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Neural representation of conceptual knowledge in schizophrenic patients
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1. Introduction

1.1 Organization of conceptual knowledge

Information acquisition, processing and storage are fundamental for social interactions and communication among humans, and therefore constitute an important factor for human survival. Information about entities is subdivided into smaller units in order to provide a rapid and easy access and recall. On a first level information is organized into different domains, the most important being a distinction essential for survival, living or nonliving. The domains themselves are subdivided into categories, for example animals, and subsequently into sub-categories, like elephants. It is still unknown, however, how domains and categories are exactly realized and organized on a neuro-anatomical level in the human brain leaving this question discussed controversially [for reviews, see Tyler & Moss 2001; Grossman 2002; Caramazza & Mahon 2003; Martin 2007]. Brain-lesion studies led to the development of different views about the organization of conceptual knowledge.

1.1.1 Brain lesion studies

Case studies of patients showing deficits in semantic categorization can provide some indication of how categorical information might be implemented in the brain. Neuropsychological tests with these brain-lesioned patients gave first evidence of how perception of socially meaningful stimuli might be altered and effected by pathological brain states. In patients with disproportionally impaired recognition of living objects, lesions of different origin (HSE, trauma, dementia, infarction, etc) were found in the anterior and inferior parts of the bilateral temporal lobes. Patients with a category-specific deficit for nonliving artifacts but preserved knowledge of living objects were found to present lesions in the dorso-lateral convexity of the left hemisphere [Gainotti 2000]. Correlations between the affected areas and the resulting impairment suggested a category-specific organisation of semantic processing located in specific brain areas.

Other authors [Damasio *et al.* 1996; Tranel *et al.* 1997; Damasio *et al.* 2004] support the view that retrieval of conceptual knowledge is mediated by partially segregated neural systems, situated in higher-order cortices (other than classical language areas) like the left temporal pole and the left inferotemporal area. In lesion studies [Damasio *et al.* 1996] they showed that impaired person recognition was associated with lesions in the right temporal polar region, impaired recognition of animals was associated with lesions in the bilateral mesial occipital cortex and the right ventral temporal region, and that impaired recognition of tools correlated with lesions in the left occipital - temporal - parietal junction. Thus, they proposed impaired word retrieval of different categories being correlated with the affection of separate areas in higher-order cortices [Damasio *et al.* 2004].

Thus, category-specific semantic deficits have provided some insight into how conceptual knowledge could be represented in the human brain. Subsequent studies that addressed this question can be assigned to three different theories.

1.1.2 Sensory-functional theory

The first and oldest theory was proposed by Warrington and others [Warrington & Shallice, 1984; Warrington & McCarthy 1987], stating that conceptual knowledge is organized according to the type of semantic property (sensory-visual and functional) and hence according to the corresponding modality. It is thought to be stored and processed in the same areas active during perception and action. In their view, the organization of living and nonliving domains depends on discriminative identification features relative to their differential importance for survival, with sensory-visual information being more important for the recognition of living things. Thus, the identification of living objects is thought to be based on their sensory properties, therefore mostly being represented in brain areas dealing with sensory information. Likewise, categorisation of nonliving objects is assumed to depend on functional features, so they would be represented in brain areas involved in processing functional information. Consequently, the authors propose damage to an area processing sensory properties to result in impaired recognition and processing of living

objects, and vice versa. Thus, a specific deficit in identification of living things should be correlated with difficulties concerning the entire sensory modality.

Warrington *et al.* based their theory of modality-specific semantic organisation on studies with patients suffering from Herpes simplex encephalitis (HSE) with lesions in the bilateral temporal lobe. These patients were unable to identify living objects or performed at least much worse in identifying living things compared to their ability in identifying nonliving objects. Martin and others [Chao *et al.* 1999; Martin & Chao 2001; Martin 2007] agree to emphasize the importance of intrinsic properties of an object. Livings things are characterized by their sensory-visual information, while artifacts are mostly characterized by their function. They suggest the storage of conceptual knowledge not to be randomly distributed but to mirror the organization of the sensory and motor system. Thus, stored information on sensory- and motor-based properties defining an object is represented not in an individual brain area but in a distributed network, including posterior regions of the ventral (object property: form) and lateral temporal cortex (object property: motion). However, Martin [Martin 2007] recently admitted that some property-based regions also show a categorical organization. He now suggests a domain-specific neuro-anatomical organization in modality-specific stores supporting the theory that categorical distinction precedes acquisition of specific perceptual facts.

Other authors also support the sensory-functional view but argue against a strict and simple modality-specific representation [Thompson-Schill *et al.* 1999]; instead they suggest an interactive modality-specificity hypothesis. For example living things are predominantly represented by visual features; however, representations of an object are distributed, with each part of the object's representation contributing to other parts. This could account for category-specific and cross-modal impairments which have been seen in brain-lesioned patients.

Another theory supporting the sensory-functional view is brought forward by Lawrence W. Barsalou [Barsalou 1999; Barsalou *et al.* 2003; Barsalou 2007] saying that knowledge is grounded in modality-specific systems, which are organized by the aspects of sensory and motor features of objects, and thereby able to implement whole conceptual systems. As an experience occurs, we

acquire perceptual, motor and introspective states across modalities. Schematic presentations of perceptual components are extracted from this experience and stored in memory by the use of selective attention. When needed, a multimodal representation is reactivated by simulation of perception, action and introspection. Thus, conceptual processing is grounded on re-enactment of states. Barsalou´s theory is based on empirical evidence brought forward by behavioural experiments and brain imaging experiments demonstrating that conceptual processing activates modality-specific brain areas [e.g. Barsalou *et al.* 1999; Martin & Chao 2001].

1.1.3 Domain-specific theory

A category-specific representation in the brain where neuro-anatomically distinct circuits are thought to represent and process the different categories is suggested by a theory brought forward by Caramazza and others [Caramazza & Shelton 1998; Caramazza & Mahon 2003]. So rather than being structured by sensory – functional modalities, they propose semantic knowledge to be organized in domains in order to make rapid categorical distinctions, preceding acquisition of specific perceptual facts or being independent of them. A possible explanation is thought to be the evolutionary pressure on animals to identify certain domains, e.g. reliable and fast identification of objects belonging to the living domain. This might have produced specialized neural networks for particular categories in order to obtain survival and reproductive advantages. Differentially impaired domains, together with equivalent impairment of both sensory and functional knowledge (e.g. visual and non-visual information is impaired for entities of the “living” domain living but preserved for entities of the “nonliving” domain) in patients with category-specific semantic deficits seem to support this hypothesis [Farah & Rabinowitz 2003].

In line with this hypothesis, infant studies [Pauen 2000; Pauen 2002] show that only a few months-old infants not yet able to understand or produce complex language are already capable of “living” – “nonliving” domain discrimination and differentiation within the “living” domain. This points towards a biological determination of at least some evolutionary important categorical distinctions. At least at the age of 9 months infants have already developed a

conceptual system, beginning to categorize objects at a basic level from the age of 3 months on [Mandler 2004].

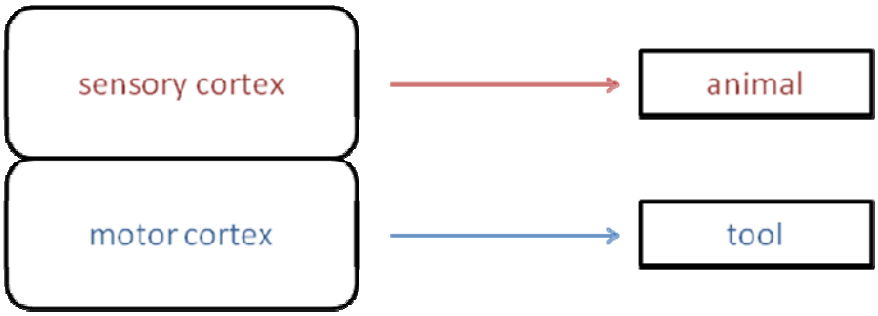
Another advocate of the category-specific theory of semantic knowledge organization is Spitzer, however later mixing the two approaches by favouring the view that categories are implemented in the brain as an interplay between different feature-based semantic maps represented by neuroanatomically distinct subdivisions of the conceptual space [Spitzer *et al.* 1998; Kiefer & Spitzer 2001]. Thus, according to the authors, there is nothing like a "tool center" in the brain, but the concept "tool" is represented by multiple cortical areas in a map-like fashion.

1.1.4 Conceptual structure theory

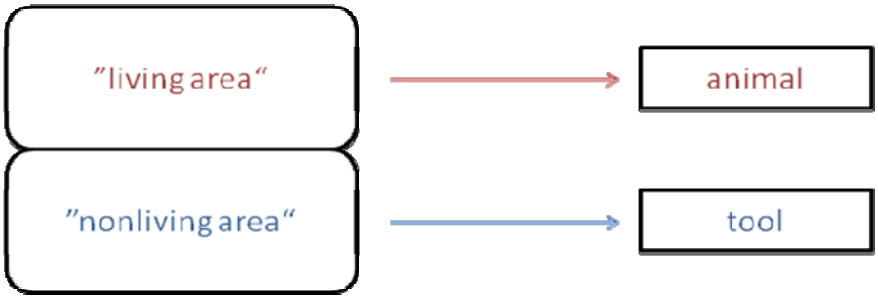
The third theory brought forward by Tyler, Moss and others [Tyler *et al.* 2000; Tyler & Moss 2001; Moss & Tyler 2001; Moss & Tyler 2003] suggests a unitary distributed neuronal system which is independent of specialized neuro-anatomical stores representing domain or modality type of knowledge. Domain and category are thought to emerge as a result of correlated properties of structure and content of semantic representations which characterize members of one category. The conceptual structure account suggests that 1) objects belonging to the same category share common features, that 2) semantic concepts which share common features are represented close to each other and that 3) activations caused by the various properties defining an object are highly intercorrelated, therefore resistant to damage. Thus, without sharp anatomical distinction, a self-organization of domains is created by means of neural networks.

Living entities are mostly characterized by their biological function and share many common robust perceptual properties correlated to each other. Since semantic categories with highly correlated properties are more resistant against damage, the common properties result in being difficult to damage. Nonliving objects have fewer shared properties than living entities. However, they have distinctive features related to the object's form and function, which are strongly correlated to each other and therefore resistant to damage.

Theory 1: Sensory – functional approach



Theory 2: Domain – specific approach



Theory 3: Conceptual – structure approach

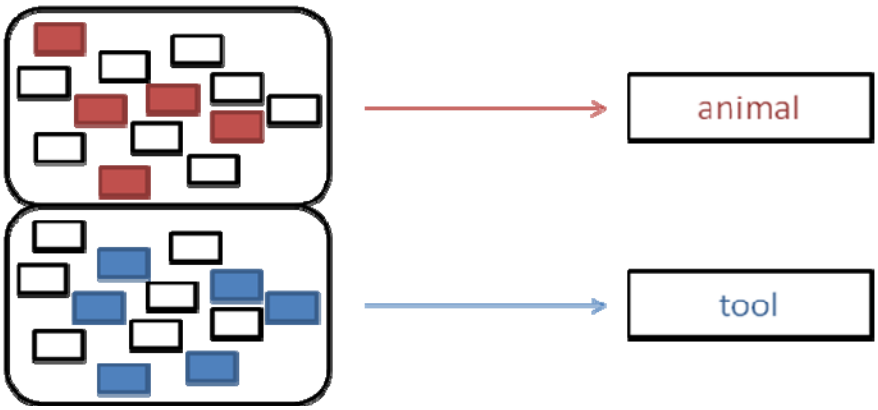


Figure 1: Schema representing the 3 different theories.

1.2 Investigation methods and empirical data

In this section, an overview about the empirical data is given. Several methods have been used to approach the question how conceptual information is represented in the brain: behavioural experiments and event-related potentials (ERP), brain lesion studies with patients showing category-specific semantic deficits, neuroimaging and connectionist models. Data on patients with category-specific semantic deficits, see the above-mentioned studies [Gainotti 2001; Warrington & Shallice, 1984; Warrington & McCarthy 1987; Damasio *et al.* 1996], neither provide a strict and clear-cut evidence for the modality-based sensory-functional theory on one hand, nor do they prove the existence of distinct neuro-anatomical stores for different domains and categories, as suggested by the domain-specific theory on the other hand.

1.2.1 Empirical data for the sensory-functional theory

Neuroimaging data supporting the modality-specific view of semantic organization was provided by Chao and Martin. In a positron emission tomography PET study [Martin *et al.* 1996] investigating healthy subjects which performed a picture-naming task, they found activations in the left medial occipital lobe (calcarine gyrus) for naming animal pictures, and activation of a left premotor area and of the left middle temporal gyrus for naming tool pictures. Both categories, animals and tools, also activated an area located in the bilateral ventral temporal lobes and the Broca area. In an fMRI study [Chao *et al.* 1999], Chao and colleagues investigated the naming and viewing of pictures and words of animals and tools. The lateral fusiform gyrus, the medial and inferior occipital gyrus and the right superior temporal sulcus (STS) were activated by animal stimuli, while tool stimuli elicited activations in the bilateral medial fusiform gyrus and in the left medial temporal gyrus. In another fMRI study [Chao *et al.* 2000], the authors found that viewing and naming tools selectively activated the left ventral premotor cortex, a region where motor - based information is stored, and a region in the left posterior parietal cortex. Both regions were also identified in monkey studies [for a review see Rizzolatti & Arbib 1998] to be involved in the visual presentation of graspable objects.

An fMRI study by Thompson-Schill [Thompson-Schill *et al.* 1999] which investigated the retrieval of visual and non-visual knowledge, found increased activity in the left fusiform gyrus and the left middle temporal gyrus for nonliving stimuli and living stimuli. The activity of these two regions was, however, not only dependent on the modality but also on the category of the presented stimuli. The left middle temporal gyrus was activated more by nonliving than by living stimuli, and the activation caused by nonliving stimuli was greater when the presentation was nonvisual, which was the opposite case for the living stimuli. In the left fusiform gyrus, nonvisual living stimuli elicited greater activation than nonvisual nonliving stimuli. However, visually presented stimuli elicited the most activity, with a greater activity for nonliving stimuli. So Thompson-Schill *et al.* concluded that semantic memory is organized in modality-specific regions taking into account category-specific knowledge.

Further evidence for conceptual knowledge being organized at the level of object features has been given by electrophysiological experiments [Sitnikova *et al.* 2006]. Event-related potentials (ERPs) were modulated by those features which were most salient for object recognition. Animals elicited an increased anterior negativity, which can be associated with semantic processing of visual object attributes. Tools evoked an enhanced posterior left-lateralized negativity, which was shown to reflect the knowledge of characteristic motion and general functional properties of objects.

1.2.2 Empirical evidence for the domain - specific theory

Connectionist models, claiming that an overlap of features produces clusters corresponding to certain categories or domains [Caramazza & Mahon 2003], seem to be in line with brain lesion studies. According to their theory, random damage occurred to the conceptual system of these patients, and, depending on the severity of damage, a number of sets of intercorrelated features was destroyed.

Empirical data supporting the domain-specific view is brought forward by Perani and colleagues in a PET study investigating healthy subjects in a picture and word matching task [Perani *et al.* 1999]. It shows that there are different, anatomically segregated brain networks for identification of living and nonliving

objects, independent of modality. Living entities, in this case pictures of animals, activated the left fusiform gyrus and the bilateral occipital lingual gyrus, while nonliving objects (pictures of tools) elicited activations in the left dorsolateral frontal and temporal cortex. In word matching tasks, animal identification was processed in a network comprising the left fusiform and inferior occipital gyrus, the right superior parietal lobe and the left thalamus, while identifications of tools elicited activation in the left middle temporal gyrus, the left precuneus and bilateral occipital regions. The authors drew the conclusion that especially the left fusiform gyrus was important for the processing of living entities and the left middle temporal gyrus was an important area for nonliving object processing. In another PET study, Damasio and colleagues compared results of healthy subjects performing a word retrieval task with results acquired in brain-lesioned patients [Damasio *et al.* 1996]. Naming persons activated the left temporal pole, the right temporal pole, and the inferotemporal area, naming of animals elicited activation in the left inferotemporal area, and naming tools elicited activation in an area posterior to that activated by animals.

Another example for categorical organization of semantic knowledge is given by an fMRI study investigating healthy subjects while performing categorization tasks [Leube *et al.* 2001]. The authors found activations in the right inferior frontal, middle temporal and right fusiform gyrus elicited by living stimuli. Common areas of activations were the bilateral inferior occipital gyri, the left inferior frontal gyrus and the left inferior parietal lobe. Other studies supporting the view that brain regions operate in a domain-specific way are performed by Nancy Kanwisher, showing an area located in the fusiform cortex specialized for face processing and representation [Kanwisher *et al.* 1997; Kanwisher 2000].

An ERP study by Kiefer showed category-specific effects between living and nonliving things across different input modalities, reflecting neuroanatomically distinct subdivisions of the conceptual system [Kiefer 2001]. And electrophysiological studies in humans by Kreiman showed the distributed nature of conceptual representation by demonstrating that neurons in the ventral temporal cortex responded selectively to different categories [Kreiman 2000].

1.2.3 Empirical evidence for the conceptual - structure theory

Pilgrim and Tyler observed that neuroimaging data, namely fMRI and PET studies performed by several authors [for a review see Martin & Chao 2001] to identify the involved brain areas did not show consistent regional specialization for the individual domains and categories, since significant activations found in a specific region by one group could not be replicated by another group. They conducted an event-related fMRI study [Pilgrim *et al.* 2002] in contrast to the previous block-designed studies, to investigate semantic categorization in healthy subjects. Areas involved in all semantic processing tasks were the bilateral inferior frontal lobes and the left inferior and medial temporal gyrus, all already been identified by previous studies. However, no significant differences between activations caused by artifact and natural kinds' concepts could be found, which lead to the conclusion that conceptual knowledge is organized in a unitary, distributed neural system undifferentiated by domain of knowledge. This distributed system is thought to comprise the above mentioned regions. Concerning the different activations found in other studies, Pilgrim and Tyler assumed them to be due to different tasks, deviating significance threshold levels, absence of multiple comparison corrections, and inadequate matching of stimuli and block design leading to a habituation effect.

When reviewing the existing neuroimaging data and averaging several fMRI and PET studies, which investigated neuronal representation of conceptual knowledge, Devlin and colleagues. found little consistent data supporting an anatomical specialization [Devlin *et al.* 2002]. A large area including (predominantly left) temporal and frontal lobes was found to be activated. Thus, they conducted a series of PET and fMRI experiments investigating lexical decision tasks, and found a large number of brain regions activated by the different categories animals, fruits, tools, and vehicles. They did not find consistent evidence for a domain specialization of the brain, yet proposed a network comprising the inferior frontal and posterior temporal gyrus, the medial superior frontal, the TOP junction, the medial cerebellum, left and middle temporal gyrus, medial frontal gyrus, superior frontal gyrus, precuneus, and thalamus to be involved in semantic processing. This network is thought to be lateralized with differential representation of concepts across both

hemispheres. In a behavioural study [Pilgrim *et al.* 2005] the authors found hemispheric differences for living concepts, and observed a disadvantage for nonliving objects in the right hemisphere.

	Living	**Nonliving**	**Both**
Martin 1996 (pictures)	left med. occip. lobe (calcarine gyrus)	left premotor area; left middle temp. gyrus	bilateral ventr. temp. lobes; Broca area
Chao 1999 (pictures and words)	lat. fusiform gyrus; med. and inf. occip. gyrus; right sup. temp. sulcus (STS)	bilateral med. fusiform gyrus ; left med. temp. gyrus	
Chao 2000 (pictures)		left ventr. premotor cortex; left post. pariet. cortex	
Thompson - Schill 1999 (questions)	(left fusiform gyrus - nonvisual)	(left middle temp. gyrus - nonvisual); (left fusiform gyrus – visual)	left fusiform gyrus; left middle temp. gyrus
Perani 1999 (images)	left fusiform gyrus; bilateral occip. lingual gyrus	left dorsolateral. front.; temp. cortex	
Perani 1999 (words)	left fusiform; inf. occip. gyrus; right sup. pariet. lobe; left thalamus	left middle temp. gyrus; left precuneus; bilat. occip. regions	
Damasio 1996 (words)	left temp. pole; right temp. pole / inferotemp. area (persons); left inferotemp. area (animals)	left post. inferotemp. Area	
Leube 2001 (words)	right inf. front.; middle temp.; right fusiform gyrus		bilat. inf. occip. gyri; left inf. front. gyrus; left inf. pariet. lobe
Kanwisher 2000 (pictures)	fusiform cortex (faces)		
Pilgrim 2002 (words)			bilat. inf. front. lobes; left inf. and med. temp. gyrus
Devlin 2002 (words)			inf. front. and post. temp. gyrus; med. sup. front. / TOP junction; med. cerebellum; left and middle temp. gyrus; med. front. gyrus; sup. front. gyrus; precuneus; thalamus

Table 1: Overview of results of the mentioned neuroimaging studies

1.3 Schizophrenia

1.3.1 Definition and Epidemiology

Schizophrenia or schizophrenic psychosis is a chronic mental disease with a prevalence of 1% of the world population, without displaying gender or ethnic preference. However, the prevalence is higher in urban regions than in rural areas. The incidence of the disease is about 0.2 – 0.6 per 1000 inhabitants and year. Men are typically affected between the ages of 15 to 30 with a manifestation peak at the age of 21, while the onset of the disease for women is typically about 5 to 10 years later. Risk factors are difficult births, birth in winter and spring, childhood impairments like language, motor, coordination, attention and social functioning deficits [Buckley *et al.* 2001].

Emil Kraepelin first described the symptom complex in 1898 and named it “dementia praecox”, having in mind the unfavourable progress of the decline of the patients’ personality. Egon Bleuler used the term “schizophrenia” in 1911 for the first time, referring to the psychopathology characterized by the splitting of different cognitive and emotional domains. A disruption or perturbation of thinking, perception, and language, affection of memory and attention, as well as a dysfunction of affectivity and social cognition characterizes the disease. It comprises a large complex of symptoms such as delusion, hallucination, formal thought disorder, affective disorder, disorder of the self (*Ich-Störung*), perturbation of will and psychomotor function as well as a dysfunction of social and impulsive behaviour [for a review see Kurachi 2003].

