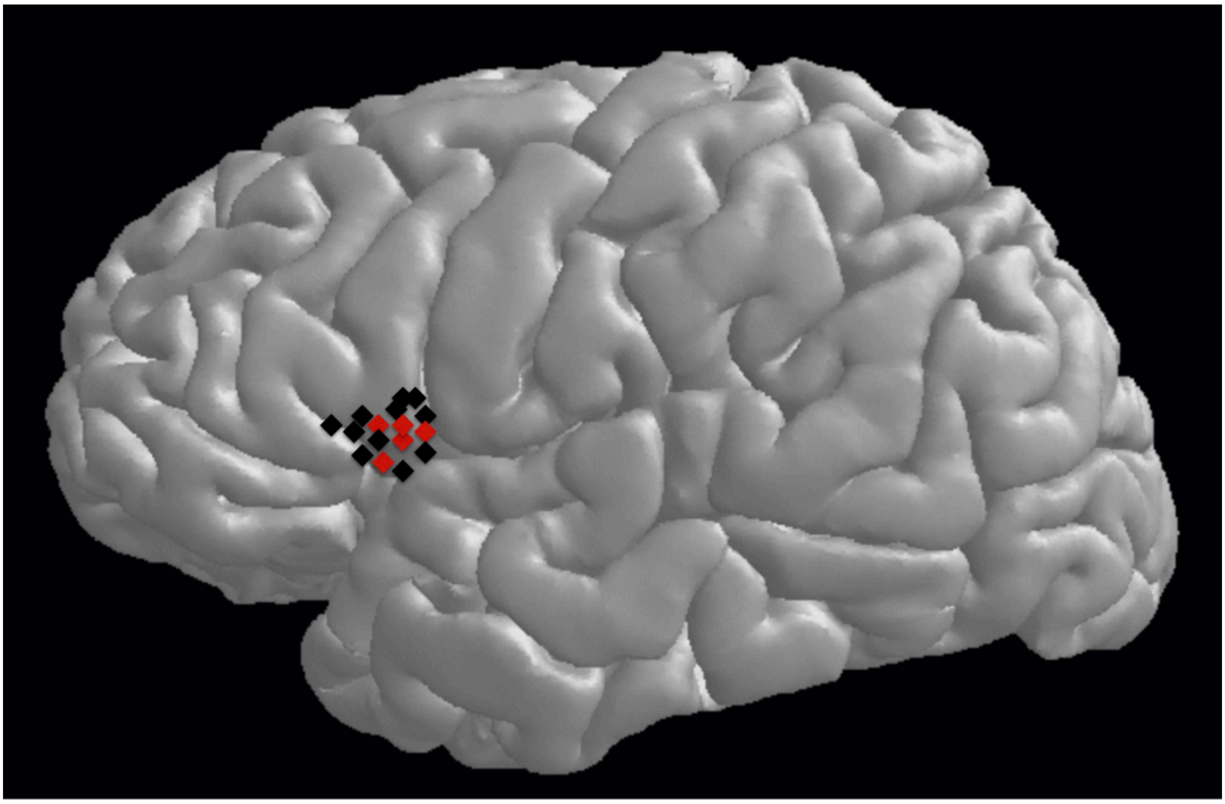

Figure 5.3. MDG's stimulation sites. *Black = "negative" stimulation; Red = speech arrest.*

SDA	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lexical decision	Abstract words accuracy	100	90	100	100	100	-	-	-	100	100	100	100	100	100	100	100	-
	Concrete words accuracy	100	100	100	100	100	-	-	-	100	100	100	100	100	100	100	100	-
	Speech arrest	no	no	no	no	no	yes	yes	yes	no	no	no	no	no	no	no	no	yes

SDA	Site	18	19	20	21	22	23	24	25	26	27	28	29
Lexical decision	Abstract words accuracy	100	100	100	-	-	100	100	-	-	-	100	100
	Concrete words accuracy	100	100	100	-	-	100	100	-	-	-	100	100
	Speech arrest	no	no	no	yes	yes	no	no	yes	yes	yes	no	no

Table 5.4. SDA's intraoperative performance per stimulation site.