1.3.2 Aetiology and Pathophysiology

The underlying causes of schizophrenia are still unknown. Accordingly, there are many hypotheses speculating on the origin of this disease [Sawa & Snyder 2002], and instead of a single event or cause being responsible, a multifactor development is assumed. However, there is a general agreement on the evidence of a genetic disposition being the basic component. The risk of falling ill is increased in related family members of schizophrenic patients, and studies of identical twins [Sullivan *et al.* 2003] show a highly correlated incidence of the disease (concordance of more than 50 %), even if they are not living in the

same family. There are some attempts to identify single genes, although it is more likely to be a matter of polygenetic inheritance [for an overview see Austin 2005]. High paternal age at conception is also thought to be a potential risk factor, which would support the genetic aspect, since mutations in germ cells increase with age. Furthermore, other theories suggest inaccurate perinatal brain development to be an important factor as well. Damage occurring to the developing brain in the form of infection or hypoxia may lead to subsequent schizophrenia, especially in children with genetic predisposition [Rees & Inder 2005].

An additional environmental component is likely, because not all people with a genetic disposition for developing the disease fall ill. Vulnerability caused by genetic factors or impaired brain development in addition with a second hit in terms of a releasing factor, ”environmental stressors” like certain life events, psychosocial over stimulation or frequent use of hallucinatory drugs like cannabis seem to facilitate the onset of schizophrenia. Other stressors can be an impaired development during childhood and adolescence [Morgan & Fisher 2007], but also the family structure and social status play a certain role.

In addition, adult brain anatomy in schizophrenic patients differs from those in healthy subjects. There are subtle and diffuse structural brain abnormalities, like enlarged lateral and third ventricles, loss of volume, for example decreased frontal lobe size, smaller medial and superior temporal lobe and hippocampus and a decreased thalamus size, hinting towards a pathologic process which occurred during brain development [for an overview see Shenton *et al.* 2001]. Besides these anatomical differences, there are also changes in metabolism and neurotransmitter systems. In frontal brain areas, studies have shown less blood circulation and consequently a lower metabolism [e.g. Erbas *et al.* 1990].

Another theory on a functional level argues that an over-activity of dopaminergic brain structures in the mesolimibic system either based on over-production of dopamine or hypersensitivity of dopaminergic receptors, leads to reduced filtering of information and decreased attention. This theory is supported by the fact that most of the neuroleptic medication is based on a dopamine antagonist mechanism. Yet, not only is the dopamine system

involved but also other neurotransmitter systems, especially the glutamate system [Emilien *et al.* 1999; Lang *et al.* 2007]

1.3.5 Language in schizophrenic patients and Formal Thought Disorder

Neuropsychological deficits constitute a core symptom complex in schizophrenia [Bilder *et al.* 2000], among them is an impaired language function, also called formal thought disorder. It is defined as disturbed language production, affecting many aspects of language like prosody, voice quality, syntax and semantics while comprehension and phonology remain intact. It consists of characteristics such as (semantic) incoherence of speech, loosening of associations and use of peculiar or newly created words. Patients with formal thought disorder are easily distracted, lose their goal of speech and are often lost in tangentiality and circumstantiality. They express unusual thoughts with relative ease. On the other hand, their speech may also be reduced in amount and content [Covington *et al.* 2005].

All these symptoms may also occur in the speech of healthy subjects, but they would correct their errors immediately. Formal thought disorder symptoms can also occur in maniac or depressed patients, but this is rather uncommon. Contrary to patients with aphasia, schizophrenic patients suffering from FTD do not seem to be troubled by their language.

Abnormal language processing is seen as a possible cause for formal thought disorder; some authors regard abnormal lateralization of language functions, namely a failure to establish left-hemispheric dominance, as a possible reason [Mitchell & Crow 2005]. Conform to this hypothesis, others suggest the superior temporal gyrus (STG) to be affected [Kircher *et al.* 2001; Kircher *et al.* 2002], after seeing a reversed lateralization of its activation (right hemisphere in schizophrenic patients as compared to left hemispheric activation in healthy subjects).

Goldberg and Aloia [Goldberg *et al.* 1998; Aloia *et al*. 1998] suggested that formal thought disorder in schizophrenic patients results from semantic processing abnormalities, like aberrations in the spreading of activation or inhibition in semantic networks. This was already assumed by Spitzer and colleagues [Spitzer *et al*. 1993; Weisbrod *et al.* 1998], who interpreted an

indirect semantic priming effect found in schizophrenics during a lexical decision task as evidence for altered spreading activation and inhibition. In line with these studies Moritz and colleagues found increased automatic spreading activation in healthy subjects with schizophrenia-like language problems [Moritz *et al.* 1999].

1.3.6 Semantic categorisation in schizophrenic patients

Concerning semantic categorisation, there are some studies performed in schizophrenic patients, most of them focussing on behavior without using brain imaging. In studies by Keri and colleagues [Keri *et al.* 1999, Keri *et al.* 2004] schizophrenic patients displayed impaired categorization performances after visual learning, leading to the assumption that they have deficits in category learning and perceptual abstraction. The patients were thought to use verbal knowledge as a compensation strategy since they improved when giving verbally descriptions of the categories.

Other studies show [Elvevag *et al.* 2001; Elvevag *et al.* 2005] that despite of a disorganized semantic network leading to thought disorder, the semantic system of schizophrenic patients remains intact. They still have the capability to make precise distinctions between categorical representations. Their category structure with respect to content and organization is similar to those in healthy subjects. Thus, according to them, priming anomalies, over-inclusiveness, looseness of association, and semantic memory problems of schizophrenic patients are not related to a reduced awareness of boundaries between semantic category memberships or entities. On the contrary, the boundaries of semantic category entities or representational nodes seem to be intact. Thus, Elvevag and colleagues concluded that a specific deficit in spreading activation might cause the disturbances in priming, as well as an impaired “movement” between representations.

A different study, performed by Green and colleagues [Green *et al.* 2004] demonstrated that an abnormal semantic memory (a long term information store for the use of language) may not be the primary cause of disturbances in reasoning and thought in schizophrenics, as it does not necessarily have an effect on the thought process. They suggested that ad hoc generated

categories unsuited to the current context and misunderstanding or false judgements of social situations lead to impaired performance in semantic memory tasks. A different approach was brought forward by Moelter and colleagues, stating that schizophrenic patients have higher-order categorization strategies, possibly due to diffuse spreading of activation [Moelter *et al.* 2005].

An fMRI - study of semantic processing in patients, showed decreased activation in the left inferior prefrontal cortex and increased left superior temporal gyrus as compared to controls; which could be interpreted as a disrupted frontal - temporal network involved in semantic processing [Kubicki *et al.* 2003].

Schizophrenia does not only cause cognitive impairments but also leads to emotional disturbances. It is out of interest to investigate how emotional content affects categorisation in schizophrenic patients. Since formal thought disorder is characterized by affective processing deficits, it was assumed that affective priming would be different altered. However, a study by Rossel [Rossel 2004] has shown that affective semantic priming in schizophrenic patients does not differ from affective priming in healthy controls, with neutral and happy prime targets yielding significant semantic priming while fearful and sad pairs showed no or only modest semantic priming facilitation. Thus, patients do not show increased sensitivity to affect, especially not to negative affect, when compared to healthy subjects. A different study [Hempel *et al.* 2005] demonstrated that although schizophrenic patients and controls did not differ in their subjective evaluation of the arousal and valence of emotional pictures (IAPS), patients showed an increased physiological response (heart rate and breathing rate) to pictures with positive emotional account. In a study which investigated the processing of environmental sounds in schizophrenic patients, the authors [Tüscher *et al.* 2005] found a higher error rate in sound identification in patients, while the emotional recognition was unaltered.

1.4 Social cognition

Social interaction is crucial for survival of animals, thus, being socially competent must have evolutionary advantages. In humans, defined by their unique social and communicative skills, social cognition is highly evolved and supposed to be much more complex than in other animals.

Social cognition is a term defined by a broad number of specialists like philosophers, psychologists, neuroscientists, or anthropologists. Depending on the defining author, it comprises social behaviour and various other skills, like perception of social skills, motivation, emotion, attention, memory and decision-making which are crucial for social competence. Social cognition is "the sum of processes that allow individuals of the same species to interact with each other, which is a matter of survival and which depends upon the exchange of signals" [Frith & Frith 2007].

Adolphs [Adolphs 2003] defines it as "the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behaviour. For Couture [Couture *et al.* 2006], social cognition comprises, among others, "emotion perception (the ability to ascertain social cues from behaviour provided in a social context), social perception (the comprehension of social rules and conventions), theory of mind (the understanding that others have mental states different from one's own and the capability to make correct inferences about their content) and attributional style (the individual characteristic tendency in explaining the causes of events in their lives)".

Brain structures important for human social behaviour are thought to be higher-order sensory cortices like the fusiform gyrus, superior temporal gyrus and left frontal operculum, involved in representation of perceptual stimuli and their features; the amygdala, striatum and orbitofrontal cortex, connecting the perceptual representation with emotional response, cognitive processing, judgements and behavioural motivation; and higher-order cortical regions like the left prefrontal, right parietal and anterior and posterior cingulated cortex [Adolphs 2001]. The latter regions are thought to be responsible for the "construction of an internal model of the social environment", involving

representations of others and the social relationship with them, and the value of one's actions in a social context [for a review see Adolphs 2003]. Special attention on the prefrontal cortex was given by Amodio, explaining its important role in action monitoring, outcome monitoring, self-knowledge, person-knowledge, and mentalizing [Amodio & Frith 2006].

Mental simulation, related to activity in premotor and posterior parietal areas also has an important impact on social interaction, as imagining one's own and other's behaviour helps us to discriminate reality and fiction, to understand others, and to have self-awareness and self-agency [Decety & Grezes 2006]. Simulation might also be helpful in conversation, since alignment of situation models, as well as multimodal representations of space, time, causality and intentionaliy, facilitate language processing [Garrod & Pickering 2004].

A similar aspect of social cognition is imitation, a process not only involved in learning but also in reading others' gestures and understanding their intentions, with the help of the mirror neuron system. Mirror neurons have been identified in the posterior part of the inferior frontal lobe and the anterior part of the inferior parietal lobe in monkeys [Rizzolatti & Craighero 2004]. In an fMRI study with humans, imitation of finger movements elicited activation in the pars operculum of the inferior frontal gyrus and in the rostral posterioir parietal cortex [for a review, see Iacoboni & Dapretto 2006]. The superior temporal sulcus (STS) is thought to provide the main visual input to these regions. The STS itself gets input from the ventral and dorsal visual pathway [Goodale & Milner 1992; Ungerleider & Haxby 1994], and by integrating form and motion it is responsible for the perception of biological motion [Puce & Perrett 2003, Giese & Poggio 2003], for example the perception of hand and body movement of other persons [Allison *et al:* 2000; Beauchamp *et al.* 2002]. Thus, the STS performs several functions which constitute important aspects of social cognition. A percept of animacy is induced by responding to movements therefore leading to identification of living entities [Schultz *et al.* 2005]. Additionally, it contributes to the decoding of visual cues in a social context and thereby to the understanding of the direction of other people's attention. Higher

cognitive functions, like attributing mental states to others are also thought to be processed in the STS [Frith & Frith 1999].

One aspect of social cognition, the theory of mind, is most highly developed in humans and is thought to be an adaptive mechanism to increasing social complexity [for a review see Brüne and Brüne-Cohrs 2006]. In humans, conceptual knowledge of self and others, as well as self-recognition in mirrors emerge by the age of 18 - 24 months. This is seen as the onset of a theory of mind, and by the age of 4 - 5 years, children acquire an understanding of beliefs and knowledge states as mental representations.

During evolution, the human species went through a brain enlargement, especially of the prefrontal cortex, a region with executive function in the cognitive system, supervising and regulating attention, memory and action [for an overview see Thompson.Schill *et al.* 2005]. The prefrontal cortex is thought to be responsible for the insightful, self-reflective character of humans [Mitchell *et al*. 2005].

Brain regions forming the “mentalizing system” [Frith and Frith 1999] include the STS (detection and analysis concerning goals and outcome of the behaviour of others), inferior frontal regions (representations of actions and goals) and the anterior cingulated / medial prefrontal cortex (representations of mental states). Others regard also the inferior parietal gyrus to be involved in this system [Brüne 2005]

Since social cognition plays an important role in human interaction, its dysfunction, due to brain damage caused by accidents [Blair and Cipolotti 2000; Grafman et al. 1996] or surgery [Damasio 1990] as well as developmental diseases like autism [Dapretto et al. 2006], and psychotic disorders like schizophrenia leading to deficits in social behaviour, constitute an enormous impact on the functional outcome of the individual. Social impairments are probably independent of deficits in non-social cognitive functions like attention, memory or intelligence although these systems are interacting [Brüne & Brüne-Cohrs 2006; Stone & Gerrans 2006].

Social dysfunction is a common finding in schizophrenia, with poor social and communication skills having an effect on vocational functioning [Dickinson *et al.* 2007]. Frith suggested that an impaired theory of mind (the ability to know

and understand unobservable mental states in one-self and others, like desires, intentions and beliefs) is responsible for poor social behaviour and many other symptoms in schizophrenic patients [Frith 2004]. Lacking discrimination between self-agency and other agency due to dysfunction in temporoparietal regions, could lead to thought insertion and delusion of alien control [Decety & Grezes 2006]. Pickup [Pickup 2006] even suggested an impaired theory of mind to be a trait marker of schizophrenia, since nonclinical individuals with schizotypic traits did not show signs of a malfunctioning theory of mind.

Brüne and colleagues showed that an impaired theory of mind is the single-best predictor of social competence in schizophrenia [Brüne *et al.* 2007]. An impaired theory of mind does not only influence the way schizophrenic patients use language and interpret speech, but it also leads to difficulties in planning and executing strategic social behaviour [Brüne 2005]. However, not only an impaired theory of mind, but also deficits in other aspects of social cognition, like emotion and social perception, as well as attributional style, have an impact on the functional outcome of schizophrenic patients [Couture *et al.* 1996].

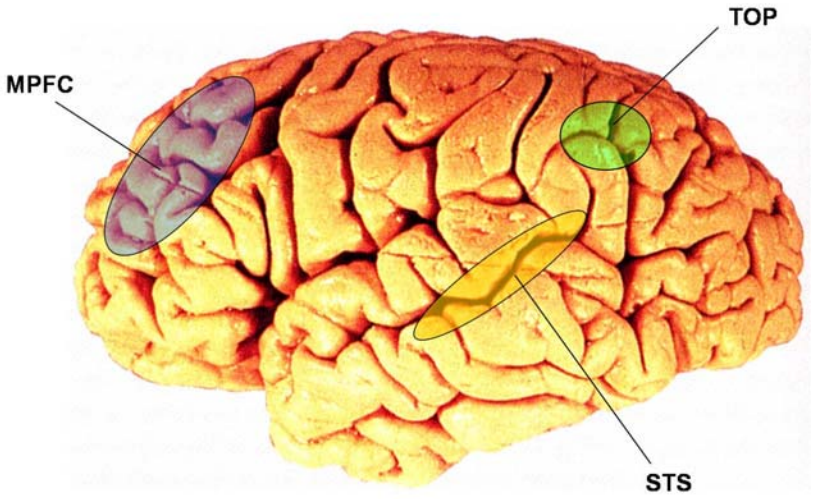


Figure 2: Brain regions, involves in social cognition; MPFC medial prefrontal cortex; TOP temporo-parietal junction; STS superior temporal sulcus; for explanation see text

1.5 (Functional) Magnetic Resonance Imaging ((f)MRI)

Magnetic resonance imaging (MRI) is a non-invasive imaging method, nowadays widely used in clinical medicine to investigate anatomical structures and pathological changes of any part of the human body, but it is especially useful to study the brain, soft tissue structures, and joints at a high spatial resolution. As an addition, functional MRI is broadly utilized to investigate functional processes in the brain, such as neural activity during cognitive operations or body movements by employing the BOLD signal.

The principle of magnetic resonance imaging is based on the spin of positively charged atomic nuclei, e.g. hydrogen atoms in the brain. When protons spin around their axis (precession), they are moving electrical charge, producing a magnetic field. Changes of these magnetic fields lead to the emission of tissue specific radio wave signals, which can be recorded with a highly sensitive MRI scanner. However, the precession frequency of the protons shows local differences, they do not spin in phase. Thus, an inhomogeneous magnetic field is produced, being characteristic for each tissue as they contain different amounts of protons. Spatial localisation is performed by applying gradient magnetic fields, perpendicular to each other.

Functional MRI however, is not used to study anatomical structures, but is an important method for brain mapping and investigating neural activity underlying cognition. While performing cognitive, motor or sensory tasks in the MRI scanner, the respective brain areas are activated and can be identified. The method is based on the BOLD (blood oxygen level dependent) effect [Ogawa *et al.* 1990], utilizing the different magnetic properties of oxygenated and deoxygenated haemoglobin. Different magnetic fields arise and produce corresponding signals, according to the predominant state. De-oxygenated blood is paramagnetic as opposed to the diamagnetic oxygenated blood, therefore inducing significant field changes through stronger dephasing of the spinning protons. Consequently, a weaker resonance signal is recorded (susceptibility effect). T2*-weighted sequences measuring local magnetic field inhomogenities are especially appropriate for recording this effect.

fMRI is based on the hypothesis that cerebral blood flow and the level of haemoglobin oxygenation in a certain brain area correlate with neural activity [Fox & Raichle 1985]. Active neurons consume oxygen and require new supply by oxygenated haemoglobin delivered by arterial blood while the venous blood system carries away the de-oxygenated haemoglobin. During brain activity, e.g. when performing a cognitive task, cerebral blood flow (CBF) increases in this area with an onset time delay of a few seconds, which is called the haemodynamic response. The increased CBF leads to a higher oxygenated to deoxgenated haemoglobin ratio in this region (since the supply of oxygen is higher than the demand), thereby producing a stonger fMRI signal. This is called the blood-oxygen-level-dependent (BOLD) effect. The signal starts with a dip due to initial higher oxygen consumption than supply and peaks after about 6 seconds, followed by a long undershoot.

The exact neurophysiological basis of the BOLD effect is still unknown. However, studies performed by Logothetis *et al.* [Logothetis *et al.* 2001; Logothetis *et al.* 2002] indicated a correlation with the local field potential (LFP) signal resulting from synaptic input and information processing. Correlation with multiple unit spiking (MUA), corresponding to neuronal output activity was shown to be rather unlikely.

1.6 Aim of the Study

The aim of the present work was to investigate neural correlates of semantic processing and categorization in schizophrenic patients as compared to healthy subjects. With the following fMRI experiments we located specific brain activation during categorization tasks, using pictorial stimuli from the living domain (human, animal) and the nonliving domain (tool, food) taken from a validly rated picture data base (IAPS). These complex stimuli, including pictures of humans and naturalistic scenes, gave us the opportunity to investigate neural networks relevant for social cognition, as they specifically activate regions like the STS and the TOP junction, which are involved in the representation of theory of mind and other cognitive functions important for social behaviour.

We examined schizophrenic patients mainly for the following reasons: They (1) often show a confusion of categories in the presence of formal thought disorder, they (2) often suffer from delusions resulting from confusion of some of the most basic general concepts which build our beliefs about reality and they (3) display profound social deficits in behaviour. The aim of this study was to explore whether these deficits are related to a different neural processing of categorical stimuli as seen in healthy subjects.

In healthy subjects, numerous studies have already been performed concerning the neuro-anatomical organization of conceptual knowledge. Each study can be assigned to a different theory, of how information processing is implemented in the brain. We hypothesized that a network of distributed brain areas is involved in semantic processing, suggesting that representation of a certain category is not performed in a single category-specific brain region, but in a network of specialized brain areas each processing a different feature belonging to this category.

We assume conceptual knowledge to be represented differently in schizophrenic patients, and hope these abnormalities in concept representation and processing might give a clue how higher order disturbances of thinking, like e.g. delusions, formal thought disorder and impaired social behaviour emerge.

2. Methods

2.1 Subjects

11 patients diagnosed with schizophrenia and 15 healthy controls participated in this study; only right-handed subjects were included. The control subjects, evaluated as healthy and aged between 20 – 54 years (mean age 31.4), were recruited from the University of Tuebingen (Clinic staff) and the surrounding community. For the two-group comparison 11 controls were matched with respect to gender (the controls including 4 women) and age (20 – 43 years, mean age 30.8) according to gender and age of the patients. Patients were drawn from the University Hospital of Psychiatry, Tuebingen and underwent medical and psychiatric evaluation. They were diagnosed with Schizophrenia according to DSM-IV criteria. The mean age was 32.7, ranging from 20 – 47 years, including 5 women. Mean PANSS value (positive and negative syndrome scale; see Table 2) was 70.5 [Kay *et al.* 1987].

The study was approved by the local ethical committee (University of Tuebingen Medical School). Prior to participation all subjects signed written informed consent after being introduced to the experimental procedure, as well as being given information and reconnaissance of potential risks of the used method. They were paid 10 € per hour of participation. Yet, the participants were encouraged to stop the experiment whenever they felt uneasy or afraid. Data of subjects who discontinued with the experiment were excluded from the analysis.

Schizophrenic Patients	Mean value (+/- standard deviation)
Mean age (years)	32.7 (20 – 47)
Sex	6 males, 5 females
Duration of illness (years)	12,1 +/- 8,4
PANSS	70,5 +/- 16,5
Neuroleptic medication	4xRL; 3xCL; 3xZN; 1xON

Table 2: Characterization of schizophrenic patients. RL (Risperdal), CL (Clozapin), ZN (Ziprasidon), ON (Olanzapin)

2.2 Stimuli

Visual stimuli were taken from the International Affective Picture System (Lang *et al.* 1997), a series comprising more than 700 pictures rated for mean valence, arousal and dominance by an US-American sample.

Number	*Object*	*Valence*	*Arousal*
6800	Gun	4.87	4.01
7090	Book	2.61	5.19
7281	Food	4.41	6.40
1540	Cat	4.54	7.15
2311	Mother	4.42	7.54
1390	Bees	5.29	4.50
2700	Woman	4.77	3.19
2540	Mother	3.97	7.63
7481	Food	4.92	6.53
1030	Snake	5.46	4.30
1590	Horse	4.74	7.18
1720	Lion	5.32	6.79
7080	Fork	2.32	5.27
7352	Pizza	4.58	6.20
2221	Judge	3.07	4.39
1602	Butterfly	3.43	6.50
7270	Icecream	5.76	7.53
1640	Coyote	5.13	6.27
2250	neutr. Baby	4.19	6.64
7233	Plate	2.77	5.09
2345	Children	5.42	7.41
1510	Dog	4.28	7.01
1670	Cow	3.05	6.81
7004	Spoon	2.00	5.04
7000	rolling pin	2.42	5.00
2270	neutr. Child	3.15	6.28
1660	Gorilla	4.57	6.49
1121	Lizard	4.83	5.79
7185	abstract art	2.64	4.97
7286	Pancakes	4.44	6.36
6150	Outlet	3.22	5.08
7390	Icecream	4.56	6.84
7010	Basket	1.76	4.94
2160	Father	5.16	7.58
7020	Fan	2.17	4.97
1463	Kittens	4.79	7.45
2341	Children	4.11	7.38
2850	Tourist	3.00	5.22
7460	french fries	5.12	6.81
7009	Mug	3.01	4.93

2030	Woman	4.54	6.71
7430	Candy	4.72	7.11
6910	Bomber	5.62	5.31
7351	Pizza	4.25	5.82
2370	three men	2.90	7.14
7410	Candy	4.55	6.91
7450	Cheeseburger	5.05	6.40
7035	Mug	2.66	4.98
1931	Shark	6.80	4.00
1810	Hippo	4.45	6.52
2165	Father	4.55	7.63
2214	neutr. Man	3.46	5.01
7350	Pizza	4.97	7.10
1603	Butterfly	3.37	6.90
7100	fire hydrant	2.89	5.24
2190	Man	2.41	4.83
7034	Hammer	3.06	4.95
1302	Dog	6.00	4.21
1450	Gannet	2.83	6.37
1080	Snake	5.69	4.24
7475	Shrimp	4.17	6.33
7190	Clock	3.84	5.55
2058	Baby	5.09	7.91
2020	Adult	3.34	5.68
7200	Brownie	4.87	7.63
7470	Pancakes	4.64	7.08
1740	Owl	4.27	6.91
7480	Pasta	4.55	7.08
7235	Chair	2.83	4.96
7050	Hairdryer	2.75	4.93
2150	Baby	5.00	7.92
7400	Candy	5.06	7.00
7320	Desserts	4.44	6.54
1812	Elephants	3.60	6.83
7140	Bus	2.92	5.50
7002	Towel	3.16	4.97
7260	Torte	5.11	7.21
2000	Adult	3.32	6.51
2500	Man	3.61	6.16
7330	Icecream	5.14	7.69

Table 3: 80 IAPS pictures and the corresponding arousal and valence values

A total of 80 pictures were grouped into two main domains, consisting of 40 “living” and 40 “nonliving” items. “Animal” and “human” were categories of the “living” domain, “food” and “tool” constituted categories of the “nonliving” domain, each category comprising 20 IAPS pictures. A complete list is given in Table 3, examples are given in Figure 3 and 4. The pictures selected for the presentation were matched with regard to similar valence and arousal values.

Only pictures with mean valence and low arousal levels were chosen, mean values are reported as in the IAPS ratings with a range of values from 1 to 9 for both valence and arousal, as shown in Table 4. They were not matched according to visual complexity or brightness.

Pictures were centred, reduced to 80 % of their original size, and presented with E-prime v1.1 (Psychology Software Tools, Inc.). Although an exact timing of each stimulus was set by the program, uploading of the images required substantial computer working memory, resulting in presentation delays between 0 - 500 ms. Thus, the non-simultaneously starting of the slices for each stimulus produced a handy jittering, shifting stimuli onsets onto different time points of the haemodynamic response function, allowing a complete mapping. To correct for the delay, actual picture presentation times (instead of programmed picture presentation times) were used as vectors when calculating contrasts in SPM2. Additionally, inter-stimulus intervals were randomized for the individual subjects (see below), independent of the preceding stimulus presentation.

Affective norm	*Category*	*Number*	*Mean*	*Standard Deviation*	*Std. Error Mean*
Arousal	Animal	20	4,6220	1,0197	0,22802
	Human	20	3,9740	0,87708	0,19612
Valence	Animal	20	6,1110	1,16199	0,25983
	Human	20	6,4380	1,33174	0,29779
Arousal	Food	20	4,7655	0,38140	0,08528
	Tool	20	2,9760	0,90955	0,20338
Valence	Food	20	6,8285	0,50041	0,11190
	Tool	20	5,0440	0,30722	0,06870

Table 4: Standard deviation and mean error of the affective norms arousal and valence

Figure 3: Example IAPS pictures for the “animal” and “human” category

Figure 4: Example IAPS pictures for the “food” and “tool” category

2.3 Experimental design

The experimental paradigm was designed to investigate processing and representation of semantic domains and categories. It was realized with E-prime Version 1.1 (Psychology Software Tools, Inc.), a program for experiment generation and stimulus presentation. During the experiment, 80 IAPS pictures of items belonging to the four categories were presented in a random order for each subject. The paradigm was designed as an event-related experiment [Friston *et al.* 1999; Josephs & Henson 1999] with a short stimulus presentation of 0.5 seconds each with inter-stimulus intervals varying between 10.5, 12.5, or 14.5 seconds to avoid expectancy effects and to improve data quality by the jittering effect. During inter-stimulus intervals a white fixation cross on a black background was shown.

Pictures were presented via video beamer projection on a transparent screen which could be seen by means of a mirror attached to the head coil in front of the subjects' head. All pictures were projected into the center of visual attention and could easily be seen without eye movement. If necessary, participants wore fMRI-compatible glasses to ensure optimal visual acuity. Prior to scanning, subjects were informed once again via screen about the experimental structure and the task they were going to perform. During the stimulus presentation the subjects had to decide about the category of the presented item and then immediately respond by pressing a button with the right thumb (left button for nonliving items and right button for living items).

2.4 Data Acquisition

Data were acquired with a 1.5 T MR whole-body scanner (Siemens Sonata; Erlangen, Germany). The subjects lay supine in the scanner, their head movement was limited by wearing headphones (for noise reduction) and foam padding within the standard head coil. Twenty-five parallel axial slices (thickness = 4.5 mm, inter-slice gap = 1.0 mm) were obtained across the complete brain volume using a T2* weighted echo planar imaging (EPI) sequence [64 × 64 matrix, field of view = 192 mm, echo time (TE) = 40 ms, repetition time (TR) = 2 s, flip angle = 90º, voxel size = 3 × 3 × (5.49) mm^3]. A total of 480 volumes were acquired during one continuous run.

High resolution anatomical images were obtained with a T1-weighted 3-D turbo flash sequence (MPRAGE; 176 sagittal slices, thickness 1.0 mm, 256 × 256 matrix, field of view 256 mm, TE 3.22 ms, TI 660 ms, TR 1300 ms, voxel size = 1 × 1 × 1 mm) after the functional imaging session. They served as anatomical reference for the functional images. The experimental session was preceded by 5 scans to allow T1 saturation, yet, which were not discarded prior to data analysis.

2.5 Data analysis

Functional data were preprocessed using SPM2 (Wellcome Department of Imaging Neuroscience, London) running under Matlab 7 (The Mathworks Inc., Natick, Massachusetts, USA). Preprocessing steps [Klose *et al.* 1999] were applied to the functional images before statistical analysis. Data were slice-time corrected to the middle slice to compensate for acquisition time delay between slices of a functional image volume. They were then realigned across all scans to the first volume in the time series for head motion correction. For coregistration, the mean of these functional images was then aligned to the individual T1-weighted anatomical image to compensate for acquisition differences between functional and structural images. Afterwards, images were spatially normalized to the SPM T1 template in the Montreal Neurological Institute (MNI) space [Collins *et al.*, 1994], which approximates the Talairach space [Tailarach & Tournoux 1998] to correct for neuroanatomical differences between the individual subjects' brains, and to allow for reporting and comparing signal locations in a standard stereotactic space [Ashburner & Friston 1999; Brett *et al.* 2001]. These normalized images were then averaged and smoothed using an isotropic full-width, half-maximum (FWHM) Gaussian filter of 12 mm to enhance the SNR and to correct for persisting neuroanatomical differences.

Preprocessed data were statistically analyzed using SPM2 (Wellcome Department of Imaging Neuroscience, London). A robust fMRI signal normally elicits a BOLD effect which constitutes only 1 - 5 % of the baseline signal and therefore has to be statistically enhanced. Statistical parametric mapping (SPM) allowed us to make inferences about regionally specific effects of reproducible and significant brain activation. By applying the general linear model [Friston *et al.* 1994; Friston *et al.* 1995] to the time course of each voxel in the activation map (representing the activity of a certain coordinate in 3D - brain space), SPM tested the probability of the null hypothesis, thereby estimating subject and category effects.

Within-subject design matrices comprised 4 conditions, since all 80 stimuli were subdivided into four main event types (animals, food, humans,

tools) according to the category they belong to. Picture presentation onset times varied for each individual subject. Estimation of the BOLD effect was performed by convolving the haemodynamic response to the onset of each event with the canonical haemodynamic response function (HRF) of SPM2 and the first-order time derivative. So, stimulus regressors were constructed, assuming a duration of 0 seconds for each stimulus. A high-pass filter with a cutoff period of 196 seconds was applied to filter out low frequency variations.

Single-subject contrasts were defined as follows: 1. “main effect” (including all 4 categories), 2. “animal”, 3. “food”, 4. “human”, 5. “tool”, 6. “living” (including the categories “animal” and “human”), 7. “nonliving” (including the categories “food” and “tool”). These contrasts images were computed for every subject and the resulting individual contrast images were then entered into second-level random-effects analyses to determine within-group effects and two-sample t-tests for between-group analyses, ensuring a generalization with respect to the population. Significance levels were calculated for between-subject contrasts for “main effect”, “animal”, “food”, “human”, “tool”, “living” and “nonliving” for each group (all patients and all controls). Differential contrasts were calculated for: “animal vs. food”, “animal vs. human”, “animal vs. tool”, “food vs. human”, “food vs. tool”, “human vs. tool” for two groups (all patients and all controls). Two-sample analyses were calculated comparing the 11 patients and 11 matched controls for: “main effect”, “animal”, “food”, “human”, “tool”, “living” and “nonliving” contrasts and the “living vs. nonliving” differential contrast.

In a second analysis, in addition to the condition representing the event type “main” (including items of all categories), two covariates, namely arousal and valence values of each IAPS picture, were included for every subject to evaluate their influence. Single-subject contrast maps were defined as follows: 1. “main effect” (all stimuli), 2. “arousal” (only voxels positively correlated with arousal), 3. “negative arousal” (only voxels negatively correlated with arousal), 4. “valence” (only voxels positively correlated with valence), 5. “negative valence” (only voxels negatively correlated with arousal). We chose a first level model combining both covariates arousal and valence, since these p-values did

not differ greatly from those when only one covariate was included; the p-values were even lower when using the combination of arousal and valence.

The contrast images with covariates were also computed for all subjects and then included into second-level random effects analyses using one-sample t-tests to determine within-group effects and two-sample t-tests for between-group analyses. Significance levels were calculated for: between-subject contrasts for “main effect”, “arousal” and “valence” for each group (patients and 11 controls). Two-sample analyses were calculated comparing all patients and 11 matched controls for: “main effect”, “arousal” and “valence”.

All statistical maps were transformed into Z maps. Activations are reported if the alpha error probability falls below 0.001 on the single voxel level (uncorrected). Corrected p values on the single voxel level and cluster level are reported as follows: ** = very significant $p<0.01$; * = significant $p< 0.05$; (*) = trend $p<0.1$. Significance at cluster level takes into account the peak activation and extent of a cluster. To further reduce the likelihood of false positive results only clusters of more than 5 suprathreshold voxels are reported. Correction for multiple comparisons was performed based on the Gaussian field theory (FDR). Activation maxima were labelled using the Automated Anatomical Labelling (AAL) software [Tzourio-Mazoyer *et al.* 2002] with coordinates of activated voxels being reported in MNI space. Activations are shown on a MNI single-subject T1 - weighted anatomical image, with the left hemisphere being on the left side.

Behavioural data concerning reaction time and correctness of the subjects’ responses were not analysed. They were not considered to be of great importance for this study since we used the button pressing simply to keep the subjects concentrated. Correct and immediate recognition of the stimuli was assumed as necessary prerequisite for participation in this study. Subjects not being able to solve this task would have been excluded from the data analysis.

3. Results

3.1 Representation of single contrasts

3.1.1 Main contrasts in healthy controls

After generating contrast images of the 7 different conditions (main, animal, human, food, tool, living, nonliving) for each individual subject in a first-level analysis, within-group contrasts for all 15 healthy controls were calculated against baseline with a second-level model. These contrasts elicited a widely spread and strongly activated network distributed over the whole cortex for each condition. Significantly activated regions are described in detail in the following paragraph. For a résumé of all results see Table 5.

The contrast “main”, comprising all four conditions, yielded significant activation in a large cluster located in the left fusiform area / inferior TOP junction. The right precentral gyrus / medial-superior frontal gyrus as well as the left frontal inferior gyrus and the left rolandic operculum were also significantly activated (Figure 5). In the contrast “animal” against baseline the left fusiform gyrus / inferior TOP junction were significantly activated, as were the right fusiform gyrus / inferior temporal gyrus and the right parahippocampal / lingual gyrus (Figure 6). Significant activation of the left insular / superior temporal gyrus, and of the right inferior TOP junction / fusiform gyrus were obtained for the contrast “food” (Figure 7).The “human” condition showed a significant activation in the left rolandic / inferior frontal operculum, and in the left fusiform gyrus / inferior TOP junction (Figure 8). The contrast “tool” yielded significant activation in a large cluster located in the left inferior TOP junction / fusiform area (Figure 9).

The contrast “living”, consisting of the “animal” and “human” condition elicited activation in the left fusiform area / the inferior temporal gyrus and the left medial TOP junction as well as in the left inferior frontal gyrus / rolandic operculum and the left insula (Figure 10). The left inferior TOP junction /

fusiform gyrus, as well as the right TOP junction, were significantly activated in the “nonliving” contrast, comprising “food” and “tool” (Figure 11)
Thus, to summarize, a network of brain areas comprising inferior frontal and prefrontal areas, temporal regions and the TOP junction was involved in processing categorization tasks. Brain areas significantly activated in all contrasts were the bilateral fusiform gyri / inferior TOP junctions, with a predominance of the left hemisphere.

3.1.2 Main contrasts in patients

The first-level between-subject contrast images for the 11 patients diagnosed with schizophrenia were entered into a second-level random effect analysis, calculating within-group contrasts against baseline. The resulting second-level contrasts showed a brain activation which was even more wide-spread and non-specific than in the healthy controls. Again, significantly activated brain regions could be identified for each condition, described in the following section. For a complete overview on the single contrasts see Table 6.

For the contrast “main”, which consisted of all four conditions, we obtained significant activation in the bilateral cerebellum, the bilateral fusiform gyri, in the left cingulum and bilateral supplementary motor area (Figure 5). Significant activation patterns in the right fusiform gyrus / inferior temporal gyrus, the left fusiform and the left superior / medial temporal gyrus, as well as in the left cerebellum, the left hippocampus and right inferior frontal triangular gyrus were observed for the contrast “animal” (Figure 6). The contrast “food” produced a large network of significantly activated areas comprising: the right cerebellum and right fusiform area, the right superior temporal gyrus, the bilateral inferior parietal gyrus, the right inferior frontal operculum, the right precentral and postcentral gyrus, as well as the bilateral supplementary motor area, the right superior frontal gyrus, and the right insula (Figure 7). Both fusiform gyri / inferior temporal gyri, bilateral supplementary motor areas as well as the right superior and medial temporal gyrus, the left inferior frontal operculum, the left pre- and postcentral gyrus, the bilateral anterior cingulum and the left cerebellum were significantly activated when contrasting the condition “human” against baseline (Figure 8). The contrast “tool” elicited a

significant activation pattern comprising the left cerebellum, the left fusiform gyrus, the left postcentral gyrus, the left inferior occipital gyrus, the left inferior parietal gyrus, the left thalamus and hippocampus, and the right pre- and postcentral lobe, the right inferior frontal operculum, the right insula, the right inferior frontal orbital gyrus, the right medial / inferior temporal lobe, and the basal ganglia (Figure 9).

The contrast “living”, consisting of the “animal” and the “human” condition elicited significant activation in the right fusiform area and the left fusiform gyrus / inferior temporal gyrus, the left cingulum, the superior-medial frontal gyrus, the bilateral supplementary motor area, the left medial-superior frontal gyrus, and the right superior / medial frontal gyrus (Figure 10).

The “nonliving” contrast, comprising “food” and “tool”, showed significant activation of the left and right fusiform area, the left cerebellum, the left and right cingulum, the left medial-superior and inferior frontal gyrus, the inferior frontal triangular and orbital gyrus, the left superior occipital gyrus and cuneus, the left insula, the bilateral supplementary motor area and the right hippocampus and parahippocampus (Figure 11).

To summarize, each contrast resulted in a large number of significantly activated areas, more than in healthy controls. The network involved in semantic processing in schizophrenic patients, comprised orbitofrontal, inferior frontal and prefrontal regions, the anterior cingulum, temporal and parietal areas, as well as the TOP junction. Activations were often bilateral, a strong overall lateralization to the left hemisphere was not observed, since three contrasts (“animal”, “food” and “human”) elicited their strongest activation in the right hemisphere.

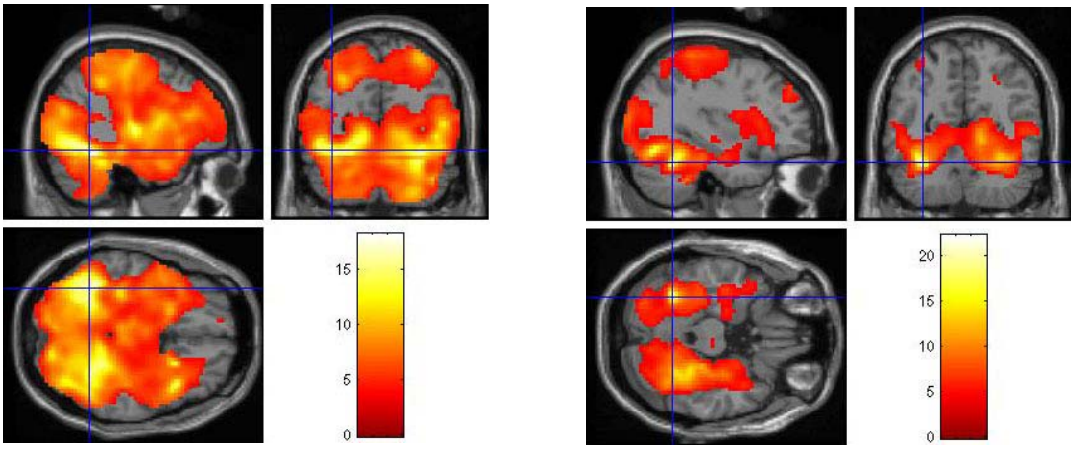


Figure 5: Contrasts for the condition “main”, left for controls, right for patients

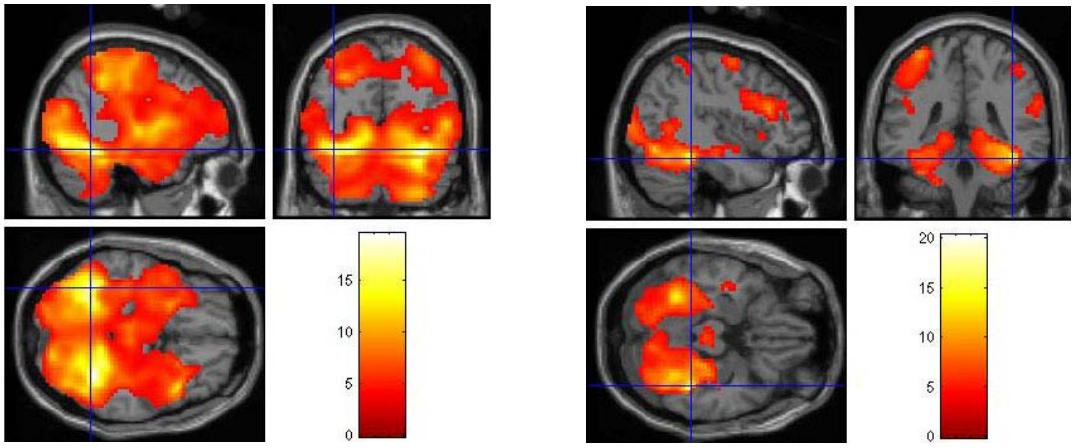


Figure 6: Contrasts for the condition “animal”, left for controls, right for patients

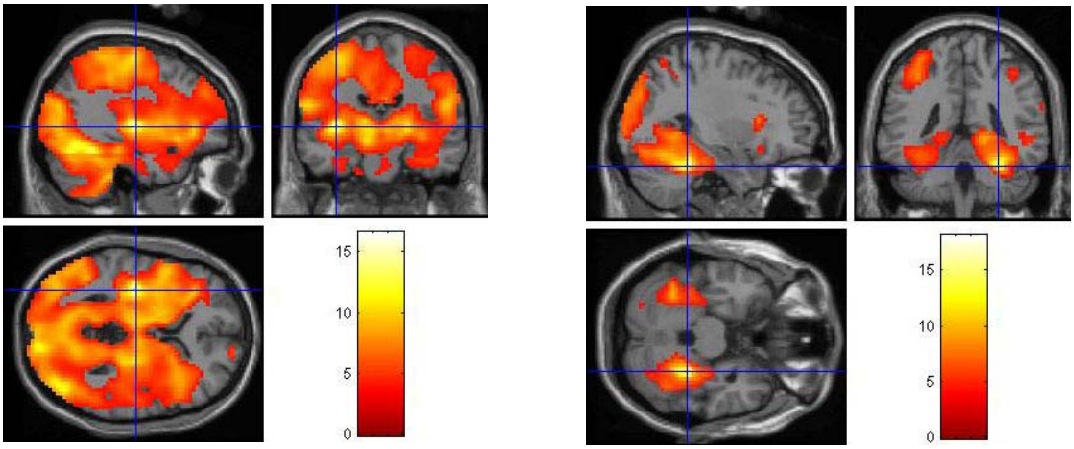


Figure 7: Contrasts for the condition “food”, left for controls, right for patients