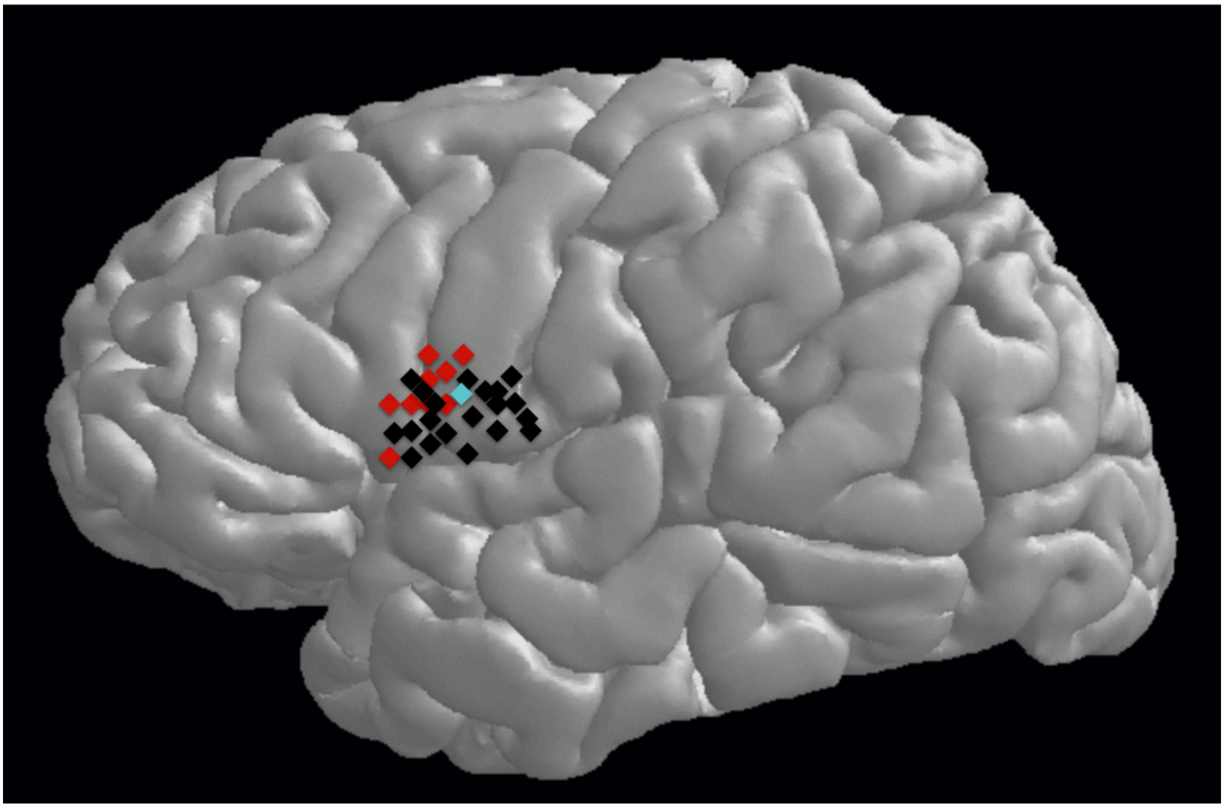

Figure 5.4. SDA's stimulation sites. *Black = "negative" stimulation; Red = speech arrest; Light blue= abstract word errors.*

AC	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lexical decision	Abstract words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	-	-
	Concrete words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	-	-
Semantic judgement	Abstract words accuracy	100	100	100	100	100	100	90	100	100	100	100	90	100	100	100	-	-
	Concrete words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	-	-
	Speech arrest	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	yes	yes

AC	Site	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Lexical decision	Abstract words accuracy	-	90	100	-	100	100	100	100	100	100	100	100	-	-	100	100	100
	Concrete words accuracy	-	90	100	-	100	100	100	100	100	100	100	100	-	-	100	100	100
Semantic judgement	Abstract words accuracy	-	80	100	-	100	100	100	100	100	100	100	100	-	-	100	100	100
	Concrete words accuracy	-	90	100	-	100	100	100	100	90	100	100	100	-	-	100	100	100
	Speech arrest	yes	no	no	yes	no	no	no	no	no	no	no	no	yes	yes	no	no	no

Table 5.5. AC's intraoperative performance per stimulation site.

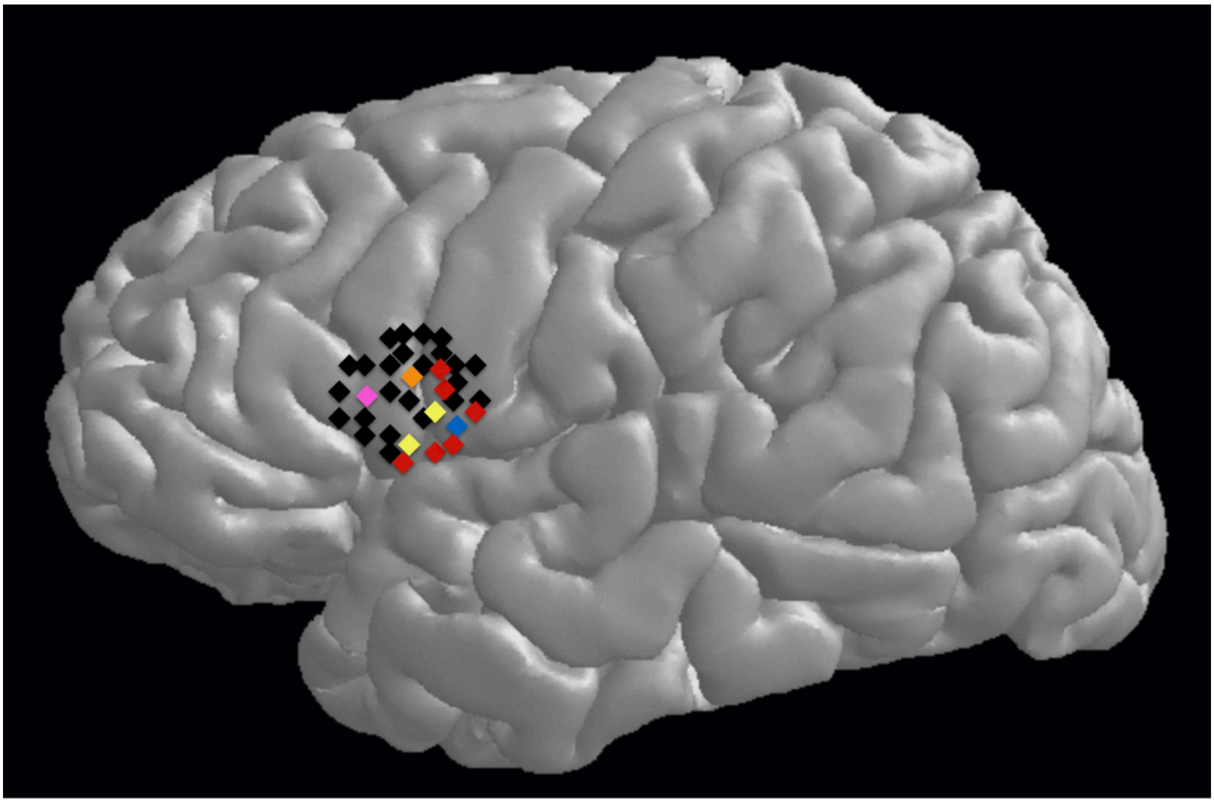

Figure 5.5. AC's stimulation sites. *Black = "negative" stimulation; Red = speech arrest; Lexical decision: Orange: both concrete and abstract word errors;Semantic judgment: Yellow=abstract word errors; Pink=concrete word errors; Blue: both concrete and abstract word errors.*