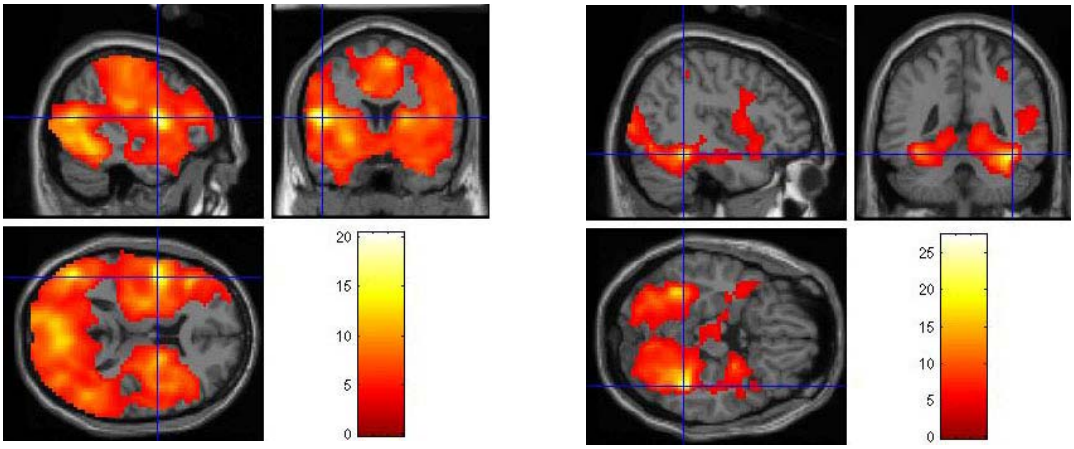


Figure 8: Contrasts for the condition “human”, left for controls, right for patients

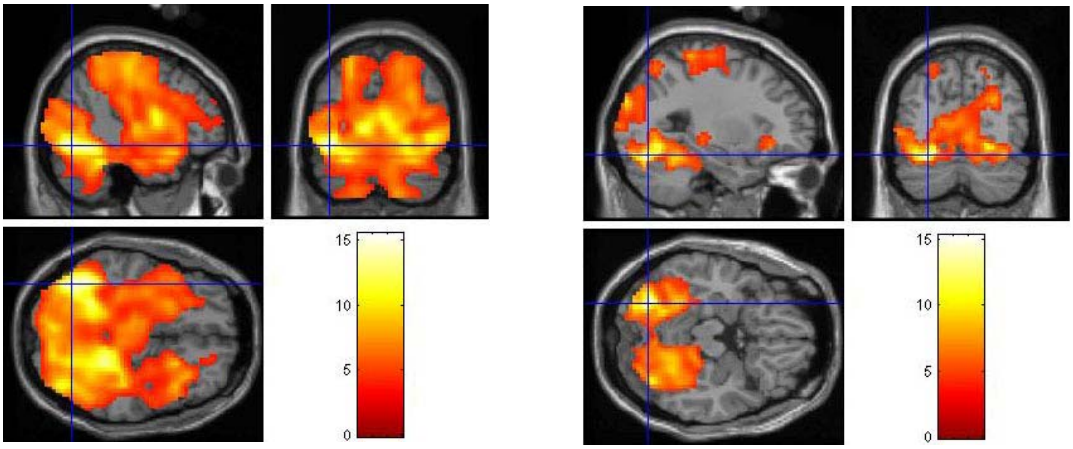


Figure 9: Contrasts for the condition “tool”, left for controls, right for patients

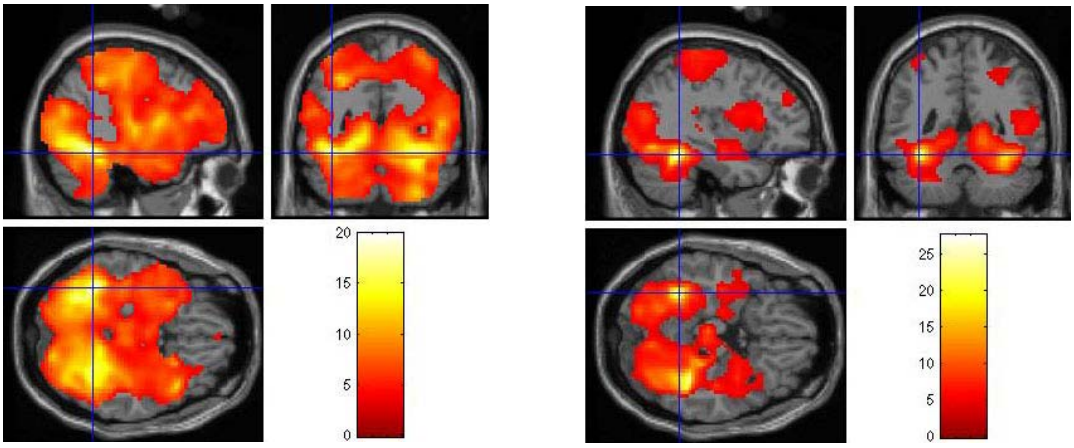


Figure 10: Contrasts for the condition “living”, left for controls, right for patients

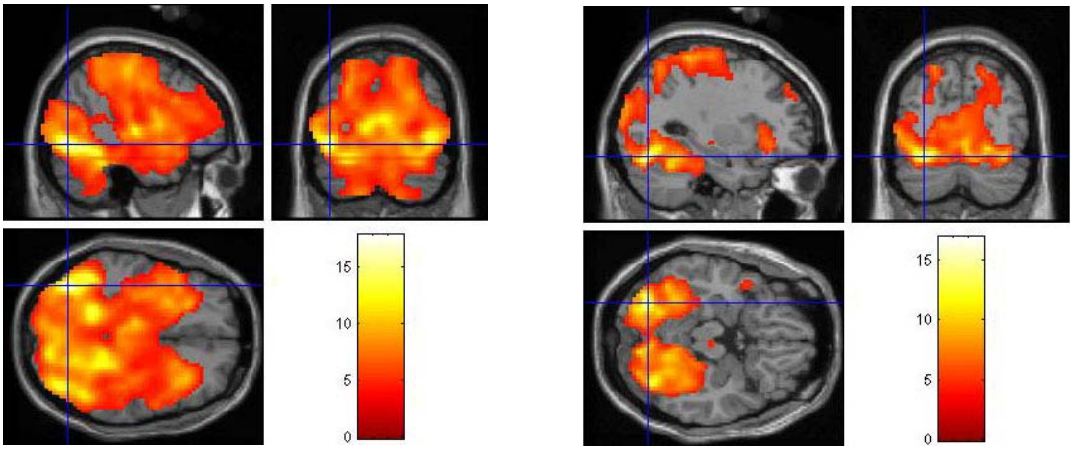


Figure 11: Contrasts for the condition "nonliving", left for controls, right for patients

3.2 Representation of differential contrasts in healthy controls

In a second-level analysis differential contrasts of the four basic conditions and the 2 domains "living" and "nonliving" were calculated in healthy controls. Only a few differential contrasts resulted in significant activation. Contrasts where the condition "food" was subtracted from the conditions "animal" or "human" resulted in higher activation, as well as when "tool" was subtracted from "food" or "human". The "living vs. nonliving" contrast elicited significant activation of the right medial / inferior temporal gyrus and the left precuneus. Results are described in detail below and a complete overview is given in Table 7.

3.3.1 Animal vs. food, human, and tool

In the contrast "animal vs. food" a cluster located in the right medial occipital gyrus and adjacent to the inferior temporal gyrus (TOP junction) reached a trend towards significance. Another cluster, comprising the right hippocampus and right precuneus, was activated, however not significantly when considering the corrected p value. Other clusters were located in the left inferior occipital gyrus and the left temporal lobe.

The differential contrast "animal vs. human" did not elicit any significantly active brain region. Three somewhat larger clusters, in the left medial / superior

occipital gyrus, the right inferior parietal / angular gyrus and in the left insular gyrus / inferior frontal gyrus were activated, yet, not significantly. The contrast “animal vs. tool” did not even result in clusters comprising at least 5 voxels.

3.3.2 Food vs. animal, human, and tool

The contrast “food vs. animal” did not show any clusters comprising more than 4 voxels. In the contrast “food vs. human” the left inferior frontal gyrus was activated, as well as a cluster located in the left superior / medial occipital gyrus, both however not significantly.

The third contrast, “food vs. tool” elicited a significantly active cluster in the left medial occipital / angular gyrus, see also Table 7 and Figure 12.

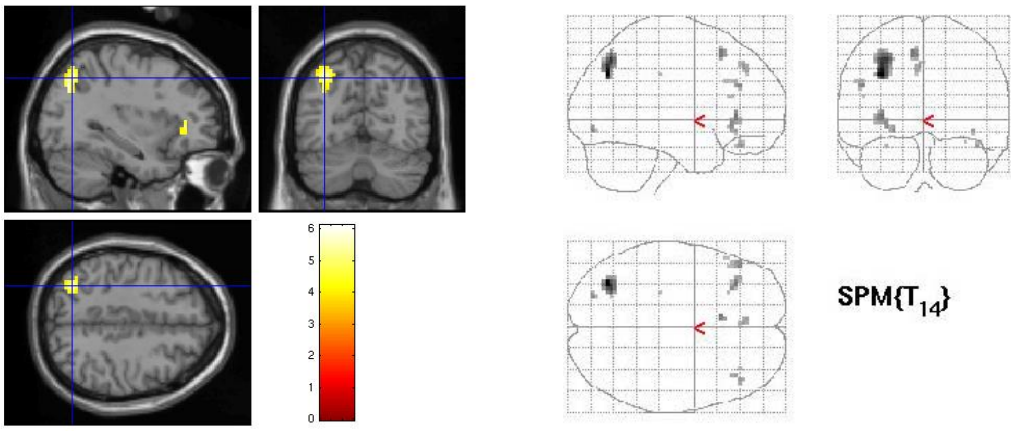


Figure 12: Differential contrast “food vs. tool” in healthy controls

3.3.3 Human vs. animal, food, and tool

The contrast “human vs. animal” did not significantly activate brain regions, but yielded a cluster located in the left medial temporal gyrus / angular gyrus. The contrast “human vs. food” resulted in a network comprising the significantly activated predominantly right rectus gyrus and clusters (however not significant) in the right medial / superior temporal gyrus, in the left TOP junction, as well as in the right precuneus / cuneus (see also Figure 13).

The contrast “human vs. tool” showed activation reaching a trend towards significance in the following brain regions: the right medial / inferior temporal gyrus (TOP junction), and the bilateral precuneus / cuneus. Clusters in

the right fusiform cortex / inferior temporal gyrus, the left angular / medial temporal gyrus and the bilateral rectus gyrus were also activated to a greater extent, however not significantly when considering the corrected p value.

3.3.4 Tools vs. animals, human and food

The two contrasts “tool vs. animal” and “tool vs. food” did not result in any significant brain area activation, while the contrast “tool vs. human” elicited neural activation in the right medial-superior occipital gyrus, yet not significantly. Activated clusters were also found in the left medial/superior occipital gyrus, yet again no significance was observed.

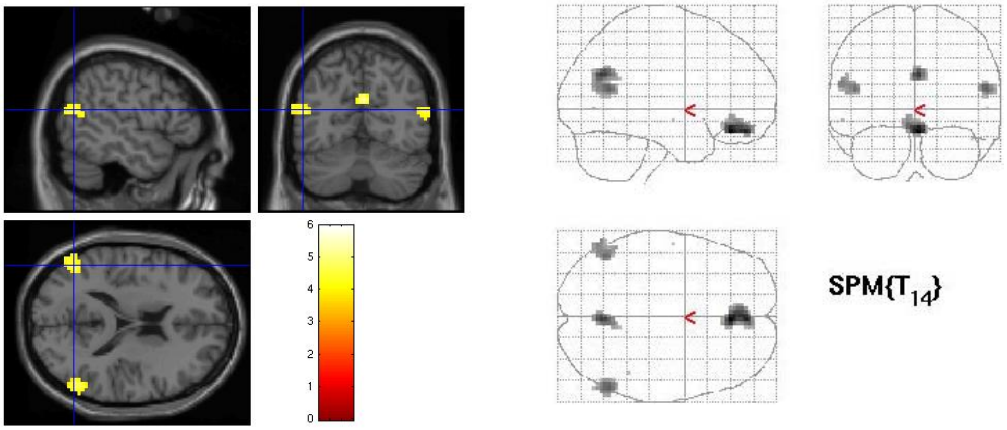


Figure 13: Differential contrast “human vs. food” in healthy controls

3.3.5 Living vs. nonliving and vice versa

In this differential contrast activations obtained from the “living” condition (“human”, “animal”) were contrasted with activations obtained in the “nonliving” condition (“food”, “tool”). This contrast “living vs. nonliving” resulted similar regions as the “human” contrasts. Significant activation was obtained in the right medial / inferior temporal gyrus and the left precuneus. It also produced activated clusters in the left medial / inferior occipital gyrus and left medial / superior occipital gyrus (TOP junction). Another cluster was activated in the left medial orbital frontal gyrus (see also Figure 14). The opposite contrast “nonliving vs. living” did not show any suprathreshold voxels.

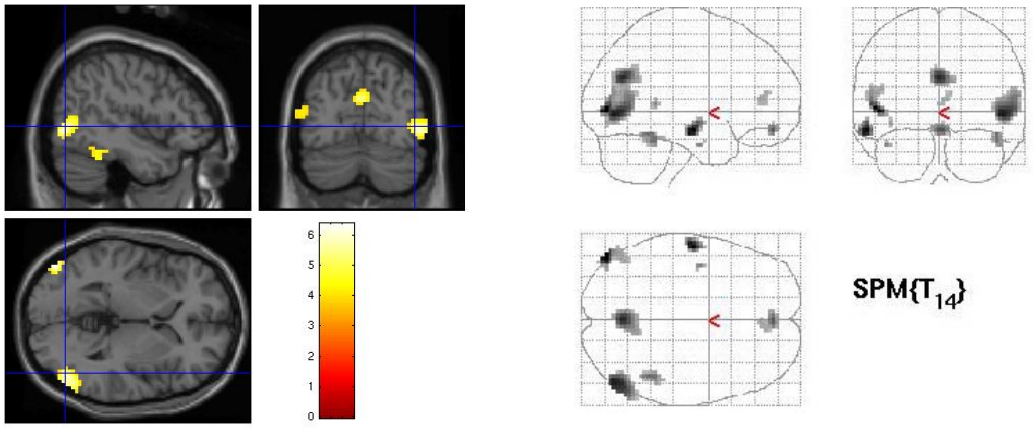


Figure 14: Differential contrast "living vs. nonliving" in healthy controls

3.4 Representation of differential contrasts in patients

When calculating differential contrasts of the four different conditions and the 2 domains "living" and "nonliving" in patients, even less contrasts than in healthy controls resulted in activated brain regions. Many contrasts did not even show any suprathreshold voxels. Only the contrast "human vs. tool" reached significant activation in a region in the medial-superior temporal gyrus. The contrast "living vs. nonliving" elicited regions similar to those in the corresponding contrast in healthy controls, yet not significantly. More details are given below, and for a complete overview on the results see Table 8.

3.4.1 Animal vs. human, tool, and food

Out of these three differential contrasts only the "animal vs. human" contrast resulted in a higher activation of the left supplementary motor area / superior frontal gyrus, but this was not significant. To a lower degree also the right supplementary motor area was activated. The contrast "animal vs. tool" resulted in small, not significantly activated brain regions, like the right inferior / medial occipital gyrus and the right medial superior temporal gyrus and the left medial /

inferior frontal gyrus. The contrast “animal vs. food” did not show any suprathreshold voxels.

3.4.2 Food vs. animal, human, and tool

While the differential contrast “food vs. animal” did not show any suprathreshold voxels, the contrasts “food vs. human” resulted in a small cluster in the left lingua / precuneus are. The “food vs. tool” contrast did not elicit any significantly activated brain region.

3.4.3 Human vs. animal, food and tool

While the contrast “human vs. animal” did not produce suprathreshold voxels and the contrast “human vs. food” did not result in any significant activation, the differential contrast “human vs. tool” elicited significant activation of the right superior / medial temporal gyrus, as shown in Figure 15.

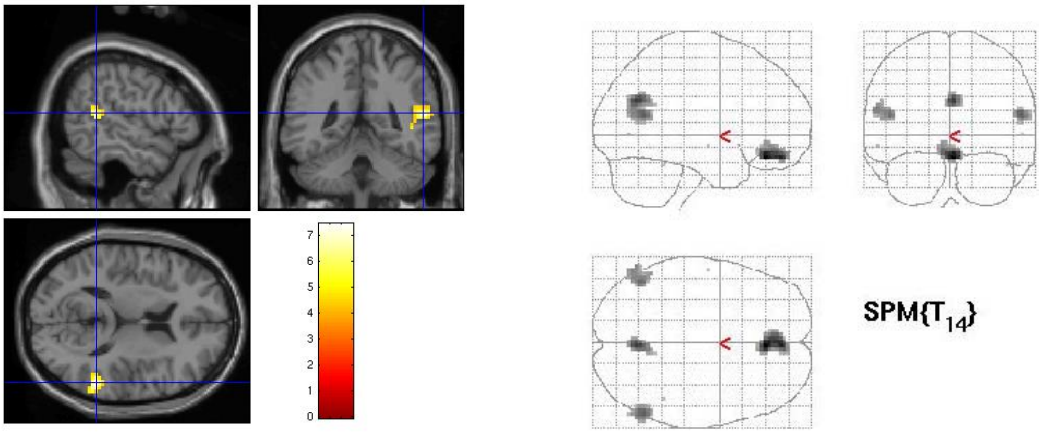


Figure 15: Differential contrast “human vs. tool” in patients

3.4.4 Tool vs. animal, human and food

The differential contrasts “tool vs. animal” and “tool vs. food” did not show any suprathreshold voxels, nor did the contrast “tool vs. human” yield any significant activation.

3.4.5 Living vs. nonliving and vice versa

The differential contrast “living vs. nonliving” revealed a network of (however not significantly) activated brain regions (see Figure 16), comprising the left TOP junction and the right medial / superior temporal gyrus, whereas the contrast “nonliving vs. living” did not result in any suprathreshold voxels.

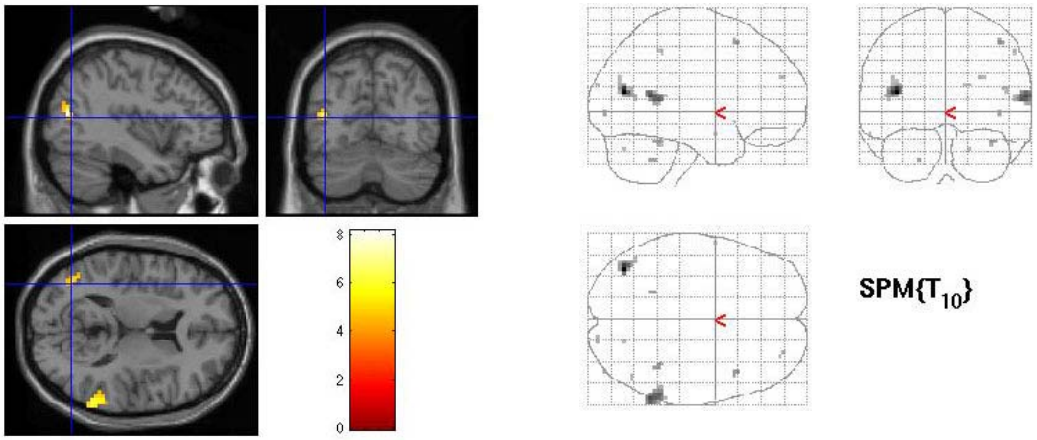


Figure 16: Differential contrast “living vs. nonliving” in patients

3.5 Comparison of patients and healthy controls

Two-sample analyses were calculated by comparing 11 patients and 11 matched controls for the four conditions (plus “main”) and the domains “living” and “nonliving”. Again, significant activations were rarely obtained, only the conditions “main”, “human” and “tool” elicited some activation, however, this was only the case for the “patient vs. controls” contrasts. Additionally, two-sample analyses were also calculated for the “living vs. nonliving” differential contrast, which did not elicit any activation when considering the standard thresholds. All results are explained in the following and shown in Table 9 - 15.

3.5.1 Two-group comparison for the condition “main”

The two-group comparison “patients vs. controls” showed significant activation of the right putamen and the right insula, as well as a non-significant activation in the left inferior and right superior orbital frontal gyri and in the right temporal lobe, see Table 9 and Figure 17. The opposite comparison did not result in any suprathreshold voxels.

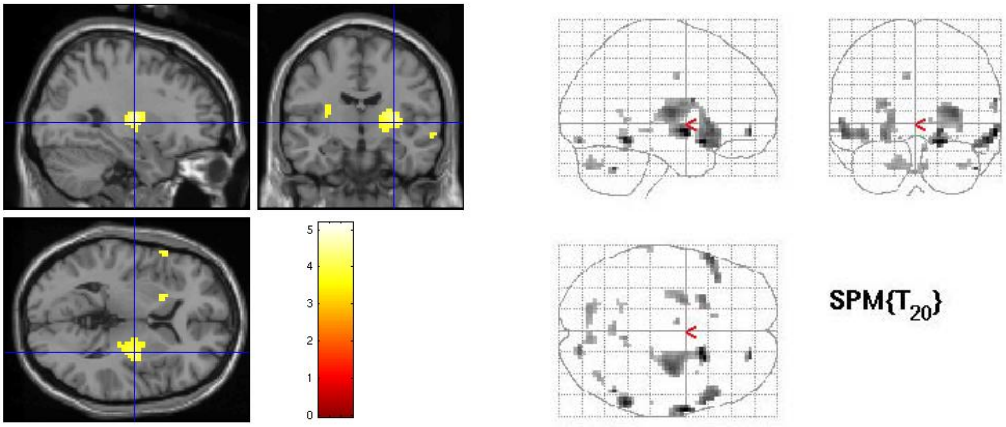


Figure 17: Two-group comparison “patients vs. controls” for the condition “main”

3.5.2 Two-group comparison for the condition “animal”

The two-group comparison “patients vs. controls” did not result in significant brain activation but showed some activated cluster in the left cerebellum, basal ganglia, and thalamus (see Table 10). The opposite comparison “controls vs. patients” did not show any suprathreshold voxels.

3.5.3 Two-group comparison for the condition “food”

As in the previous comparison, also the two-group comparison “controls vs. patients” for the condition “food” did not show any suprathreshold voxels nor did the opposite comparison “patients vs. controls” result in significantly activated brain regions. However, a network of activated clusters comprising the right cerebellum, the right superior frontal orbital gyrus, the right superior temporal gyrus, the bilateral cuneus and the left inferior triangular / orbital frontal gyrus was observed, see Table 11.

3.5.4 Two-group comparison for the condition “human”

The two-group comparison “patients vs. controls” elicited higher activation of the bilateral inferior frontal orbital /rectus gyri, the left lingua / fusiform area and the bilateral putamen, however not reaching significance or a trend, as shown in Table 12. The opposite comparison “controls vs. patients” for the condition “human” did not show any suprathreshold voxels.

3.5.5 Two-group comparison for the condition “tool”

The two-group comparison “patients vs. controls” for the condition “tool” revealed significant activation of the right putamen and right insula (Figure 18), and higher activation of a network of cluster located in the right orbital frontal gyrus, the left medial / inferior frontal gyrus, the left fusiform area and parahippocampus, the left cuneus / superior occipital gyrus, the left putamen / insula, the right cingulum, and the right thalamus. The opposite comparison “controls vs. patients” for the condition “human” did not show any suprathreshold voxels, see Table 13.

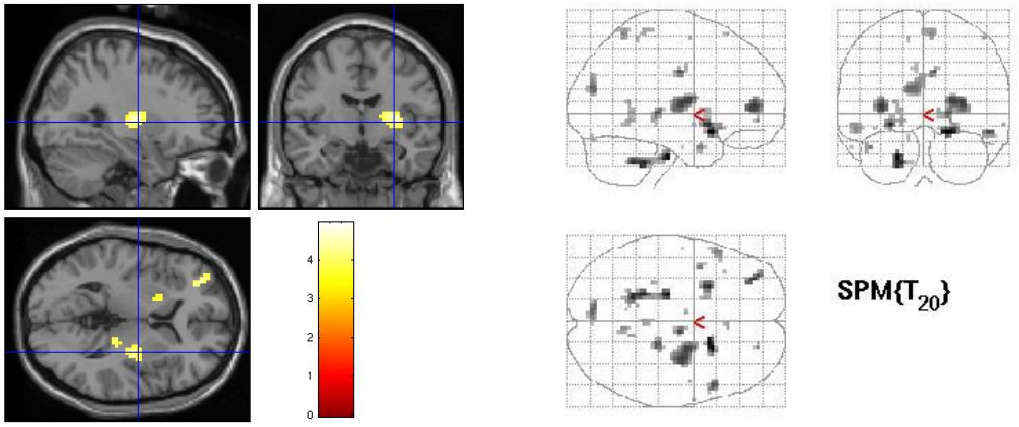


Figure 18: Two-group comparison “patients vs. controls” for the condition “tool”

3.5.6 Two-group comparison for the condition “living”

The two-group comparison for the category “living” resulted in activation of the following areas: the left cerebellum, the right putamen and right insula which reached a trend towards significance. The right cerebellum, the left and right superior orbital frontal gyri were also activated; as well as areas in the right

temporal lobe, see also Figure 19 and Table 14. The comparison “controls vs. patients” for the condition “living” did not elicit any suprathreshold voxels.

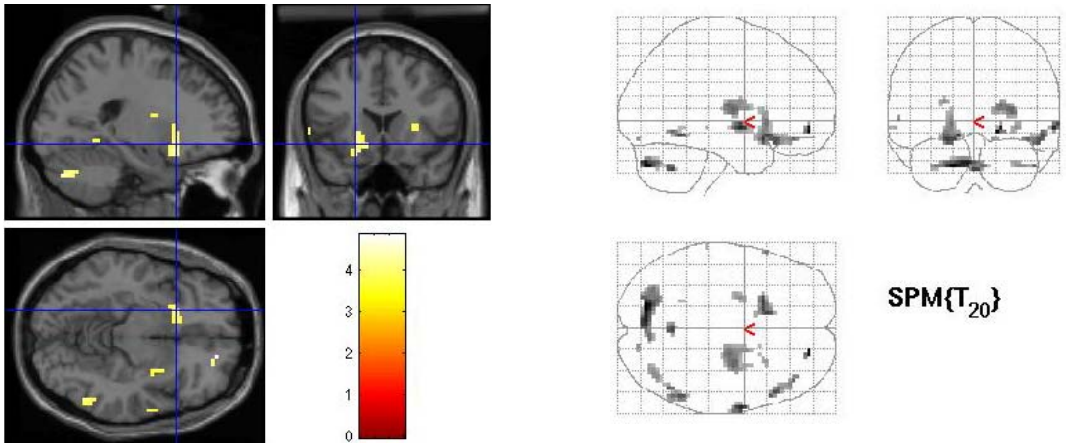


Figure 19: Two-group comparison “patients vs. controls” for the condition “living”

3.5.7 Two-group comparison for the condition “nonliving”

The two-group comparison “patients vs. controls” revealed activation of the left superior / medial temporal gyrus which reached a trend towards significance, as shown in Figure 20 and Table 15. Additional activation was found in a network comprising the right orbital frontal gyrus, the right superior / medial temporal gyrus, the bilateral cuneus, and the right and left putamen and insula, yet not significantly. The opposite comparison “controls vs. patients” for the condition “nonliving” did not show any suprathreshold voxels.

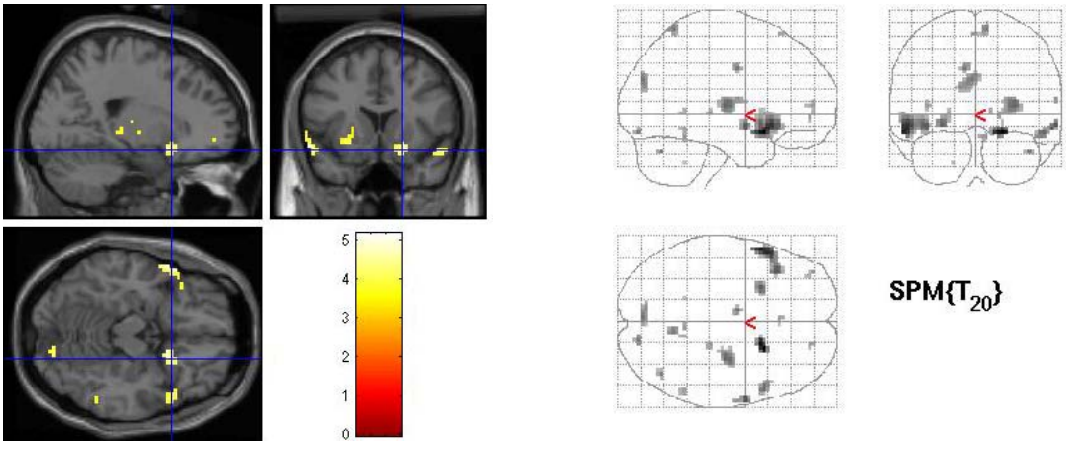


Figure 20: Two-group comparison “patients vs. controls” for the condition “nonliving”

3.5.8 Two-group comparison between differential contrasts “living” and “nonliving” in patients and controls

The two-group comparison [living vs. nonliving]$_{controls}$ minus [living vs. nonliving]$_{patients}$ did not lead to significantly activated clusters of at least 5 voxels.

However, in two areas little activation was found: in the left TOP junction and in the anterior STS, as shown in Table 16 and Table 17. After performing a small volume correction with a sphere (search radius 15mm), the activation of the left TOP junction [MNI -39 -72 15; puncorr<0.001; z=3.32] reaches a statistical significance of pFWE-corr =0.041* after correction for multiple testing. The second activation in this differential contrast in the anterior STS [MNI -54 15 -21 puncorr<0.001; z=3.15] reaches significance (p=0.026*) after correction with a 10 mm sphere. The opposite comparison for patients did not yield any activated clusters.

3.6 Effect of arousal and valence

Including arousal and valence ratings of IADS pictures as covariates did not have a strong effect on the representation of semantic categories. Not a single contrast which was correlated either positively or negatively with these covariates elicited any significant activation.

3.6.1 Single contrasts with covariates

Both caudate nuclei are activated in healthy individuals when evaluating the influence of arousal on control group contrasts, while the left thalamus and pallidum were activated in the corresponding contrast for the patient group. The negative correlation of arousal did not elicit any activation patterns.

Correlation of valence with patient or control group contrasts did not reveal any activation. The negative correlation of group contrasts with valence elicited activation of the left precentral cortex in healthy individuals, however not in patients (see Table 18)

3.6.2 Differential contrasts with covariates

When regarding the differential contrast “patients vs. controls” correlated with arousal, the right anterior cingulum and the left middle temporal cortex were activated, equal to the negative correlation of the differential contrast “controls vs. patients” with arousal. Neither the negative correlation of the group contrast “patients vs. control” with arousal, nor the positive correlation of the contrast “controls vs. patients” with arousal elicited activation.

The group contrasts or patients and controls correlated positively and negatively with valence did not result in any supratheshold activation (see Table 19).

4. Discussion

4.1 Results

In this section, results will be discussed in relation to findings in lesion studies and previous functional imaging studies which have investigated category-specific impairments and activations. In the following part, the activations seen in schizophrenic patients will be compared to those found in healthy controls.

4.1.1 Main contrasts in controls

Within-group single contrasts against baseline for all 15 controls resulted in significant but widespread activation of the brain for all conditions. Despite a network–like distribution, strongest activations were obtained with predominance for the left hemisphere in most contrasts. Thus, in single contrasts we saw a lateralized semantic network, with all categories being processed in the same hemisphere. Contrary to neuroimaging studies showing a preferential processing of "living" in the right hemisphere [e.g. Leube *et al.* 2001]; and brain lesion studies where "living" was also shown to be represented in the right hemisphere [Tranel *et al.* 1997] and "nonliving" was represented in left brain areas [Tranel *et al.* 1997; Gainotti 2000], domain-specific preferences for a hemisphere were not observed in this work.

In the following, individual results for each condition will be discussed in relation to previous findings in healthy subjects. However, one region commonly activated in **all conditions** was the fusiform gyrus / inferior TOP junction, part of the ventral object processing stream. It has already been associated by previous studies with the representation of visual object features (form) and the processing of predominantly living concepts [Kanwisher *et al.* 1997, Chao *et al.* 1999, Leube *et al.* 2001, Thompson-Schill *et al.* 1999, Perani *et al.* 1995].

In the **"animal" condition** the left fusiform area / inferior TOP junction constituted the strongest activated region. Additional activations were also found in the corresponding right area and in the adjacent right parahippocampal

gyrus. This region has been associated with retrieving semantic information from episodic memory [Shallice *et al.* 1994].

The contrast for the **condition "human"** also produced activation in the left fusiform / TOP junction area; yet, stronger signals were achieved in a region located in the left inferior frontal gyrus / rolandic operculum, a region also known as Broca area. The Broca area is part of the frontal lobe and critically involved in speech production, together with the Wernicke area in the temporal lobe they constitute the classical "language" area. The left inferior frontal gyrus / rolandic operculum can also be interpreted as being part of the "social brain", involved in representing actions and goals [Frith & Frith 1999]. Mirror neurons were found to be located in this area, active during imitation, execution and observation of action [for a review, see Iacoboni & Dapretto 2006], helping to better understand others and possibly to develop a theory of mind.

In the **"food" condition**, instead of the left fusiform gyrus / TOP junction area, its right counterpart was significantly activated; however, the strongest activation was elicited in the left insular and superior temporal gyrus. The activity in the insula is related to taste perception [Simon *et al.* 2006], which constitutes an important aspect of "food" processing. The superior temporal gyrus is associated with various functions [e.g. Allison *et al:* 2000]; however, in this case it might contain higher-order association areas for taste processing, as its activation was for example found during chocolate tasting [Smeets *et al.* 2006].

The strongest significant activation for the "**tool" condition** was, again, found in the left fusiform gyrus / TOP junction. However, the activation in the fusiform / TOP junction area for the "tool" condition was situated more laterally than the region activated by the "animal" condition. It has been described that the activity of the fusiform gyrus is modulated by categories, with its activation being stronger influenced by living entities than by nonliving objects [Perani *et al.* 1999, Thompson-Schill *et al.* 1999]. However, "nonliving" things are able to activate the fusiform gyrus, as our results show. A study by Chao and colleagues demonstrated that the lateral fusiform gyrus is activated more by animals and the medial fusiform gyrus is stronger activated by tools (Chao *et al.* 1999, Chao *et al.* 2002). Yet, the results we obtained were exactly the opposite.

This could be due to the different stimulus material, since we used pictorial stimuli instead of displaying simple items, leading to additional activation of adjacent areas.

The **contrast "living"** consisting of the "animal" and "human" condition elicited activation in the left fusiform area / TOP junction and the left inferior frontal / rolandic operculum, thereby being influenced by both conditions and giving an understandable result. Significant activation in the more lateral left inferior TOP junction and fusiform area was found in the **"nonliving" contrast** (localized more lateral and posterior than in the "living" contrast), therefore mostly being influenced by the "tool" contrast. Perhaps the contrast "food" was not defined clearly enough as being strictly part of the "nonliving" domain, as some foods have been "living" entities before.

Thus, we found activation in the fusiform gyrus for nonliving objects, an area already known for being involved in processing categories. However, more typical "tool" areas, like the left posterior middle temporal gyrus and the left premotor and left posterior parietal cortex were not activated. The left posterior middle temporal gyrus was consistently activated throughout various studies by artefact concepts, especially tools [Martin *et al.* 1996, Chao *et al.* 1999; Perani *et al.* 1999; Thompson-Schill *et al.* 1999, Beauchamp *et al.* 2002]. It was also shown to be active even when subjects did not perform any action but simply generated action words [Martin *et al.* 1995]. The left premotor and left posterior parietal cortex were strongly associated with tools in many studies [Chao & Martin 2000; Chao *et al.* 2002; Martin *et al.* 1996) and are thought to be linked to motor-control and motor-imagery, additionally the left premotor area is thought to be responsible for retrieving and selecting information from semantic memory [Thompson-Schill *et al.* 1999].

4.1.2 Main contrasts in patients

Within-group single contrasts for schizophrenic patients elicited a spatially more distributed activation throughout a wide range of brain regions, without a consistent predominance of the strongest significant areas in one hemisphere. Again, the fusiform gyrus was significantly activated in all conditions. In addition, the cerebellum was also activated in all contrasts. In the following, results for

each condition will be discussed individually and in relation to each other to those obtained in healthy controls.

In the **"animal" condition** both fusiform gyri were activated, with a predominance of the right hemisphere. Additionally to significant activation of the left superior temporal gyrus (STS), a region involved in processing biological motion [Puce & Perrett 2003, Giese & Poggio 2003] and the theory of mind [Frith & Frith 1999], there was significant activation in the right inferior triangular gyrus, part of the Broca area. This activation can be seen in relation to findings by Leube and colleagues [Leube *et al.* 2001] where animals elicited activation in this area, however in healthy subjects.

When contrasting the **condition "human"** against baseline, the right STS and bilateral fusiform gyri were activated; and the right fusiform gyrus was activated the strongest; approximately in the same area as the activation of the "animal" condition. Bilateral supplementary motor and left prefrontal areas, the left inferior frontal operculum, the bilateral anterior cingulum were also activated; regions involved in the processing of "social cognition" [Adolphs 2003]

The **condition "food"** also yielded the strongest signals in the right fusiform gyrus, however this time the activation was located more medially than in the "animal" and "human" condition, corresponding to studies [Chao *et al.* 1999, Perani *et al.* 1999] where nonliving objects were represented in the medial fusiform cortex. Additionally, the right superior temporal gyrus, the right inferior frontal operculum, the right prefrontal gyrus, as well as the bilateral supplementary motor areas, were also activated. These regions were seen in the "human" contrast and make sense as representing the "social brain". However, in the "food" condition, the activation of these results remains unclear. The right insula and left supramarginal gyrus were also activated. In a study by Martin [Martin *et al.* 1996] the right supramarginal gyrus was activated by nonliving objects. The activation of the right insula could be seen as the only "food"-specific activation.

The **condition "tool"** resulted in significant activation of both fusiform gyri, however in this case, the left one was stronger activated, together with significant activation of the right insula and activation in the bilateral prefrontal

and inferior parietal areas. These latter mentioned areas correspond to a network of motor-associated areas [e.g. Halsband & Lange 2006] and could be involved in the functional processing of “nonliving” objects.

In both contrasts “living” and “nonliving”, both fusiform gyri were activated, the strongest significant activation was located in the left fusiform gyrus although the individual contrasts, apart from the “tool” condition, showed stronger activations in the right hemisphere. Yet again, the area for the “nonliving” condition was located more laterally than in the “living” contrast, similar to the location of the “tool” contrast. These results constitute the exact opposite of results obtained in other studies [e.g. Chao *et al.* 1999] Both contrasts elicited additional activation in the left anterior cingulum and bilateral supplementary motor areas. Further, the “nonliving” contrast resulted in activated frontal, parahippocampal and occipital areas. These regions might be interpretated as higher association areas involved in visual object processing [Miyashita & Hayashi 2000, for a general overview see Van Hoesen 1993].

Thus, similar regions were activated by patients and controls, e.g. the fusiform gyrus. However, single contrasts in schizophrenic patients elicited a larger number of significant regions which were spatially more distributed across the brain. Contrasts of healthy controls elicited focussed activation limited to a small number of regions with the strongest signals obtained in the left hemisphere, contrary to equal activations of both hemispheres for patients. These observations could support the assumption that semantic networks are more distributed and spatially diffuse in schizophrenics, thereby leading to typical symptoms like delusions or formal thought disorder [Goldberg *et al.* 1998; Aloia *et al*. 1998; Spitzer *et al*. 1993; Weisbrod *et al.* 1998].

4.1.3 Differential contrasts in controls

To gain more insight into more specific effects of the different conditions, we calculated a second - level model with differential contrasts.

They were calculated for all conditions within the control group. However, significant activations were obtained for only a few contrasts; namely “food vs. tool”, “human vs. food”, and “living vs. nonliving”. Some other contrasts did not even produce clusters containing at least 5 voxels, e.g. “animal vs. tool”, “food

vs. animal" , "tool vs. animal", and "nonliving vs. living". In contrast with strong activations, signals were distributed equally across both hemispheres; no preference for one side could be detected. Especially in the "human" and "living" contrasts a symmetric pattern of activated brain regions was obtained. This is contrary to the single contrast findings of a lateralized network of activations involved in semantic processing of all conditions. Below, individual results are discussion in relation to previous findings.

The differential contrasts for the "animal" condition vs. other conditions elicited distributed and rather unspecific activations, among those, however, the bilateral TOP junctions and the right precuneus, as well as the right inferior parietal / angular gyrus and the left insula / inferior frontal gyrus. The contrast "animal vs. tool", often investigated by previous studies [for a review see Martin & Chao 2001] did not elicit any activations.

The "human vs. others" contrasts elicited a network of strong and consistently activated regions, comprising the bilateral TOP junctions and the predominantly right precuneus, like in the "animal vs. food" condition, but also the bilateral rectus gyrus and the right fusiform gyrus / inferior temporal gyrus.

In the "living vs. nonliving" contrast the same regions as in the "human" contrast" are activated, together with an additional activation of the left superior temporal gyrus. Besides being involved in the processing of biological motion [Puce & Perrett 2003] and the theory of mind [Brune 2005, Frith & Frith 1999], the STS was shown to be related to faces and animals [Kanwisher *et al.* 1997, Chao *et al.* 1999]. The common activation of the bilateral TOP junctions together with the right precuneus, in "human" and "animal" contrasts, leads to the assumption that these areas are involved in processing especially the "living" domain. The activation at the TOP junction has already been implicated in the analysis of social meaningful animate stimuli [Decety & Grezes 2006; Schultz *et al.* 2005]. The rectus gyri might be responsible for human specific processing. They are part of the orbitofrontal area, which itself belongs to the medial frontal cortex, a region involved in social cognition [for a review, see Amodio & Frith 2006]. The orbitofrontal brain areas have also been implicated before in social cognition by lesion studies and functional imaging studies [Amodio & Frith 2006, Grafman *et al.*, 1996, Leube *et al.* 2001].

Strong activations in the left medial and superior occipital / angular gyrus and the left inferior frontal gyrus were found in the “food vs. others” contrasts, however the “vs. animal” contrast did not elicit any activation. The occipital regions can be seen as part of the visual system; however their explicit activation for this contrast remains unclear. The left inferior frontal gyrus as part of the Broca area is involved in many aspects of language processing [Bookheimer 2002].

The “tool vs. others” contrasts did not produce many activated areas, only in the “vs. human” contrast bilateral medial superior occipital regions were activated; again we do not have an explanation for this specific activation of visual system areas.

The “nonliving vs. living” did not result in any activated clusters; although individual contrasts elicited some activation (see above). This is a finding that is difficult to explain, given the fact that other studies have obtained differential activation in this contrast [e.g. Devlin *et al.* 2002].

4.1.4 Differential contrasts in patients

Contrary to the results obtained in single contrasts, differential contrasts calculated for the schizophrenic patients elicited less activation than in healthy controls. Very few contrasts in patients yielded any activation, and the obtained signals were also less strong. Unlike the single contrasts where similar regions were activated in both groups, differential contrasts in schizophrenic patients resulted in activation of different brain areas.

Again, the “animal vs. others” contrasts elicited a distributed and weak activation, including bilateral supplementary motor areas, right medial temporo-occipital regions (TOP junction) as well as the left inferior frontal gyrus and the left cerebellum. The “vs. food” did not show any strong activation. These regions are in line with findings of other studies [Martin & Chao 2001, Leube *et al.* 2001] investigating the “animal” concept.

In the “human vs. others” condition, stronger activations in the right superior / medial temporal gyrus and the right thalamus / putamen were obtained, however only when subtracting “tool”. Again, the STS activation is

explainable according to previous findings (see above), yet the activation of the thalamus and the putamen seem to be rather unspecific.

In the “living vs. nonliving” contrast we found activation of the left TOP junction and in the right medial / superior temporal gyrus (as in the “human vs. tool” contrast), an expected result, since these two regions were typically identified by previous studies [e.g. Chao *et al*. 1999; Perani *et al.* 1999; Leube *et al.* 2001] as to be involved in the processing of living stimuli.

“Food vs. others” contrasts resulted in very weak activation, only when subtracting “human”, one area was activated: the left lingua / precuneus, a region identified to be involved in the processing of nonliving stimuli [Perani *et al.* 1999]

Similarly, the “tool vs. others” contrasts elicited only weak activation. Only the “vs. food” contrast resulted in activation of the bilateral olfactory gyrus - perhaps a misinterpretation of the anatomical location. One could imagine olfactory gyrus involvement to be more appropriate for the opposite contrast, since the sense of taste and smell are important for the concept “food”. Consequently, as the individual contrasts resulted in only very weak activation, in the “nonliving vs. living” contrast there were no activations.