MT	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lexical decision	Abstract words accuracy	100	100	100	100	100	100	100	100	100	100	100	-	-	-	-	100	100
	Concrete words accuracy	100	100	100	100	100	100	100	100	100	100	100	-	-	-	-	100	100
Semantic judgement	Abstract words accuracy	100	100	100	100	100	100	100	100	100	100	70	-	-	-	-	100	100
	Concrete words accuracy	100	100	100	100	100	100	100	100	100	100	100	-	-	-	-	90	100
	Speech arrest	no	no	no	no	no	no	no	no	no	no	no	yes	yes	yes	yes	no	no

MT	Site	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Lexical decision	Abstract words accuracy	100	100	100	100	100	100	100	-	-	100	100	100	100	100	90	100	100
	Concrete words accuracy	100	100	100	100	100	100	100	-	-	100	100	100	100	100	100	100	100
Semantic judgement	Abstract words accuracy	100	100	100	100	100	100	100	-	-	100	100	80	90	100	100	100	100
	Concrete words accuracy	100	100	100	100	100	100	100	-	-	100	100	100	90	100	100	100	100
	Speech arrest	no	no	no	no	no	no	no	yes	yes	no	no	no	no	no	no	no	no

MT	Site	35	36
Lexical decision	Abstract words accuracy	100	100
	Concrete words accuracy	100	100
Semantic judgement	Abstract words accuracy	90	100
	Concrete words accuracy	100	100
	Speech arrest	no	no

Table 5.6. MT’s intraoperative performance per stimulation site.

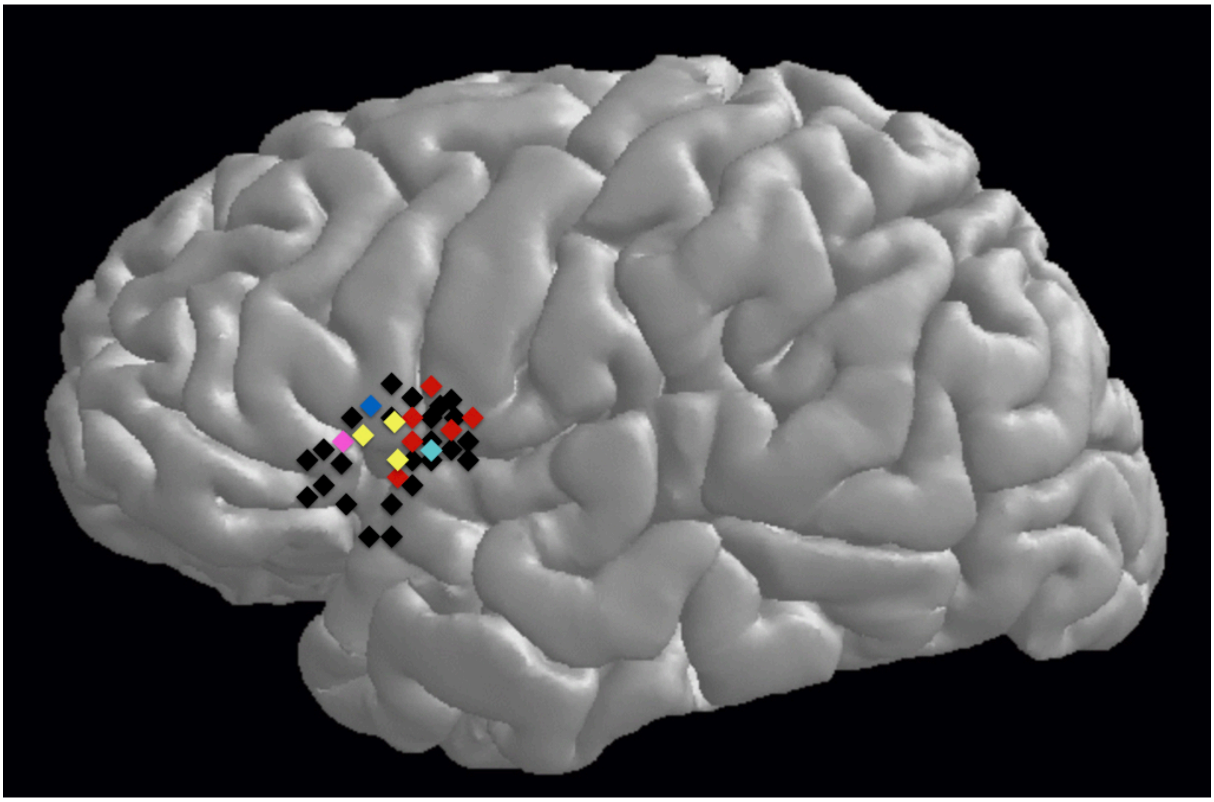

Figure 5.6. MT's stimulation sites. *Black = "negative" stimulation; Red = speech arrest; Lexical decision: Light blue = abstract word errors; Semantic judgment: Yellow: abstract word errors; Pink: concrete word errors; Blue: both concrete and abstract word errors.*