Comparing the results for schizophrenic patients and their controls, it becomes clear that not only fewer regions are activated in the differential contrasts of the patient group, but that they also show different activation patterns. For example, the contrast “human vs. food” that activates a clear activation pattern in healthy subjects does not elicit any activated regions in schizophrenic patients at all. In the patient group there was no or very little activation when another condition was subtracted from the “food” or “tool” condition. Perhaps this can be interpreted with borders between categories that are not as defined and strict in schizophrenic patients as in healthy controls, therefore differential contrasts, subtracting categories from each other do not result in many activated regions. This might be true for the contrasts of the individual categories. The combined contrasts “living vs. nonliving” and “nonliving vs. living” show similarities in both groups. In the patient “living vs. nonliving” contrast only two areas were activated, the left TOP junction and the right medial / superior temporal gyrus. The same regions, specific for the living

domain, were also activated in the corresponding control group contrast, however with stronger signals. The opposite contrast did not elicit activation in the patient nor the control group. Therefore we suggest the processing of domains to be rather similar in both groups, yet with a reduced activation for “living” in patients, while the processing of categories is different due to diffuse representation and ill-defined borders in schizophrenics.

4.1.5 Two-group comparisons

Given the differing results of patients and healthy controls for the differential controls we calculated two-sample t-tests for each condition. It is striking that only “patients vs. controls” contrasts elicited signals, which were distributed and unspecific, while in the opposite contrasts there were no activated brain areas at all. This reflects the fact that more regions were activated in schizophrenic patients than in controls in single contrasts.

The “animal” contrast elicited activation in the left cerebellum, basal ganglia and thalamus, seeming to be a rather unspecific activation. The “human” contrast elicited activations in the bilateral inferior frontal orbital /rectus gyri, the left lingua / fusiform area, and the bilateral putamen. Similarly, in the “living” contrast, cerebellum, basal ganglia, orbital frontal cortex, and the left fusiform area were activated. Additional activation was found in the right inferior / medial temporal gyrus. Thus, these regions are assumed to be important for “living” processing in schizophrenic patients. In the “food” contrast a network comprising right frontal and temporal regions, as well as the right cerebellum, the bilateral cuneus and the left orbital frontal gyrus was activated. The “tool” contrast activated regions in the left fusiform area, the left cuneus, bilateral orbital frontal gyri, in the right superior temporal gyrus and in the basal ganglia. Some common regions were shared by the two conditions, which is expressed in the “nonliving” contrast which contains the same regions apart from the left fusiform area. These regions can thus be assumed to be responsible for the representation of “nonliving” stimuli in patients.

In the combined contrast $[\text{living vs. nonliving}]_{\text{controls}}$ minus $[\text{living vs. nonliving}]_{\text{patients}}$ very little activation was found. The 2 clusters consisted of only 1 and 2 voxels, respectively; however, the activated regions were interesting:

the left TOP junction and the left superior / medial temporal pole. These regions were already previously described as being involved in the processing of living stimuli. The TOP junction is involved in the analysis of socially meaningful animate stimuli [Decety & Grezes 2006; Schultz *et al.* 2005], while biological motion is processed in the superior temporal sulcus [Puce & Perrett 2003, Giese & Poggio 2003]. The fact that the activation is so low in these contrasts could be due to only small differences in the processing of “living” entities in schizophrenic patients as compared to healthy controls. As already seen in the single and differential contrasts, “living” and “nonliving” were similarly represented in both groups.

4.2 Methodical issues

In this section experimental setup and data analysis will be discussed with respect to their possible effects on the obtained results.

4.2.1 Subjects

We conducted an fMRI experiment with 11 schizophrenic patients and 15 matched healthy subjects. In two-group comparisons we selected 11 controls to match the patients, taking age and gender as matching criteria. In order to draw further conclusions from our results we could have classified and grouped the patients according to the type, stage and severity of their disease, and whether they take medication or not. This might have shown different results for individual subgroups of patients. It would have been interesting to know whether patients classified with formal thought disorder presented different or stronger brain activation as, for example, patients with delusions. However, it would have been necessary to recruit many more patients to have at least 10 in each subgroup for reasonable statistics. Yet, it was already difficult to find this number of patients willing to cooperate, being able to understand the paradigm and being able to carry out the semantic task.

4.2.2 Stimuli

We used 80 IADS (International Affective Picture System) pictures to display the 4 different categories “animal”, “food”, “human”, and “tool”. We chose the IADS system because it provides a large standardised choice of pictures which have already been rated according to arousal, valence, and dominance by a representative US-American sample. We selected 20 pictures for each category and matched them with respect to arousal and valence values to avoid pictures with very emotional or violent content. However, some IADS pictures did not display only one simple item but contain several elements when showing a visually complex scene. In order to use IADS pictures for the investigation of category-specific brain activation we chose pictures which were as unambiguous and simple as possible, and if there was more than one item in the picture, the main object occupied the majority of the space. But the pictures

were not, however, matched according to some kind of measurement of visual complexity, nor were they controlled for equal brightness. This could have caused unwanted effects on some results; however, visual complexity and brightness were not the same in one category, so they might level out across the categories.

Concerning the category “food”, there might be different opinions about the decision which kind of food is strictly nonliving, since there are types of food which were produced out of living entities, like plants or animals. Thus, we chose food which we thought to be as unambiguously nonliving as possible.

4.2.3 Experimental design and data acquisition

In total, 80 pictures were presented with a duration of the scanning time of approximately 16 minutes, short enough for the subjects and especially the patients to keep concentrated. Yet, a continuous run of 16 minutes leads to decreased acquisition quality due to body motion artefacts [van der Kouwe *et al.* 2006]. Thus, multiple shorter runs would have improved the acquisition quality.

The pictures were presented in an event-related design for a short time period of 0.5 seconds each. The event-related design is more closely related to physiological processes in the brain, and with modern fMRI we are able to detect brief stimulus durations and integrate them over time approximating linear summation making block-designs no longer necessary [Rosen *et al.* 1998]. Varying interstimulus intervals (ISIs) between 10.5, 12.5, and 14.5 seconds and the unpredictable onset delay of the picture presentation of 0 to 500 ms produced a jitter effect enabling stimuli onsets to be on every point of the haemodynamic response function (HRF). Thereby, the complete mapping of the HRF prevented a bias. The long ISIs were chosen to allow the blood flow response to rise and then to reach baseline again before presenting a second stimulus. It is also thought to avoid an artificial initial negative response (“the dip”) at stimulus onset, however, one study has shown that the observed dips are not a consequence of short ISI [Yacoub 1999], yet, these results were obtained with a 4T scanner.

The paradigm was designed in an easy understandable way, to keep the experiment as simple as possible for the patients. The subjects were instructed

to decide about the domain of the presented picture (“living” or “nonliving”) and to transmit their decision by pressing a specific button. This ensured the constant attention of the subjects and informed us about their ability to perfom category decision tasks. We considered the independent analysis of the behavioural data (reaction time and correctness of the answers) as not necessarily important for our study. If subjects failed to perform correctly during the experiment they would have been excluded from the group.

4.2.4 Data analysis

Data analysis was performed with SPM2, to detect reproducible and significant brain activation by applying a general linear model [Friston *et al.* 1994] to the time course of each voxel in the activation map. Thereby, the probability of the null hypothesis was tested and regionally specific effects were estimated.

Before statistical analysis we performed preprocessing according to standard procedures. The 5 scans preceding the experimental session to allow T1 saturation were not discarded prior to data analysis. They were thought to have little or no effect on the results, since they constitute less than one percent of the scans. For the statistical model we calculated single and differential contrasts with six conditions (and the main effect) for each group and compared them in a two-sample t-test. Standard model conditions and thresholds were used to ensure statistical reliability. However, with this setting, only few contrasts yielded significant brain activation. Thus, many results we present in this study might not be specific. Perhaps, more subjects or longer scans would have been necessary to obtain reliable and consistent data.

In a second analysis, we decided to include the parameters “arousal” and “valence” in our model as covariates to discover possible effects. However, since no significant activations were detected, we suppose that affective values do not have an effect on semantic categorization.

4.3 Theoretical background

4.3.1 Categorisation in healthy subjects

As brain-lesion studies demonstrated, bilateral temporal regions are important for object-specific information (impaired recognition of living [Warrington 1984; Warrington 1987]), and left prefrontal cortex for the retrieval of lexical and semantic information [Baldo & Shimamura 1998]. Predominance for the representation of animals and persons was found in the right hemisphere [Tranel *et al.* 1997], while impaired recognition of tools was due to lesions in the left hemisphere, in the left TOP junction [Tranel *et al.* 1997], and the left dorsolateral convexity [Gainotti 2000].

Regions identified to be involved in semantic processing are numerous and when concept-related activity is elicited in a certain region, the activation in this area is generally thought to be category specific. Among others, following regions with a preference for one category or concept were most consistently identified by other studies: the posterior ventral temporal cortex / fusiform gyrus (lateral – living, medial – nonliving), the right posterior superior temporal sulcus (pSTS - living), the posterior middle temporal gyrus (nonliving), and the left premotor / posterior parietal cortex (nonliving) [for reviews, see Martin & Chao 2001, Chao *et al.* 2002, Bookheimer 2002].

However, regions are not only activated by one category, but also by other categories, yet to a smaller extent, since the number of categories exceeds the number of brain regions. Thus, object representation is not restricted to a single anatomically distinct area but is widespread, distributed and overlapping. Information about objects shared by members of a category is represented in feature–based maps [Martin 2001].

According to some authors, the distribution of object representation is not random but mirrors the organization of sensory and motor systems (Chao *et al.* 1999; Martin & Chao 2001; Chao *et al.* 2002]. Others suggest the organization of the semantic system to be category-specific instead [Caramazza & Shelton 1998; Caramazza & Mahon 2003]. However, instead of supporting feature based or category specifc organization semantic memory, others [Tyler & Moss 2001; Devlin *et al.* 2002] criticized that precise locations of the obtained

activations are not consistent across studies, nor are they conform to brain-lesion data. In addition, since their studies failed to replicate any category-specific effects [Devlin *et al.* 2002; Pilgrim *et al.* 2002; Tyler *et al.* 2003], they suggest a distributed semantic space where similar concepts are represented close to each other when sharing many highly correlated features.

Each of the different views has its own logical construct of assumptions, with empirical data supporting their hypothesis. Our data support the view that semantic information is processed in a distributed network comprising different brain areas that each contributes to specific features of the object, generating a specific output for each concept. Thus, brain regions are only category-specific to a certain extent; they do not exclusively process only one category and can be activated to a different account by other categories. So a concept of a certain domain or category originated from simultaneous activation of various regions . Another concept is represented by a network of different but overlapping brain regions. Therefore the closest approach to our results is the category-specific view, originally suggested by Caramazza [Caramazza & Shelton 1998].

However it is not to be seen in the sense of a restricted area being responsible for the representation of a certain concept, but rather an activated network of brain regions. A similar proposal has been made by Kiefer [Kiefer & Spitzer 1998] who suggested conceptual knowledge to be represented in a map-like fashion in multiple localisable cortical areas encoding different aspects of knowledge.

This might explain the fact that on one hand stimuli from previous studies (even when presented in a different modality) activate a network overlapping to some extent with the results of the current study. However, on the other hand, there are differences in activation of brain regions across studies, which can be explained by different stimulus material leading to different feature patterns.

4.3.2 Semantic categorisation in schizophrenic patients

Schizophrenic patients are able to classify categories properly [Elvevag *et al.* 2001; Elvevag *et al.* 2005] and to make correct decisions in category discrimination tasks.

The above mentioned results can lead to a better understanding of formal thought disorder in schizophrenia. As seen in the results obtained by calculating single contrasts, more regions were activated in contrasts of patients and they were also spatially more distributed than in healthy controls. This does not necessarily lead to the assumption that category representation is more unspecific in patients. This effect is also known from semantic priming tasks where schizophrenic patients show a stronger indirect priming effect pointing to a faster spreading activation in semantic networks and a related stronger activation in semantic networks [Kuperberg *et al.* 2007].

Regions also involved in processing other tasks, might be activated in semantic processing. This could lead to an association of semantic categories with totally different aspects, effacing the borders between them. Thus, the information output could be disturbed by activating more regions than necessary, leading to confusion of concepts and resulting in incoherence in speech, loosening of association or neologisms, symptoms subsumed as formal thought disorder (FTD).

It has been suggested that these symptoms are caused by a malfunctioning in semantic networks with a loosening of associations due to an uncontrolled semantic spreading in these networks [Spitzer *et al*. 1993; Weisbrod *et al.* 1998; Goldberg *et al.* 1998; Aloia *et al*. 1998; Kircher *et al.* 2001].

Disturbances on the concept level may also form the basis of delusional thinking. Concepts in language contain and transmit an important part of our basic knowledge about reality because the individual concepts are embedded within a framework of theories about the world [Tyler & Moss 2001].

The greater amount of involved regions could be due to a coarser input filter, resulting in a higher amount of information and broader distribution of stores. This could lead to connections with other types of information and modalities, contributing to the formation of delusions. While semantic networks are not activated specifically enough to ensure clear borders between them, concepts contaminate each other and by consequence distort the conceptual reality of schizophrenic patients facilitating the emergence of delusional thinking.

4.3.3 Semantic categorization related to social cognition in schizophrenia

Schizophrenic patients do not only confuse basic general concepts and categories in formal thought disorder, but they also display profound social deficits in behaviour, which leads to a decreased functional outcome in our society. In the present work, we investigated the neural processing of such concepts in patients. The naturalistic stimulus material that was used in our study may have contributed to a valid activation of these social brain networks in the participants such that differences between patients and controls could be assessed.

When looking at the results obtained in healthy controls, we observe a consistent activation of a network comprising the fusiform cortex, the TOP junction, the STS and the inferior frontal cortex. These regions, which have been shown to be involved in social cognition, are typically activated when "living" stimuli are presented or "living" differential contrasts are calculated.

Our results obtained by calculating differential contrasts in patients show a weaker activation of regions involved in the processing of "living" entities. The left TOP junction, being involved in the analysis of social meaningful stimuli [Schultz *et al.* 2005], thereby contributing to processing of social cognition, and considered to constitute a part of the "social brain" [Adolphs 2003] is less strong activated in schizophrenic patients. In addition, also the superior temporal region which is involved in the processing of the theory of mind [Frith & Frith 1999] shows decreased activation. A malfunctioning of these networks might influence social behaviour in schizophrenic patients, e.g. by impairing their ability to understand mental states of others and to make interferences about others' intentions. It was already suggested by others [e.g. Frith 2004; Brune 2005; Brune *et al.* 2007] that an impaired theory of mind is a characteristic symptom in schizophrenic patients.

We conclude that disturbed conceptual representations might lead to a different representation of the own species and prevent the development of social skills resulting in an impaired social behaviour. Thus, an altered representation of socially meaningful stimuli might contribute to social deficits in schizophrenia.

5. Conclusion

Neural representation of conceptual knowledge in healthy subjects has already been investigated by lesion studies, as well as by functional neuro-imaging experiments, resulting in the implementation of mainly three different theories to explain the obtained data. Here, we investigate the representation of semantic concepts by studying the processing of “living” and “non-living” categories in schizophrenic patients, as compared to healthy controls. Distinction between “living” and “nonliving” constitutes an important aspect of social cognition where schizophrenic patients are impaired.

We used a set of complex and naturalistic stimuli from a standardized picture data base (IAPS) to compare the differential brain activation induced by different categorical stimuli (humans, animals, food, tools). 11 schizophrenic patients and 15 healthy controls were measured with fMRI while watching the pictorial stimuli and performing a categorization task (discrimination between “living” and “nonliving” stimuli which were presented in a randomized order).

A fronto-parietal network comprising orbito-frontal regions and regions at the occipito-temporal junction, as well as the superior temporal sulcus (STS) was found to be more strongly activated by “living” stimuli (human, animal) than by “nonliving” stimuli (food, tool), supporting the theory that conceptual knowledge is stored in a specialized network of brain areas, differentially active when representing and processing entities belonging to different categories.

During the differential contrast for the living category (“living” items minus “nonliving” items), schizophrenic patients show less activation in the left occipito-temporal region, a region typically involved in processing cognitive skills important for social behavior. We conclude that an altered representation of socially meaningful stimuli might contribute to social deficits in schizophrenia and discuss how these findings might be connected to the symptoms of formal thought disorder and delusions in schizophrenia.

6. References

Adolphs R.
The neurobiology of social cognition.
Curr Opin Neurobiol. 2001 Apr;11(2):231-9. Review.

Adolphs, R.
Cognitive neuroscience of human social behaviour.
Nat Rev Neurosci. 2003 4(3), 165-78.

Allison T, Puce A, McCarthy G.
Social perception from visual cues: role of the STS region.
Trends Cogn Sci. 2000 Jul;4(7):267-278.

Aloia MS, Gourovitch ML, Missar D, Pickar D, Weinberger DR, Goldberg TE.
Cognitive substrates of thought disorder II: specifying a candidate cognitive mechanism.
Am J Psychiatry. 1998 Dec;155(12):1677-84.

Amodio, DM, Frith, CD.
Meeting of minds: the medial frontal cortex and social cognition.
Nat Rev Neurosci. 2006. 7(4), 268-77.

Ashburner J, Friston KJ.
Nonlinear spatial normalization using basis functions.
Hum Brain Mapp. 1999;7(4):254-66.

Austin J.
Schizophrenia: an update and review.
J Genet Couns. 2005 Oct;14(5):329-40.

Baldo JV, Shimamura AP.
Letter and category fluency in patients with frontal lobe lesions.
Neuropsychology. 1998 Apr;12(2):259-67.

Barsalou, L.W., Solomon, K.O., & Wu, L.L. (1999).
Perceptual simulation in conceptual tasks.
In M.K. Hiraga, C. Sinha, & S. Wilcox (Eds.):
Cultural, typological, and psychological perspectives in cognitive linguistics: The proceedings of the 4th conference of the International Cognitive Linguistics Association, Vol. 3 (209-228). Amsterdam: John Benjamins.

Barsalou LW.
Perceptual symbol systems.
Behav Brain Sci. 1999 Aug;22(4):577-609; discussion 610-60. Review.

Barsalou LW, Kyle Simmons W, Barbey AK, Wilson CD.
Grounding conceptual knowledge in modality-specific systems.
Trends Cogn Sci. 2003 Feb;7(2):84-91.

Barsalou LW.
Grounded Cognition.
Annu Rev Psychol. 2007 Aug;15:1-21

Beauchamp MS, Lee KE, Haxby JV, Martin A.
Parallel visual motion processing streams for manipulable objects and human movements.
Neuron. 2002 Mar 28;34(1):149-59.

Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA.
Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates.
Am J Psychiatry. 2000 Apr;157(4):549-59.

Blair, RJ, Cipolotti, L.
Impaired social response reversal. A case of 'acquired sociopathy'.
Brain 2000 (123), 1122-41.

Bookheimer, S.
Functional MRI of language: new approaches to understanding the cortical organization of semantic processing.
Annu Rev Neurosci 2002 (25), 151-88.

Brett M, Johnsrude IS, Owen AM.
The problem of functional localization in the human brain.
Nat Rev Neurosci. 2002 Mar;3(3):243-9. Review.

Brune M.
"Theory of mind" in schizophrenia: a review of the literature.
Schizophr Bull. 2005 Jan;31(1):21-42. Review.

Brune M, Brune-Cohrs U.
Theory of mind--evolution, ontogeny, brain mechanisms and psychopathology.
Neurosci Biobehav Rev. 2006;30(4):437-55.

Brune M, Abdel-Hamid M, Lehmkamper C, Sonntag C.
Mental state attribution, neurocognitive functioning, and psychopathology: what predicts poor social competence in schizophrenia best?
Schizophr Res. 2007 May;92(1-3):151-9.

Buckley PF, Dayem M, Parker G, Weisser L.
Schizophrenia today: what do we know-and how sure are we?
J Psychiatr Pract. 2001 Jul;7(4):244-6.

Caramazza A, Shelton JR.
Domain-specific knowledge systems in the brain the animate-inanimate distinction.
J Cogn Neurosci. 1998 Jan;10(1):1-34. Review.

Caramazza A, Mahon BZ.
The organization of conceptual knowledge: the evidence from category-specific semantic deficits.
Trends Cogn Sci. 2003 Aug;7(8):354-361.

Chao LL, Haxby JV, Martin A.
Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects.
Nat Neurosci. 1999 Oct;2(10):913-9.

Chao LL, Martin A.
Representation of manipulable man-made objects in the dorsal stream.
Neuroimage. 2000 Oct;12(4):478-84.

Chao LL, Weisberg J, Martin A.
Experience-dependent modulation of category-related cortical activity.
Cereb Cortex. 2002 May;12(5):545-51.

Collins DL, Neelin P, Peters TM, Evans AC.
Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space.
J Comput Assist Tomogr. 1994 Mar-Apr;18(2):192-205.

Couture SM, Penn DL, Roberts DL.
The functional significance of social cognition in schizophrenia: a review.
Schizophr Bull. 2006 Oct;32 Suppl 1:S44-63.

Covington MA, He C, Brown C, Naci L, McClain JT, Fjordbak BS, Semple J, Brown J. Schizophrenia and the structure of language: the linguist's view.
Schizophr Res. 2005 Sep 1;77(1):85-98. Epub 2005 Apr 2. Review.

Damasio AR, Tranel D, Damasio H.
Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli.
Behav Brain Res. 1990 Dec 14;41(2):81-94.

Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR.
A neural basis for lexical retrieval.
Nature. 1996 Apr 11;380(6574):499-505.

Damasio H, Tranel D, Grabowski T, Adolphs R, Damasio A.
Neural systems behind word and concept retrieval.
Cognition. 2004 May-Jun;92(1-2):179-229. Review.

Dapretto, M, Davies, MS, Pfeifer, JH, Scott, AA, Sigman, M, Bookheimer, SY, Iacoboni, M.
Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders.
Nat Neurosci. 2006. 9(1), 28-30.

Decety, J, Grezes, J.
The power of simulation: imagining one's own and other's behavior.
Brain Res. 2006, 1079(1), 4-14.

Devlin JT, Russell RP, Davis MH, Price CJ, Moss HE, Fadili MJ, Tyler LK.
Is there an anatomical basis for category-specificity? Semantic memory studies in PET and fMRI.
Neuropsychologia. 2002;40(1):54-75.

Dickinson D, Bellack AS, Gold JM.
Social/Communication skills, cognition, and vocational functioning in schizophrenia.
Schizophr Bull. 2007 Sep;33(5):1213-20.

Elvevag B, Weickert T, Wechsler M, Coppola R, Weinberger DR, Goldberg TE.
An investigation of the integrity of semantic boundaries in schizophrenia.
Schizophr Res. 2002 Jan 15;53(3):187-98.