GI	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lexical decision	Abstract words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	Concrete words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Semantic judgement	Abstract words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	Concrete words accuracy	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	Speech arrest	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no

GI	Site	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
Lexical decision	Abstract words accuracy	100	100	100	-	-	-	100	100	100	100	100	100	100	100	100	100
	Concrete words accuracy	90	100	100	-	-	-	100	100	100	100	100	100	100	100	100	100
Semantic judgement	Abstract words accuracy	90	100	100	-	-	-	100	100	80	100	100	90	100	100	90	100
	Concrete words accuracy	100	100	100	-	-	-	100	100	100	100	100	100	100	100	100	100
	Speech arrest	no	no	no	yes	yes	yes	no	no	no	no	no	no	no	no	no	no

Table 5.7. GI's intraoperative performance per stimulation site.

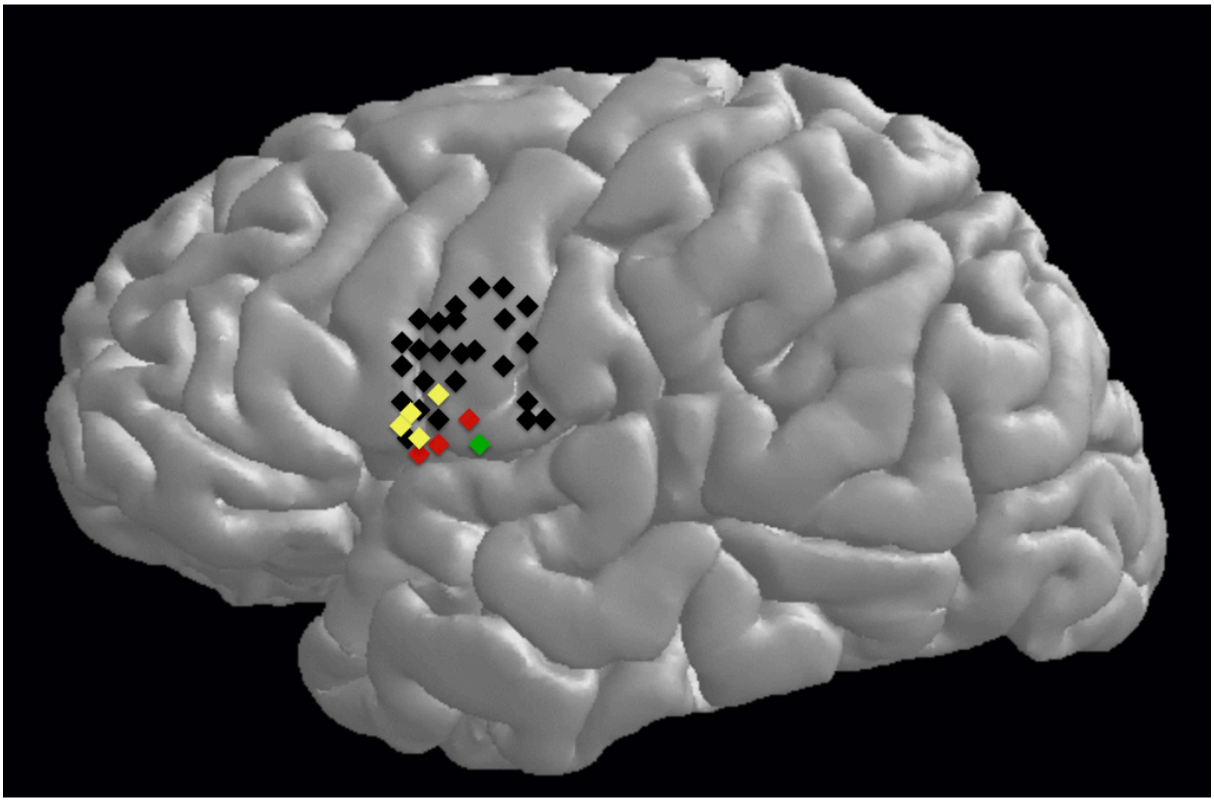

Figure 5.7. GI's stimulation sites. *Black = "negative" stimulation; Red = speech arrest; Lexical decision: Green= concrete word errors; Semantic judgment: Yellow: abstract word errors.*

CDR	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lexical decision	Abstract words accuracy	100	100	100	100	-	-	100	100	100	100	100	100	100	100	100	100	100
	Concrete words accuracy	100	100	100	100	-	-	100	100	100	100	100	100	100	100	90	100	100
Semantic judgement	Abstract words accuracy	100	80	100	100	-	-	100	70	100	100	100	100	100	100	100	100	100
	Concrete words accuracy	100	100	100	90	-	-	100	100	100	100	100	100	100	100	100	100	100
	Speech arrest	no	no	no	no	yes	yes	no	no	no	no	no	no	no	no	no	no	no

CDR	Site	18	19	20	21	22	23	24	25	26	27	28	29
Lexical decision	Abstract words accuracy	100	100	100	-	100	100	100	100	100	100	100	100
	Concrete words accuracy	100	100	100	-	100	100	100	100	100	100	100	100
Semantic judgement	Abstract words accuracy	100	100	80	-	100	100	100	90	100	100	100	100
	Concrete words accuracy	100	100	90	-	100	100	100	100	100	100	100	100
	Speech arrest	no	no	no	yes	no	no	no	no	no	no	no	no

Table 5.8. CDR's intraoperative performance per stimulation site.

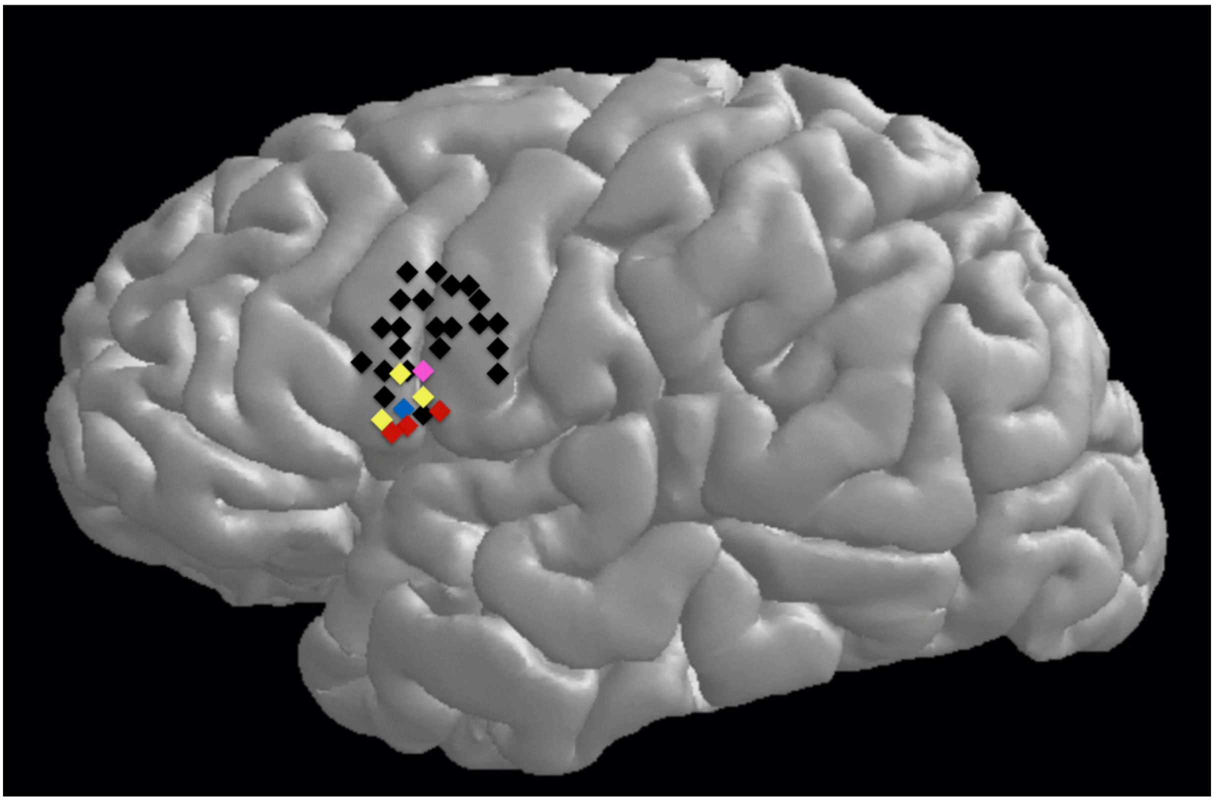

Figure 5.8. CDR's stimulation sites. *Black = "negative" stimulation; Red = speech arrest; Semantic judgment: Yellow=abstract word errors; Pink=concrete word errors; Blue: both concrete and abstract word errors.*

5.4 DISCUSSION

Based on the literature and on experiments 1 and 2, the present study aimed at investigating the specific role of the inferior frontal cortex in abstract and concrete word processing through a DCS paradigm. Patients' intraoperative performance on lexical decision revealed a small effect of DCS on both word and nonword processing. All patients showed this effect in at least one site of stimulation, and the difference between abstract and concrete errors did not seem relevant, by visual inspection only. This result would support the presence of a network within the inferior frontal cortex subserving phonological processing and verbal working memory (Paulesu et al., 1993; Binder et al., 2005). However, the number of errors in lexical decision was too small to allow some further consideration. The semantic judgment task showed an effect of DCS on both abstract and concrete words, as expected. The number of errors on abstract word categorisation was higher than that on concrete word categorisation (12 and 5, respectively), but, due to the limited sample size, this result was not formally analysed. Interestingly, a significant association was found between stimulation site and error type, since the majority of abstract errors were recorded during stimulation of BA 44, and also during BA 6 stimulation. Since all patients performed without errors at the intraoperative baseline, it is unlikely that these results were caused by abstract words being too difficult.