Elvevag B, Heit E, Storms G, Goldberg T.
Category content and structure in schizophrenia: an evaluation using the instantiation principle.
Neuropsychology. 2005 May;19(3):371-80.

Emilien G, Maloteaux JM, Geurts M, Owen MJ.
Dopamine receptors and schizophrenia: contribution of molecular genetics and clinical neuropsychology.
Int J Neuropsychopharmacol. 1999 Sep;2(3):197-227.

Erbaş B, Kumbasar H, Erbengi G, Bekdik C.
Tc-99m HMPAO/SPECT determination of regional cerebral blood flow changes in schizophrenics.
Clin Nucl Med. 1990 Dec;15(12):904-7.

Farah MJ, Rabinowitz C.
Genetic and environmental influences on the organisation of semantic memory in the brain: is “living things” and innate category?
Cognitive Neuropsychology. 2003 May; 20(3):401-408

Fox PT, Raichle ME.
Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects.
Proc Natl Acad Sci U S A. 1986 Feb;83(4):1140–1144.

Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ.
Statistical parametric maps in functional imaging : a general linear approach
Hum. brain mapp.1994-1995, vol. 2, no4, pp. 189-210 (1 p.)

Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R.
Analysis of fMRI time-series revisited.
Neuroimage. 1995 Mar;2(1):45-53.

Friston KJ, Zarahn E, Josephs O, Henson RN, Dale AM.
Stochastic designs in event-related fMRI.
Neuroimage. 1999 Nov;10(5):607-19.

Frith CD.
Schizophrenia and theory of mind.
Psychol Med. 2004 Apr;34(3):385-9.

Frith CD, Frith U.
Interacting minds--a biological basis.
Science. 1999 Nov 26;286(5445):1692-5. Review.

Frith CD, Frith U.
Social cognition in humans.
Curr Biol. 2007 Aug 21;17(16):R724-32.

Gainotti G.
What the locus of brain lesion tells us about the nature of the cognitive defect underlying category-specific disorders: a review.
Cortex. 2000 Sep;36(4):539-59. Review.

Garrod S, Pickering MJ.
Why is conversation so easy?
Trends Cogn Sci. 2004 Jan;8(1):8-11.

Giese MA, Poggio T.
Neural mechanisms for the recognition of biological movements.
Nat Rev Neurosci. 2003 Mar;4(3):179-92. Review.

Goldberg TE, Aloia MS, Gourovitch ML, Missar D, Pickar D, Weinberger DR.
Cognitive substrates of thought disorder, I: the semantic system.
Am J Psychiatry. 1998 Dec;155(12):1671-6.

Goodale MA, Milner AD.
Separate visual pathways for perception and action.
Trends Neurosci. 1992 Jan;15(1):20-5. Review.

Grafman, J, Schwab, K, Warden, D, Pridgen, A, Brown, HR, Salazar, AM.
Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study.
Neurology 1996, 46(5), 1231-8.

Green NE, Done DJ, Anthony SH, McKenna PJ, Ochocki M.
Can disorganisation of semantic memory account for the abnormalities of thought in schizophrenia - a controlled experimental study.
Schizophr Res. 2004 Oct 1;70(2-3):233-40.

Grossman M, Koenig P, DeVita C, Glosser G, Alsop D, Detre J, Gee J.
The neural basis for category-specific knowledge: an fMRI study.
Neuroimage. 2002 Apr;15(4):936-48.

Halsband U, Lange RK.
Motor learning in man: a review of functional and clinical studies.
J Physiol Paris. 2006 Jun;99(4-6):414-24. Review.

Hempel RJ, Tulen JH, van Beveren NJ, van Steenis HG, Mulder PG, Hengeveld MW.
Physiological responsivity to emotional pictures in schizophrenia.
J Psychiatr Res. 2005 Sep;39(5):509-18.

Iacoboni M, Dapretto M.
The mirror neuron system and the consequences of its dysfunction.
Nat Rev Neurosci. 2006 Dec;7(12):942-51. Review.

Iritani S.
Neuropathology of schizophrenia: a mini review.
Neuropathology. 2007 Dec;27(6):604-8.

Josephs O, Henson RN.
Event-related functional magnetic resonance imaging: modelling, inference and optimization.
Philos Trans R Soc Lond B Biol Sci. 1999 Jul 29;354(1387):1215-28. Review.

Kanwisher N, McDermott J, Chun MM.
The fusiform face area: a module in human extrastriate cortex specialized for face perception.
J Neurosci. 1997 Jun 1;17(11):4302-11.

Kanwisher N.
Domain specificity in face perception.
Nat Neurosci. 2000 Aug;3(8):759-63. Review.

Kay SR, Fiszbein A, Opler LA.
The positive and negative syndrome scale (PANSS) for schizophrenia.
Schizophr Bull. 1987;13(2):261-76.

Keri S, Szekeres G, Szendi I, Antal A, Kovacs Z, Janka Z, Benedek G.
Category learning and perceptual categorization in schizophrenia.
Schizophr Bull. 1999;25(3):593-600.

Keri S, Kelemen O, Benedek G, Janka Z.
Patients with schizophreniform disorder use verbal descriptions for the representation of visual categories.
Psychol Med. 2004 Feb;34(2):247-53.

Kiefer M, Spitzer M.
The limits of a distributed account of conceptual knowledge.
Trends Cogn Sci. 2001 Nov 1;5(11):469-471.

Kiefer M.
Perceptual and semantic sources of category-specific effects: event-related potentials during picture and word categorization.
Mem Cognit. 2001 Jan;29(1):100-16.

Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK.
Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia.
Psychol Med. 2002 Apr;32(3):439-49.

Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK.
Neural correlates of formal thought disorder in schizophrenia: preliminary findings from a functional magnetic resonance imaging study.
Arch Gen Psychiatry. 2001 Aug;58(8):769-74.

Klose U, Erb M, Raddi A, Grodd W
Funktionelle Bildgebung mit der Magnetresonanztomographie
Electromedia. 1999 ; 67, Heft 1

Kreiman G, Koch C, Fried I.
Category-specific visual responses of single neurons in the human medial temporal lobe.
Nat Neurosci. 2000 Sep;3(9):946-53.

Kubicki M, McCarley RW, Nestor PG, Huh T, Kikinis R, Shenton ME, Wible CG.
Neuroimage. 2003 Dec;20(4):1923-33.
An fMRI study of semantic processing in men with schizophrenia.

Kuperberg GR, Deckersbach T, Holt DJ, Goff D, West WC.
Increased temporal and prefrontal activity in response to semantic associations in schizophrenia.
Arch Gen Psychiatry. 2007 Feb;64(2):138-51

Kurachi M.
Pathogenesis of schizophrenia: Part I. Symptomatology, cognitive characteristics and brain morphology.
Psychiatry Clin Neurosci. 2003 Feb;57(1):3-8. Review.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997.
International Affective Picture System (IAPS): technical manual and affective ratings.
Gainesville: The Center for Research in Psychophysiology, University of Florida.

Lang UE, Puls I, Muller DJ, Strutz-Seebohm N, Gallinat J.
Molecular mechanisms of schizophrenia.
Cell Physiol Biochem. 2007;20(6):687-702.

Leube DT, Erb M, Grodd W, Bartels M, Kircher TT.
Activation of right fronto-temporal cortex characterizes the 'living' category in semantic processing.
Brain Res Cogn Brain Res. 2001 Dec;12(3):425-30.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A.
Neurophysiological investigation of the basis of the fMRI signal.
Nature. 2001 Jul 12;412(6843):150-7.

Logothetis NK.
The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal.
Philos Trans R Soc Lond B Biol Sci. 2002 Aug 29;357(1424):1003-37. Review.

Mandler JM.
Thought before language.
Trends Cogn Sci. 2004 Nov;8(11):508-13.

Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG.
Discrete cortical regions associated with knowledge of color and knowledge of action.
Science. 1995 Oct 6;270(5233):102-5.

Martin A, Wiggs CL, Ungerleider LG, Haxby JV.
Neural correlates of category-specific knowledge.
Nature. 1996 Feb 15;379(6566):649-52.

Martin A, Chao LL.
Semantic memory and the brain: structure and processes.
Curr Opin Neurobiol. 2001, 11(2), 194-201 Review.

Martin A.
The representation of object concepts in the brain.
Annu Rev Psychol. 2007;58:25-45.

Mitchell JP, Banaji MR, Macrae CN.
The link between social cognition and self-referential thought in the medial prefrontal cortex.
J Cogn Neurosci. 2005 Aug;17(8):1306-15.

Mitchell RL, Crow TJ.
Right hemisphere language functions and schizophrenia: the forgotten hemisphere?
Brain. 2005 May;128(Pt 5):963-78. Epub 2005 Mar 2. Review.

Miyashita Y, Hayashi T.
Neural representation of visual objects: encoding and top-down activation.
Curr Opin Neurobiol. 2000 Apr;10(2):187-94.

Moelter ST, Hill SK, Hughett P, Gur RC, Gur RE, Ragland JD.
Schizophr Res. 2005 Jul 4; [Epub ahead of print]
Organization of semantic category exemplars in schizophrenia.

Morgan C, Fisher H.
Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma--a critical review.
Schizophr Bull. 2007 Jan;33(1):3-10.

Moritz S, Andresen B, Domin F, Martin T, Probsthein E, Kretschmer G, Krausz M, Naber D, Spitzer M.
Increased automatic spreading activation in healthy subjects with elevated scores in a scale assessing schizophrenic language disturbances.
Psychol Med. 1999 Jan;29(1):161-70.

Moss HE, Tyler LK.
The limits of a localized account of conceptual knowledge: Reply to Kiefer and Spitzer.
Trends Cogn Sci. 2001 Nov 1;5(11):471.

Moss HE, Tyler LK.
Weighing up the facts of category-specific semantic deficits.
Trends Cogn Sci. 2003 Nov;7(11):480-1; author reply 481-2.

Ogawa S, Lee TM, Kay AR, Tank DW.
Brain magnetic resonance imaging with contrast dependent on blood oxygenation.
Proc Natl Acad Sci U S A. 1990 Dec;87(24):9868-72.

Pauen S.
Early differentiation within the animate domain: are humans something special?
J Exp Child Psychol. 2000 Feb;75(2):134-51.

Pauen S.
Evidence for knowledge-based category discrimination in infancy.
Child Dev. 2002 Jul-Aug;73(4):1016-33.

Perani D, Schnur T, Tettamanti M, Gorno-Tempini M, Cappa SF, Fazio F.
Word and picture matching: a PET study of semantic category effects.
Neuropsychologia. 1999 Mar;37(3):293-306.

Pickup GJ.
Theory of mind and its relation to schizotypy.
Cognit Neuropsychiatry. 2006 Mar;11(2):177-92.

Pilgrim LK, Fadili J, Fletcher P, Tyler LK.
Overcoming confounds of stimulus blocking: an event-related fMRI design of semantic processing.
Neuroimage. 2002 Jul;16(3 Pt 1):713-23.

Pilgrim LK, Moss HE, Tyler LK.
Semantic processing of living and nonliving concepts across the cerebral hemispheres.
Brain Lang. 2005 Jul;94(1):86-93.

Puce A, Perrett D.
Electrophysiology and brain imaging of biological motion.
Philos Trans R Soc Lond B Biol Sci. 2003: 358(1431), 435-45.

Rees S, Inder T.
Fetal and neonatal origins of altered brain development.
Early Hum Dev. 2005 Sep;81(9):753-61.

Rizzolatti G, Arbib MA.
Language within our grasp.
Trends Neurosci. 1998 May;21(5):188-94. Review.

Rizzolatti G, Craighero L.
The mirror-neuron system.
Annu Rev Neurosci. 2004;27:169-92. Review.

Rosen BR, Buckner RL, Dale AM.
Event-related functional MRI: past, present, and future.
Proc Natl Acad Sci U S A. 1998 Feb 3;95(3):773-80. Review.

Rossell SL.
Affective semantic priming in patients with schizophrenia.
Psychiatry Res. 2004 Dec 30;129(3):221-8.

Sawa, A., Snyder, S.H. (2002).
Schizophrenia: Diverse Approaches to a Complex Disease.
Science 296, 692-695.

Schultz, J., Friston, K.J., O'Doherty, J., Wolpert, D.M., Frith, C.D., 2005. Activation in posterior superior temporal sulcus parallels parameter inducing the percept of animacy. Neuron 45(4), 625-35.

Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RS, Dolan RJ.
Brain regions associated with acquisition and retrieval of verbal episodic memory.
Nature. 1994 Apr 14;368(6472):633-5.

Shenton ME, Dickey CC, Frumin M, McCarley RW.
A review of MRI findings in schizophrenia.
Schizophr Res. 2001 Apr 15;49(1-2):1-52. Review.

Simon SA, de Araujo IE, Gutierrez R, Nicolelis MA.
The neural mechanisms of gustation: a distributed processing code.
Nat Rev Neurosci. 2006 Nov;7(11):890-901. Review.

Sitnikova T, West WC, Kuperberg GR, Holcomb PJ.
The neural organization of semantic memory: Electrophysiological activity suggests feature-based segregation.
Biol Psychol. 2006 Mar;71(3):326-40.

Smeets PA, de Graaf C, Stafleu A, van Osch MJ, Nievelstein RA, van der Grond J. Effect of satiety on brain activation during chocolate tasting in men and women.
Am J Clin Nutr. 2006 Jun;83(6):1297-305.

Spitzer M, Braun U, Maier S, Hermle L, Maher BA.
Indirect semantic priming in schizophrenic patients.
Schizophr Res. 1993 Dec;11(1):71-80.

Spitzer M, Kischka U, Gückel F, Bellemann ME, Kammer T, Seyyedi S, Weisbrod M, Schwartz A, Brix G.
Functional magnetic resonance imaging of category-specific cortical activation: evidence for semantic maps.
Brain Res Cogn Brain Res. 1998 Apr;6(4):309-19.

Stone VE, Gerrans P.
Does the normal brain have a theory of mind?
Trends Cogn Sci. 2006 Jan;10(1):3-4.

Sullivan PF, Kendler KS, Neale MC.
Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003 Dec;60(12):1187-92.

Talairach J, Tournoux P.
Co-planar stereotaxic atlas of the human brain.
Stuttgart: Thieme (1998).

Thompson-Schill SL, Aguirre GK, D'Esposito M, Farah MJ.
A neural basis for category and modality specificity of semantic knowledge.
Neuropsychologia. 1999 Jun;37(6):671-6.

Thompson-Schill SL, Bedny M, Goldberg RF.
The frontal lobes and the regulation of mental activity.
Curr Opin Neurobiol. 2005 Apr;15(2):219-24. Review.

Tranel D, Damasio H, Damasio AR.
A neural basis for the retrieval of conceptual knowledge.
Neuropsychologia. 1997 Oct;35(10):1319-27.

Tuscher O, Silbersweig D, Pan H, Smith T, Beutel M, Zonana J, Erbesh V, Weisholtz D, Stern E, Engelien A.
Processing of environmental sounds in schizophrenic patients: disordered recognition and lack of semantic specificity.
Schizophr Res. 2005 Mar 1;73(2-3):291-5.

Tyler LK, Moss HE, Durrant-Peatfield MR, Levy JP.
Conceptual structure and the structure of concepts: a distributed account of category-specific deficits.
Brain Lang. 2000 Nov;75(2):195-231.

Tyler LK, Moss HE.
Towards a distributed account of conceptual knowledge.
Trends Cogn Sci. 2001 Jun 1;5(6):244-252.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15(1), 273-89.

Ungerleider LG, Haxby JV.
'What' and 'where' in the human brain.
Curr Opin Neurobiol. 1994 Apr;4(2):157-65. Review.

Van der Kouwe AJ, Benner T, Dale AM.
Real-time rigid body motion correction and shimming using cloverleaf navigators. Magn Reson Med. 2006 Nov;56(5):1019-32.

Van Hoesen GW.
The modern concept of association cortex.
Curr Opin Neurobiol. 1993 Apr;3(2):150-4.

Yacoub E, Le TH, Ugurbil K, Hu X.
Further evaluation of the initial negative response in functional magnetic resonance imaging.
Magn Reson Med. 1999 Mar;41(3):436-41.

Warrington EK, Shallice T.
Category specific semantic impairments.
Brain. 1984 Sep;107 (Pt 3):829-54.

Warrington EK, McCarthy RA.
Categories of knowledge. Further fractionations and an attempted integration.
Brain. 1987 Oct;110 (Pt 5):1273-96.

Weisbrod M, Maier S, Harig S, Himmelsbach U, Spitzer M.
Lateralised semantic and indirect semantic priming effects in people with schizophrenia.
Br J Psychiatry. 1998 Feb;172:142-6.

7. Tables

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Main	Left fusiform, inf. TOP junction	-39	-54	-15	44360	0.000*	0.000*	6.09	0.000
	Right precentral / medial - sup. frontal	30	-6	45				6.58	0.000
	Left frontal inf. /rolandic operculum	-48	6	9				6.55	0.000
Animal	Left fusiform, inf. TOP junction	-39	-54	-15	41170	0.000*	0.000*	6.74	0.000
	Right fusiform / inf. temporal gyrus	33	-51	-15				6.71	0.000
	Right parahippoc/ lingual gyrus	15	-39	-6				6.55	0.000
Food	Left insula, sup. temporal gyrus	-36	-15	3	37828	0.000*	0.000*	6.43	0.000
	Right inf. TOP jnct / fusiform gyrus	51	-54	-15					
	Right fusiform / inf. temporal gyrus	33	-54	-18					
Human	Left rolandic /frontal inf. operc /precentr	-48	3	12	39359	0.000*	0.000*	6.83	0.000
	Left fusiform / inf. TOP junction	-36	-66	-12				6.58	0.000
	Left fusiform / inf. temporal gyrus	-39	-51	-18				6.51	0.000
Tool	Left inf. TOP junction / fusiform	-42	-69	-12	38119	0.000*	0.000*	6.28	0.000
	Left fusiform / lingual gyrus	-27	-54	-15				6.13	0.000
	Left fusiform / inf. TOP junction	-39	-54	-15				6.12	0.000
Living	Left fusiform, inf. temporal gyrus	-39	-51	-18	43634	0.000*	0.000*	6.79	0.000
	Left frontal inf. / rolan. operc / insula	-48	6	9				6.78	0.000
	Left medial TOP junction	-51	-72	9				6.61	0.000
Nonliv.	Left inf. TOP junction / fusiform	-42	-72	-9	40649	0.000*	0.000*	6.57	0.000
	Left fusiform / inf. TOP junction	-39	-54	-15				6.21	0.000
	Right TOP junction	42	-78	-6				6.17	0.000

Table 5: Single contrasts in healthy controls

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Main	Left cerebellum, fusiform gyrus	-33	-54	-24	16361	0.000*	0.000*	6.16	0.000
	Left fusiform gyrus / cerebellum	-33	-69	-15				5.79	0.000
	Right fusiform / cerebellum	36	-39	-21				5.61	0.000
	Left cingulum, supp. motor area	-9	12	42	1336	0.000*	0.000*	4.99	0.000
	Right supp. motor area	9	15	45				4.74	0.000
	Bilateral supp. motor area	-3	-3	66				4.58	0.000
	Left cerebellum	-12	-30	-33	104	0.006*	0.001*	3.69	0.001
Animal	Right fusiform, inf. temporal gyrus	42	-39	-21	13883	0.000*	0.000*	6.01	0.000
	Left fusiform gyrus / cerebellum	-33	-51	-18				5.48	0.000
	Right inf. frontal triangular gyrus	57	15	21				5.34	0.000
	Left sup. temporal gyrus, hippocamp	-39	-9	-15	135	0.004*	0.001*	3.94	0.001
	Left sup. - medial temporal gyrus	-45	-15	-3				3.61	0.001
Food	Right cerebellum, Fusiform	30	-42	-27	9274	0.000*	0.000*	5.83	0.000
	Left inf. parietal /supramarginal	-54	-24	45				5.36	0.000
	Right lingual gyrus / cerebellum	9	-81	-12				5.11	0.000
	Right inf. frontal operc., precentral	54	9	27	754	0.000*	0.000*	4.54	0.000
	Right inf. frontal operc./ insula	48	18	-3				4.37	0.000
	Right insula / putamen	33	15	12				4.29	0.000
	Left supp. motor area, sup. frontal	-9	12	45	767	0.000*	0.000*	4.54	0.000
	Right medial cingulum / sup. - medial frontal	9	24	39				4.20	0.000
	Right supp. motor area	3	3	60				4.16	0.000
	Right post/ precentral gyrus	57	-15	39	347	0.000*	0.000*	4.39	0.000
	Right sup. temporal / supramarginal	66	-36	21				4.00	0.001
	Right inf. parietal / supramarginal	45	-39	48				3.63	0.001
Human	Right fusiform, inf. temporal gyrus	42	-45	-18	8892	0.000*	0.000*	6.47	0.000
	Left fusiform, inf. temporal gyrus	-36	-51	-18				5.77	0.000
	Right medial temporal gyrus	51	-72	-3				5.44	0.000
	Left inf. frontal operc., precentral	-60	12	21	1636	0.000*	0.000*	4.61	0.000
	Left postcentral / inf. parietal gyrus	-45	-30	51				4.40	0.000