The involvement of left BA 44 in abstract word processing is in line with previous studies. A number of neuroimaging studies used a lexical decision task to investigate the different substrates of concrete and abstract word processing with different techniques (PET, fMRI) (Perani et al., 1999; Fiebach & Friederici, 2004; Wang et al., 2010). They all found a significant activation of the inferior frontal cortex in the comparison of abstract > concrete word brain activation. The role of the inferior frontal cortex in abstract word processing was confirmed also by a rTMS study by Papagno and colleagues (2009), who found a significant reduction in accuracy in a lexical decision task for abstract words during frontal stimulation. However, as previously discussed, lexical decision requires the subject to assess word meaning implicitly only. In a study by Jessen and colleagues (2000), the neural basis of superior intentional encoding of concrete over abstract words was studied through an event-related fMRI paradigm. During MR data acquisition, participants were presented with three blocks of 80 items each, with a stimulus onset interval of 9 s. The subjects had to encode as many words as possible for later recognition and were not instructed to judge the words regarding their concreteness. In the comparison of abstract over concrete words, the authors found stronger activation in the left inferior frontal gyrus (namely Broca's area) and in the right lateral occipital gyrus. However, the authors only speculated that the difference in activation within the Broca's areas between abstract and concrete words might reflect a greater production (pronunciation) effort of abstract words compared to concrete words. A different explanation, consistent with the preliminary results from the present study, could be that the premotor cortex (BA 6), rather than Broca's area, is responsible for the temporary storage of abstract word articulatory motor program (what Jessen et al. defined "pronunciation effort"). Broca's area (BA 44), as suggested by neuroimaging literature, could be instead a specific location for abstract words processing and storage. This result is also consistent with neuropsychological studies on the concreteness effect and its reversal, since generally aphasic patients with frontal lesions are found to have an advantage for concrete over abstract words (e.g. Peters. et al., 2009; Roll et al., 2012), while patients who show a reversal of the concreteness effect usually suffer from temporal pole atrophy (e.g. Macoir, 2008; Papagno et al., 2009).

To my knowledge, this is the first study investigating the neural substrates of concrete and abstract word processing with DCS. A major limit of the present study is the limited sample size and conclusions should be therefore cautious. Also, subjects undergoing these procedures usually have a neurological disorder, a brain tumor in this case, and in the case of a slowly growing lesion, one cannot exclude reorganization processes due to brain plasticity. On the other hand, as previously mentioned, DCS during awake surgery has the advantage of a good experimental control, since temporary lesions can be very focal and reversible (Dreier et al., 2009).

To conclude, the recruitment of frontal brain regions, namely Broca's area, in abstract word processing, as suggested by experiments 1 and 2, was confirmed in this study. Also, results would indicate a minor involvement of BA 6, possibly because of its link to motor aspects of speech planning involved in phonological rehearsal (Paulesu et al., 1993; Salmon et al., 1996). Also, since an effect of DCS over the inferior frontal cortex (and specifically over BA 44) on abstract word processing was found only during the semantic judgement task, it is arguable that this region contributes specifically to the semantic processing of abstract words. Further investigations are needed to confirm these conclusions and to clarify the generalizability of these results.

GENERAL CONCLUSION

A well known phenomenon in language is the concreteness effect. Two main models have been classically put forward to account for the common advantage of concrete over abstract words: the dual coding theory (DCT; Paivio, 1991) and the context availability theory (Schwanenfugel & Shoben, 1983; Schwanenflugel, 1991). These theories have been disproved by the clinical observation that some patients with specific lesion of the temporal poles (e.g. patients with semantic dementia) show an advantage for abstract over concrete word processing, i.e. a reversal of the concreteness effect (Warrington, 1975; Warrington, 1981; Warrington & Shallice, 1984; Sirigu et al., 1991; Breedin et al., 1994; Marshall et al., 1996; Bachoud-Lévi & Dupoux, 2003; Macoir, 2008; Papagno et al., 2009).

As far as concerns the neural basis of word processing, neuropsychological, neuroimaging and electrophysiological studies are not clear-cut. They generally demonstrate that abstract and concrete word processing relies not only on the activity of common neural pathways (e.g. middle and inferior left temporal gyri; Binder et al., 2005), but also on the activity of dedicated networks (e.g. inferior frontal gyrus and middle temporal gyrus for abstract words, and posterior cingulate, precuneus, fusiform gyrus and parahippocampal gyrus for concrete items; Wang et al., 2010). Also, a diffuse bilateral network is thought to subserve both abstract and concrete items processing.

In the present thesis the possible neural substrates of concrete and abstract word processing were investigated through an implicit word stem completion paradigm in the setting of general anaesthesia (GA) (Experiment 1 and 2). Testing patients undergoing GA, with a continuous and careful monitoring of the depth of sedation and postoperative assessment of explicit recall, has the important advantage to exclude the contribution of (involuntary) explicit memory to the implicit test performance, which is the major concern in classical studies. Also, since the neural activations of conscious and unconscious semantic activation are thought to involve the same brain regions (even if with qualitatively different time courses) (Kiefer & Spitzer, 2000), results from these experiments allow drawing some general conclusions on concrete vs. abstract word processing.

To sum up, in Experiment 1 patients undergoing propofol intravenous GA were tested for intraoperative unconscious priming for abstract and concrete words. Results indicated selective priming for concrete words, thus supporting the hypothesis that concrete words are linked to sensory information, which is processed in posterior brain regions, whose activity is not suppressed by propofol.

In Experiment 2, the same implicit paradigm was applied in patients undergoing sevoflurane inhalational GA. The priming effect found for abstract words was greater than that for concrete words, which was not statistically significant.

Differences between the results of Experiment 1 and 2 were expected by virtue of the specific anaesthetic drug used. Propofol, in fact, modulates neuronal activity mainly in prefrontal and frontoparietal areas, , and in the inferior temporal gyri (Franks, 2008), while sevoflurane is known to suppress activity in more posterior brain areas with respect to those suppressed by propofol, namely in the cuneus, the precuneus, parietal cortex and cerebellum (Franks et al., 2008).

In sum, findings from these first two studies support the following conclusions.

First, they seem to support that concrete and abstract word processing relies on common mechanisms, possibly located in the temporal lobe (presence of priming for both type of words in Experiment 2). They also seem to point that these two categories are processed by distinct, dedicated networks. Concrete, sensory-based word processing could consistently recruit posterior cortical areas, which are not suppressed by propofol (finding of a selective priming for concrete words in Experiment 1). This perceptual advantage of concrete over abstract words, however, could not be essential for concrete word processing, since a priming effect for concrete words was also found after GA with sevoflurane, which typically inhibits posterior brain areas activity. Therefore, the activity of specific networks within frontal regions could reflect pure "linguistic" differences between concrete and abstract words.

Secondly, the results strongly support the existence of memory priming without the contribution of (unintended) conscious processing, since a priming effect was found even if the level of anaesthesia was maintained adequate through the entire surgical procedure, for all patients. In addition, unconscious memory priming could involve not only lexical, but also semantic automatic processing, thus explaining a selective priming for concrete words found in Experiment 1. Based on neurophysiological studies, in fact, semantic access is thought to occur at very early stages of verbal processing (Kiefer & Spitzer, 2000; Adorni & Mado Proverbio, 2012).

Finally, these results support the hypothesis that information processing is possible to some extent also in the absence of consciousness. Consistently with the present findings, some recent study investigated verbal processing in patients with disorders of consciousness by means of fMRI, and found that automatic lexical processing can be observed in minimally conscious state and vegetative state patients (Catricalà et al., 2016).

In the third experiment, the hypothesis of the involvement of frontal brain regions in abstract word processing was further tested. Specifically, the role of the inferior frontal cortex in abstract vs. concrete word processing was investigated in patients undergoing DES during awake surgery.

Results showed that, in this specific setting, no differences could be observed between abstract and concrete words with a lexical decision task. Instead, a significant and strong association was found between the stimulation site and the error type in a semantic (abstract vs. concrete) judgment task. This would suggest a specific role of BA 44 and BA 6 in processing of abstract words.

Overall, results from this thesis support the conclusions drawn from previous neuroimaging studies, confirming that abstract and concrete words are processed by common networks and also by specific brain regions.

Recently, Vigliocco and colleagues' (2009, 2014; Kousta et al., 2011) reported neuroimaging and behavioural results indicating that emotional content plays a crucial role in the processing and representation of abstract concepts. On this basis, the authors propose an embodiment view of semantic representation which offers the possibility to account both for abstract and concrete words, with these main assumptions: (1) experiential (sensory, motor, affective) and linguistic (verbal associations arising through patterns of co-occurrence and syntactic information) information contribute to the representation of all concepts (abstract and concrete); (2) differences between concrete and abstract word meaning, as well as differences within each of these two domains, arise as a result of types and relative proportions of experimental and linguistic information they bind; (3) the apparent dichotomy between concrete and abstract word meaning arises because of a statistical preponderance of sensorimotor information to the definition of concrete word meanings, and a statistical preponderance of affective and linguistic information to underlie abstract word meaning. Considering the specific contribution of linguistic information in abstract word processing, the authors agree with previous neuroimaging and electrophysiological studies (e.g. Perani et al., 1999; Fiebach & Friederici, 2004; Nopponey & Price, 2004; Binder et al., 2005) that the engagement of the left inferior frontal cortex by abstract words could reflect a greater reliance on linguistic information for abstract words. The results of this thesis are consistent with this suggestion. Furthermore, the embodied framework provides a working hypothesis according to which concrete and abstract words differ along a number of dimensions (including differential engagement of sensory, motor, affective and linguistic information) that may not always point to an advantage for concrete words. This is further supported by the results of Experiment 2, in which a priming effect for abstract words was found. Since general anesthetics do not suppress activity in the limbic system, it cannot be excluded that the presence of a priming effect for abstract words was facilitated by their emotional valence, consistent with Vigliocco et al.'s proposal.

Results from the present experiments support findings from previous studies on the neural substrates of concrete and abstract word processing, and suggest possible further investigations. Indeed, future research should increase the number of patients studied under the effect of different anesthetics and of those submitted to DCS. In particular, in this last case, the assessment of performance in patients with temporal lesions would clarify whether stimulation of this area impairs concrete word processing while abstract word processing is preserved.

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APPENDIX

APPENDIX 1

		Words	English	Frequency of use	Length	Imageability
Abstract	**Target**	STILE	Style	347	5	4,1
		DISTANZA	Distance	308	8	3,9
		RAPINA	Robbery	143	6	3,8
		EFFICACIA	Effectiveness	70	9	3,8
		ACCORDO	Agreement	514	7	3,6
		PAURA	Fear	698	5	3,4
		TRISTEZZA	Sadness	55	9	3,4
		CRIMINE	Crime	75	7	3,3
		IRRITAZIONE	Irritation	25	11	3,3
		ENTUSIASMO	Enthusiasm	175	10	3,2
		FURIA	Fury	58	5	3,1
		SORPRESA	Surprise	369	8	3,1
		SOLLIEVO	Relief	88	8	3,1
		ANSIA	Anxiety	137	5	3
		DEPRESSIONE	Depression	75	11	3
		MINACCIA	Threat	174	8	3
		CRITICA	Criticism	245	7	3
		DIFFERENZA	Difference	287	10	3
		VENDETTA	Revenge	112	8	3
		ANGOSCIA	Anguish	124	8	3
	Non target	FIDUCIA	Trust	346	7	2,9
		VERGOGNA	Shame	101	8	2,9
		NOIA	Boredom	63	4	2,9
		SEPARAZIONE	Separation	115	11	2,9
		CARRIERA	Carrer	355	8	2,8
		SIMPATIA	Sympathy	132	8	2,8
		AMORE	Love	1153	5	2,8
		GUASTO	Failure	43	6	2,7
		INSUFFICIENZA	Insufficiency	15	13	2,7
		SICUREZZA	Safety	474	9	2,6
		COLPA	Guilt	312	5	2,4
		FORZA	Strength	1027	5	2,3
		LEGGE	Law	1228	5	2,3
		SCOPO	Purpose	203	5	2,3
		FUTURO	Future	538	6	2,2
		ILLUSIONE	Illusion	118	9	2,1
		FUNZIONE	Function	298	8	1,8
		GIUDIZIO	Judgment	371	8	1,8
		FALLIMENTO	Failure	110	10	1,8
		PRINCIPIO	Principle	312	9	1,7