	Left supramarginal /postcentral gyrus	-57	-21	36				4.25	0.000
	Left medial - ant. Cingulum	-9	12	36	653	0.000*	0.000*	4.56	0.000
	Right cingulum / supp. motor area	12	12	42				4.35	0.000
	Bilateral supp. motor area	-3	-3	63				4.17	0.000
	Right medial - sup. temporal gyrus	51	-48	6	436	0.000*	0.000*	4.14	0.000
	Right postcentral / supramarginal	57	-18	39				3.99	0.001
	Right supramarg / rolandic operc	57	-18	24				3.83	0.001
Tool	Left cerebellum	-27	-72	-18	6418	0.000*	0.000*	5.55	0.000
	Left fusiform / left inf. occipital	-33	-63	-9				5.34	0.000
	Left cerebellum / fusiform gyrus	-21	-63	-15				5.33	0.000
	Left postcentral gyrus, inf. parietal	-48	-24	48	2380	0.000*	0.000*	4.90	0.000
	Left postcentral gyrus, inf. parietal	-42	-30	51				4.89	0.000
	Bilateral supp. motor area	6	9	60				4.68	0.000
	Right precentral, inf. frontal operc.	54	6	33	481	0.000*	0.000*	4.70	0.000
	Right postcentral / supramarginal	54	-24	48				4.39	0.000
	Right sup. frontal / precentral gyrus	33	-9	69				3.72	0.001
	Left thalamus, hippocampus	-21	-24	-3	121	0.001*	0.000*	4.54	0.000
	Bilateral thalamus	-9	-21	6				3.38	0.003
	Right insula, inf. frontal orbital gyrus	27	27	-6	211	0.000*	0.000*	4.20	0.000
	Right insula / putamen	33	21	0				3.82	0.001
	Right basal ganglia	24	21	9				3.63	0.002
Living	Left fusiform, inf. temporal gyrus	-36	-48	-18	14925	0.000*	0.000*	6.49	0.000
	Right fusiform / parahippocampal	36	-39	-18				6.27	0.000
	Right fusiform	33	-51	-21				5.83	0.000
	Left medial - ant. Cingulum	-3	12	33	1261	0.000*	0.000*	4.66	0.000
	Left med. cingulum / frontal sup. medial	-9	12	39				4.63	0.000
	Bilateral supp. motor area	-3	-3	66				4.63	0.000
Nonliv.	Left fusiform, cerebellum	-30	-72	-18	11993	0.000*	0.000*	5.71	0.000
	Right lingual / fusiform gyrus	21	-78	-12				5.53	0.000
	Left sup. occipital gyrus / cuneus	-15	-93	33				5.51	0.000
	Left supp. motor area, cingulum	-3	12	48	973	0.000*	0.000*	4.72	0.000
	Bilateral supp. motor area	3	3	60				4.59	0.000
	Right med. cingul/ frontal sup. medial	12	24	39				4.28	0.000

	Left medial - sup. frontal gyrus	-39	42	36	75	0.024	0.003*	4.53	0.000
	Right fusiform, parahippocampus	33	0	-36	75	0.024	0.003*	4.38	0.000
	Right parahippoc / amygdale	24	3	-27				3.53	0.001
	Right hippocampus / parahippocampus	33	-6	-24				3.52	0.001
	Left inf. frontal orbital gyrus, insula	-30	30	-9	115	0.004*	0.000*	4.18	0.000
	Left insula / frontal inf. triangular gyrus	-30	24	0				3.85	0.001

Table 6: Single contrasts in patients

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Animal vs. Food	Left medial - inf. occipital gyrus	-48	-84	3	26	0.508	0.091	4.45	0.140
	Left medial - sup. temporal gyrus	-57	-12	-12	26	0.508	0.091	4.45	0.140
	Left precentral / sup. frontal lobe	-27	-9	42	6	0.958	0.406	3.95	0.195
	Right inf. temporal	48	-48	-24	14	0.797	0.204	3.88	0.195
	Right medial occipit / inf. temporal	48	-75	-3	74	0.061	0.008*	3.87	0.195
	Right hippocampus /precuneus	21	-36	3	46	0.208	0.030*	3.77	0.195
	Left sup. temporal	-48	-42	21	17	0.722	0.164	3.74	0.195
	Right sup. frontal / supp. motor area	18	0	72	9	0.909	0.306	3.65	0.195
	Right cuneus / prec	6	-72	24	31	0.409	0.067	3.64	0.195
	Right supp. motor area / sup. frontal	9	18	66	10	0.889	0.281	3.58	0.195
	Left lingual / hippocampus	-12	-36	-3	25	0.530	0.097	3.51	0.195
Animal vs. Human	Left medial - sup. occipital gyrus	-24	-99	18	35	0.371	0.065	3.73	0.308
	Right inf. parietal / angular gyrus	36	-45	33	13	0.823	0.244	3.64	0.308
	Left insula /inf. frontal gyrus	-27	18	12	11	0.866	0.283	3.36	0.308
	Left cerebellum	-33	-42	-27	6	0.953	0.431	3.31	0.308
	Left cerebellum	-6	-48	-6	5	0.965	0.474	3.25	0.308
	Left med. occipital	-15	-96	0	6	0.953	0.431	3.20	0.308
Animal vs. Tool					- (1-4)				
Food vs. Animal					-(1,3)				
Food vs. Human	Left medial - sup. occipital gyrus	-33	-84	15	48	0.298	0.068	4.84	0.041

	Left inf. front. gyrus	-33	36	0	58	0.218	0.048*	4.35	0.077
	Right fusiform / cerebellum	27	-48	-15	20	0.686	0.224	3.49	0.282
Food vs. Tool	Left med. occipital / angular gyrus	-33	-69	36	81	0.045*	0.006*	4.19	0.367
	Left inf. frontal gyrus / insula	-33	33	3	20	0.646	0.132	3.58	0.367
	Left supp. motor area / sup. frontal	-9	21	51	9	0.909	0.304	3.53	0.367
	Left med. frontal	-48	36	27	10	0.889	0.279	3.46	0.367
	Left sup. - medial frontal gyrus	-3	39	42	12	0.981	0.237	3.33	0.367
Human vs. Animal	Left medial temporal gyrus / angular gyrus	-48	-63	18	24	0.573	0.120	3.68	1.000
	Right medial - sup. temporal gyrus	63	-60	15	7	0.939	0.393	3.64	1.000
Human vs. Food	Right rectus gyrus	3	36	-18	127	0.030*	0.006*	4.14	0.170
	Right precuneus	3	-66	27	61	0.199	0.043*	3.83	0.170
	Right medial - sup. temporal gyrus	57	-60	15	62	0.193	0.041*	3.65	0.170
	Left TOP junction	-48	-63	15	72	0.142	0.030*	3.57	0.170
Human vs. Tool	Right fusiform / inf. temporal gyrus	42	-27	-21	36	0.308	0.044*	4.78	0.056
	Left angular gyrus/ medial temporal	-45	-60	24	18	0.689	0.140	4.12	0.178
	Bilateral precuneus	0	-63	30	67	0.072	0.009*	4.09	0.178
	Right medial - inf. temporal gyrus	51	-69	0	73	0.055	0.007*	3.85	0.178
	Bilateral rectus gyrus	0	39	-18	31	0.390	0.060	3.65	0.195
	Right inf. - med. frontal orbital gyrus	33	42	-18	12	0.844	0.224	3.56	0.199
	Right sup. - medial frontal gyrus	6	54	18	8	0.929	0.319	3.38	0.227
	Left medial - sup. temporal gyrus	-54	-57	15	15	0.768	0.176	3.33	0.228
Tool vs. Animal					-				
Tool vs. Food	Right cuneus /precuneus	6	-72	21	6	0.958	0.403	3.30	0.970
Tool vs. Human	Right medial - sup. occipital gyrus	39	-90	15	46	0.191	0.025*	4.02	0.359
	Left medial - sup. occipital gyrus	-24	-99	18	15	0.768	0.176	3.78	0.359
	Left medial - sup. occipital gyrus	-33	-84	27	14	0.794	0.190	3.73	0.359
	Left precentral / postcentral gyrus	-24	-21	54	15	0.768	0.176	3.33	0.359
	Left postcentral / inf. parietal gyrus	-24	-45	55	8	0.929	0.319	3.27	0.359
		-15	-24	69	5	0.973	0.434	3.26	0.359
Living vs. Nonliving	Left medial - inf. occipital gyrus	-48	-81	0	82	0.060	0.009*	4.30	0.067

	Left medial - sup. temporal gyrus	-57	-12	-15	48	0.225	0.037*	4.28	0.067
	Right medial - inf. temporal gyrus	51	-75	-3	189	0.002*	0.000*	4.12	0.067
	Left precuneus	0	-69	27	126	0.013*	0.002*	4.06	0.067
	Left medial orbital frontal gyrus	0	51	-15	35	0.379	0.069	3.79	0.067
	Right inf. temporal	45	-45	24	35	0.379	0.069	3.66	0.068
	Right medial - sup. temporal gyrus	48	-42	6	11	0.865	0.291	3.50	0.076
	Bilateral anterior cingulum	3	42	9	15	0.779	0.219	3.26	0.100
Nonliving vs. Living					-(1)				

Table 7: Differential contrasts in healthy controls

Contrast	*Brain Area*	*MNI Coordinates* *X*	*Y*	*Z*	*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
Animal vs. Food					-(2,3)				
Animal vs. Human	Left supp. motor area / sup. frontal gyrus	-12	12	66	40	0.138	0.014*	3.94	0.691
	Right sup. frontal / supp. motor area	18	9	69	12	0.786	0.150	3.94	0.691
	Left supp. motor area / paracentral	-6	-6	69	7	0.935	0.266	3.25	0.691
Animal vs. Tool	Right inf. medial occipital gyrus	42	-84	-3	7	0.931	0.317	4.16	0.455
	Left medial - inf. frontal gyrus	-39	51	6	12	0.803	0.193	3.71	0.455
	Right medial - sup. temporal gyrus	57	-60	12	27	0.393	0.059	3.54	0.455
	Left cerebellum	-24	-51	-39	8	0.909	0.284	3.51	0.455
	Right cuneus / sup. occipital gyrus	12	-93	18	14	0.743	0.161	3.40	0.455
Food vs. Animal					-				
Food vs. Human	Left lingua / precuneus	-24	-51	-3	14	0.699	0.107	3.87	0.999
Food vs. Tool	Left cerebellum / fusiform gyrus	-24	-24	-36	6	0.955	0.304	3.50	0.912
Human vs. Animal					-(4)				
Human vs. Food	Left sup. - medial frontal gyrus	-3	54	0	5	0.974	0.325	3.34	0.707

Human vs. Tool	Right sup. - medial temporal gyrus	57	-45	12	73	0.013*	0.001*	4.24	0.363
	Right thalamus / putamen	24	-24	6	16	0.620	0.086	4.01	0.363
Tool vs. Animal					-				
Tool vs. Food	Bilateral olfactory gyrus	3	6	-12	10	0.853	0.188	3.70	0.985
Tool vs. Human					-				
Living vs. Nonliving	Left TOP junction	-39	-72	15	37	0.240	0.034*	4.42	0.286
	Right medial - sup. temporal gyrus	63	-51	12	41	0.194	0.027*	3.95	0.359
	Right fusiform	36	-45	-24	6	0.948	0.366	3.48	0.417
Nonliving vs. Living					-				

Table 8: Differential contrasts in patients

Contrast	*Brain Area*	*MNI Coordinates* *X*	*Y*	*Z*	*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
Controls vs. Pat.					-				
Patients vs. Con.	Right sup. temporal gyrus	63	0	-6	34	0.422	0.122	4.08	0.084
	Right sup. orbital frontal gyrus	21	15	-15	28	0.508	0.157	4.07	0.084
	Right inf. - medial temporal gyrus	57	-48	-12	30	0.478	0.144	3.93	0.084
	Right sup. orbital frontal gyrus	21	51	-6	11	0.812	0.370	3.79	0.084
	Right putamen / insula	30	-12	9	206	0.004*	0.001*	3.71	0.084
	Right sup. - medial temporal pole	57	15	-15	38	0.373	0.103	3.70	0.084
	Left inf. orbital frontal gyrus	-57	21	-6	67	0.152	0.036*	3.70	0.084
	Right precentral / rolandic operculum	63	6	18	17	0.698	0.265	3.62	0.084
	Left putamen / insula	-24	15	-9	53	0.233	0.059	3.58	0.084
	Right lingua	15	-84	-15	11	0.812	0.370	3.57	0.084
	Left basal ganglia	-24	-3	15	42	0.329	0.088	3.46	0.084
	Left cerebellum	-18	-75	-36	40	0.350	0.096	3.36	0.084
	Right cerebellum	6	-75	-36	16	0.717	0.279	3.34	0.084
	Left vermis / cerebellum	0	-57	-39	7	0.885	0.480	3.32	0.084
	Left cingulum	-6	-6	36	6	0.902	0.515	3.30	0.084
	Right cerebellum	36	-69	-33	11	0.812	0.370	3.29	0.084

	Left medial - sup. temporal gyrus	-66	-30	-6	6	0.902	0.515	3.26	0.084
	Left precuneus	-21	-51	9	6	0.902	0.515	3.13	0.084

Table 9: Two-group comparison for the condition “main”

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Controls vs. Pat.					-				
Patients vs. Con.	Left cerebellum	-30	-72	-33	23	0.593	0.215	3.64	0.290
	Left basal ganglia	-18	15	0	25	0.561	0.197	3.62	0.290
	Left cerebellum	-3	-81	-33	26	0.546	0.188	3.60	0.290
	Right thalamus /putamen	21	-15	12	12	0.787	0.369	3.40	0.290
	Right cerebellum	42	-66	-33	10	0.823	0.413	3.35	0.290
	Right inf. - medial temporal gyrus	54	-57	-9	8	0.859	0.467	3.31	0.290
	Right sup. - medial temporal gyrus	66	-9	-6	5	0.910	0.573	3.14	0.290

Table 10: Two-group comparison for the condition “animal”

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Controls vs. Pat.					-				
Patients vs. Con.	Right cerebellum	42	-66	-33	23	0.592	0.206	3.81	0.188
	Right sup. frontal orbital gyrus	21	15	-15	12	0.790	0.359	3.64	0.188
	Right sup. temporal /rolandic operculum	63	-12	6	8	0.863	0.458	3.52	0.188
	Bilateral cuneus	-3	-81	30	21	0.626	0.226	3.48	0.188
	Right precuneus / sup. parietal gyrus	9	-57	69	6	0.898	0.525	3.46	0.188
	Right lingua /cerebellum	12	-84	-12	9	0.846	0.429	3.46	0.188
	Left inf. tri. / orbital frontal gyrus	-54	21	-3	51	0.256	0.068	3.45	0.188
	Right inf. - medial temporal gyrus	57	-48	-15	10	0.827	0.404	3.44	0.188
	Left putamen / insula	-24	15	-9	14	0.753	0.322	3.40	0.188
	Left supplementary motor area	-3	30	63	6	0.898	0.525	3.23	0.188

Table 11: Two-group comparison for the condition “food”

Contrast	*Brain Area*	*MNI Coordinates* *X*	*Y*	*Z*	*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
Controls vs. Pat.					-				
Patients vs. Con.	Left inf. orbital frontal /rectus gyrus	-18	15	-18	38	0.346	0.082	4.55	0.073
	Right inf. frontal orbit./sup. temporal	48	30	-18	69	0.118	0.024*	4.27	0.073
	Right rectus / sup. frontal orbit. gyrus	6	51	-21	25	0.541	0.151	4.22	0.073
	Right olfactory / rectus gyrus	15	12	-15	17	0.697	0.232	3.90	0.085
	Left lingua / fusiform area	-21	-48	-6	38	0.346	0.082	3.61	0.154
	Right basal ganglia	33	-6	-6	15	0.739	0.261	3.52	0.177
	Left cerebellum	-21	-78	-36	17	0.697	0.232	3.47	0.181
	Left putamen / insula	-27	-6	15	24	0.559	0.159	3.44	0.181
	Right putamen / insula	30	-9	9	21	0.617	0.186	3.43	0.181
	Vermis	0	-60	-39	5	0.933	0.524	3.34	0.189
	Right cerebellum	33	-72	-36	10	0.842	0.359	3.31	0.189

Table 12: Two-group comparison for the condition “human”

Contrast	*Brain Area*	*MNI Coordinates* *X*	*Y*	*Z*	*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
Controls vs. Pat.					-				
Patients vs. Con.	Right sup. orbital frontal gyrus	21	15	-15	34	0.402	0.102	3.95	0.103
	Left fusiform area / parahippocampus	-21	-21	-36	63	0.149	0.032*	3.90	0.103
	Left putamen / insula	-27	12	-9	35	0.388	0.097	3.74	0.103
	Left medial - inf. frontal gyrus	-33	48	6	39	0.338	0.082	3.70	0.103
	Right putamen / insula	30	-9	9	119	0.026*	0.005*	3.68	0.103
	Right cingulum	9	-12	33	12	0.801	0.320	3.63	0.103
	Right sup. temporal /inf. orbital frontal	51	15	-15	13	0.780	0.300	3.60	0.103
	Right thalamus / hippocampus	18	-30	0	20	0.638	0.201	3.55	0.103
	Left cuneus / sup. occipital gyrus	-9	-81	21	49	0.239	0.054	3.50	0.103
	Left sup. temporal pole	-42	6	-27	8	0.879	0.419	3.38	0.103

Left sup. temporal / inf. frontal orbital	-54	18	-12	13	0.780	0.300	3.36	0.103
Bilateral precuneus	6	-57	63	12	0.801	0.320	3.33	0.103
Right lingua / cerebellum	12	-48	0	6	0.915	0.487	3.28	0.103
Left lingua / precuneus	-18	-51	-6	11	0.821	0.341	3.26	0.103
Right paracentral / precuneus	3	-39	66	7	0.897	0.451	3.22	0.103

Table 13: Two-group comparison for the condition "tool"

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Controls vs. Pat.					-				
Patients vs. Con.	Left cerebellum	-18	-78	-36	92	0.076	0.018*	3.89	0.128
	Right sup. - medial orbital frontal gyrus	18	51	-9	7	0.883	0.485	3.81	0.128
	Right sup. temporal gyrus	63	-3	-6	18	0.679	0.257	3.72	0.128
	Left sup. orbital frontal gyrus	-21	15	-15	74	0.127	0.031*	3.64	0.128
	Right Vermis / Cerebellum	3	-57	-39	14	0.754	0.317	3.59	0.128
	Right sup. temporal pole/inf. orb. frontal	51	24	-18	32	0.453	0.136	3.56	0.128
	Right inf. - medial temporal gyrus	54	-51	-12	18	0.679	0.257	3.55	0.128
	Right cerebellum	48	-60	-36	22	0.608	0.212	3.48	0.128
	Right putamen / insula	30	-9	9	100	0.061	0.014*	3.48	0.128
	Left basal ganglia	-24	-3	15	11	0.810	0.376	3.31	0.128
	Right basal ganglia	33	-6	-6	16	0.716	0.285	3.29	0.128
	Right basal ganglia	27	18	6	9	0.847	0.425	3.24	0.128

Table 14: Two-group comparison for the condition "living"

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Controls vs. Pat.					-				
Patients vs. Con.	Right sup. orbital frontal gyrus	21	15	-15	28	0.506	0.154	4.07	0.123
	Left sup. - medial temporal gyrus	-57	12	-15	95	0.065	0.015*	3.91	0.123
	Right sup. - medial	60	0	-12	11	0.814	0.366	3.62	0.123

temporal gyrus								
Left putamen / insula	-27	12	-9	29	0.491	0.147	3.59	0.123
Right sup. temporal /inf. orbital frontal	54	15	-15	17	0.698	0.261	3.55	0.123
Right putamen / insula	30	-15	6	61	0.179	0.043*	3.54	0.123
Bilateral cuneus	-3	-81	27	38	0.370	0.101	3.47	0.123
Left cingulum	-9	-6	36	10	0.833	0.390	3.47	0.123
Right cerebellum	42	-66	-30	5	0.921	0.552	3.46	0.123
Right precuneus / sup. parietal gyrus	9	-57	66	14	0.756	0.308	3.44	0.123
Bilateral lingua	15	-84	-15	6	0.904	0.512	3.44	0.123
Right thalamus / hippocampus	18	-27	0	5	0.921	0.552	3.30	0.123
Right rolandic operc / postcentral	63	-6	12	7	0.887	0.476	3.29	0.123
Right inf. - medial temporal gyrus	54	-48	-12	6	0.904	0.512	3.26	0.123
Left medial - inf. tri. Frontal gyrus	-39	54	6	6	0.904	0.512	3.26	0.123

Table 15: Two-group comparison for the condition “nonliving”

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Controls vs. Pat.	Left TOP junction	-39	-72	15	2	0.963	0.726	3.32	0.709
	Left sup. - medial temporal pole	-54	15	-21	1	0.976	0.817	3.15	0.709
Patients vs. Con.					-				

Table 16: Two-group comparison for the differential contrast “living vs. nonliving”

Contrast	*Brain Area*	*MNI Coordinates*			*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
		X	*Y*	*Z*					
Controls vs. Pat.					-				
Patients vs. Con.	Left TOP junction	-39	-72	15	2	0.963	0.726	3.32	0.709
	Left sup. - medial temporal pole	-54	15	-21	1	0.976	0.817	3.15	0.709

Table 17: Two-group comparison for the differential contrast “nonliving vs. living”

Contrast	*Brain Area*	*MNI Coordinates* *X*	*Y*	*Z*	*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
Arousal Controls	Left caudate / cingulum	-21	-15	33	18	0.710	0.178	3.64	0.403
	Right hippocampus / parahippocampus	18	-24	-12	5	0.964	0.480	3.53	0.403
	Right inf. triangular frontal gyrus	54	21	15	5	0.964	0.480	3.42	0.403
	Right sup. occipital / cuneus	27	-78	42	6	0.952	0.437	3.35	0.403
	Right caudate / thalamus	21	-18	24	18	0.710	0.178	3.33	0.403
Arousal Patients	Left thalamus / pallidum	-12	-12	0	13	0.749	0.133	3.71	0.948
Neg. Arousal Controls					- (2)				
Neg. Arousal Patients					- (1)				
Valence Controls					-				
Valence Patients	Right sup. - medial frontal gyrus	30	18	63	6	0.942	0.398	3.64	0.909
Neg. Valence Controls	Left precentral / postcentral	-27	-24	63	60	0.228	0.055	3.75	0.525
Neg valence Patients					- (2)				

Table 18: Single contrasts correlated with the covariated “arousal” and “valence” in patients and controls

Contrast	*Brain Area*	*MNI Coordinates* *X*	*Y*	*Z*	*Cluster Size*	*Cluster p corr*	*Cluster p uncorr*	*z-value*	*Voxel p (FDR)*
Arousal Con. vs. Pat.					-				
Arousal Pat. vs. Con.	Right medial - inf. orbital frontal gyrus	30	39	-12	7	0.904	0.431	3.87	0.392
	Bilateral cingulum	3	24	15	60	0.148	0.029*	3.48	0.392
	Left medial - sup. temporal gyrus	-45	-24	-12	13	0.783	0.280	3.40	0.392

Neg Arousal Con. vs. Pat.	Right medial - inf. orbital frontal gyrus	30	39	-12	7	0.904	0.431	3.87	0.392
	Bilateral cingulum	3	24	15	60	0.148	0.029*	3.48	0.392
	Left medial - sup. temporal gyrus	-45	-24	-12	13	0.783	0.280	3.40	0.392
Neg. Arousal Pat. vs. Con.					-				
Valence Con. vs. Pat.					-				
Valence Pat. vs. Con.					-				
Neg. Valence Con. vs. Pat.					-				
Neg. Valence Pat. vs. Con.					- (1)				

Table 19: Differential contrasts correlated with the covariated “arousal” and “valence” in patients and controls

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