Concrete	**Target**	AUTOMOBILE	Car	806	10	4,7
		CAMPEGGIO	Camping	13	9	5
		CELLULA	Cell	98	7	5
		CHIESA	Church	515	6	4,8
		CUOCO	Cook	41	5	5
		DOLORE	Pain	349	6	4,8
		FONTANA	Fountain	40	7	4,8
		GALLO	Rooster	21	5	4,5
		INSEGNANTE	Teacher	150	10	4,9
		LAVORATORE	Worker	223	10	5
		MARTELLO	Hammer	26	8	4,4
		OCEANO	Ocean	62	6	4,5
		PALMA	Palm	34	5	3,9
		PELLE	Skin	425	5	5
		PESCATORE	Fisherman	82	9	4,8
		POMODORO	Tomato	88	8	4,9
		STELLA	Star	261	6	4,3
		SVEGLIA	Alarm Clock	16	7	5
		TEMPESTA	Storm	77	8	4,5
		TURISTA	Tourist	115	7	4,9
	Non target	BOTTIGLIA	Bottle	122	9	4,8
		CARCIOFO	Artichoke	22	8	4
		CENERE	Ash	27	6	4,8
		CRISTALLO	Crystal	49	9	5
		DIAMANTE	Diamond	30	8	4,4
		FAMIGLIA	Family	1430	8	4,9
		FUNGO	Mushroom	38	5	5
		GUANTI	Gloves	41	6	4,6
		LAMPADA	Lamp	76	7	5
		LIMONE	Lemon	103	6	4,8
		MUSICA	Music	568	6	4,8
		OROLOGIO	Clock	143	8	5
		PAPPAGALLO	Parrot	12	10	4,4
		PERLA	Pearl	30	5	5
		PISTOLA	Gun	250	7	5
		PRIGIONIERO	Prisoner	63	11	4,9
		SOLE	Sun	485	4	5
		SCOPA	Broom	12	5	5
		TORRE	Tower	64	5	5
		VEDOVA	Widow	61	6	4,5

APPENDIX 2

		Concrete experimental group		Abstract experimental group		Concrete control group		Abstract control group	
		target hits	*non target hits*	*target hits*	*non target hits*	*target hits*	*non target hits*	*target hits*	*non target hits*
Concrete experimental group	*target hits* 0,5 (0,2-0,55)	-	*p*=.233	*p*=.181	-	***p*=.019**	-	***p*=.000**	-
	non target hits 0,4 (0,15-0,5)	*p*=.233	-	-	***p*=.01**	-	***p*=.009**	-	***p*=.001**
Abstract experimental group	*target hits* 0,3 (0,2-0,5)	*p*=.181	-	-	***p*=.027**	*p*=.256	-	***p*=.001**	-
	non target hits 0,175 (0,1-0,35)	-	***p*=.01**	***p*=.027**	-	-	*p*=.873	-	*p*=1.000
Concrete control group	*target hits* 0,25 (0,1-0,65)	***p*=.019**	-	*p*=.256	-	-	*p*=.120	***p*=.000**	-
	non target hits 0,25 (0,1-0,35)	-	***p*=.009**	-	*p*=.873	*p*=.120	-	-	*p*=.722
Abstract control group	*target hits* 0,15 (0,05-0,25)	***p*=.000**	-	***p*=.001**	-	***p*=.000**	-	-	***p*=.017**
	non target hits 0,2 (0,05-0,4)	-	***p*=.001**	-	*p*=1.000	-	*p*=.722	***p*=.017**	-

Within group analysis: (grey) Wilcoxon signed-rank test;

Between group analysis: (yellow) Kruskall-Wallis one-way analysis of variance and Mann-Whitney U post-hoc; (light blue) one way ANOVA and Tukey's post hoc.

Appendix 2. Double entry table reporting the *p* value of all within and between comparisons for the proportion of target and non target hits. Significant values are in bold. Descriptive statistics are reported as median (min-max). Please note that the distribution of the target hits proportion was not normal.

APPENDIX 3

Abstract words:	**Concrete words:**	**Nonwords:**
accordo	automobile	alzia
ansia	campeggio	cerrieta
carriera	cellula	cramite
crimine	musica	fenziole
efficacia	pistola	biupizio
distanza	cuoco	mecaccia
entusiasmo	fontana	rurina
fiducia	gallo	limpatio
funzione	insegnante	neie
furia	lavoratore	emare
giudizio	martello	sicurevra
illusione	oceano	lergo
irritazione	palma	scepe
minaccia	pelle	filuro
rapina	pescatore	superagione
sicurezza	pomodoro	gimpeggio
simpatia	stella	cestula
sorpresa	tempesta	mupaca
noia	turista	fostaba
vergogna	bottiglia	gacio
amore	carciofo	lamoretore
guasto	cenere	pilmi
insufficienza	cristallo	lielli
sicurezza	diamante	tempanta
colpa	famiglia	boffaglia
forza	fungo	crestullo
legge	guanti	fodiglia
scopo	lampada	cingo
futuro	limone	gainti
separazione	pappagallo	lomona