Investigation of neural correlates of bottom-up and top-down processing with functional magnetic resonance imaging and electroencephalogram. Exemplified by the binocular depth inversion-paradigm.

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Declaration

I herewith declare that I autonomously carried out the PhD-thesis entitled “Investigation of neural correlates of bottom-up and top-down processing with functional magnetic resonance imaging and electroencephalogram. Exemplified by the binocular depth inversion-paradigm”.

I did not receive any assistance in return for payment by consulting agencies or any other person. No one received any kind of payment for direct or indirect assistance in correlation to the content of the submitted thesis. I conducted the project at the Clinic for Psychiatry, Psychotherapy and Social Psychiatry, Medical School Hannover. The thesis has not been submitted elsewhere for an exam, as thesis or for evaluation in a similar context.

I hereby affirm the above statements to be complete and true to the best of my knowledge.

Danai Dima

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‘Science does not know its debt to imagination’

Ralph Waldo Emerson
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Outline

The aim of this thesis is to investigate the interaction between top-down and bottom-up processes in schizophrenia using the hollow-mask illusion. Previous studies have shown that patients suffering from schizophrenia fail to perceive this illusion. The neural mechanisms underpinning this failure are investigated by using functional magnetic resonance tomography (fMRI) and event-related potentials (ERPs). Our hypothesis is that this failure is due to a deficient functional connectivity that results from a weakening of top-down processes and a strengthening of bottom-up processes in patients suffering from schizophrenia.

Chapter 1 – Introduction – is divided into two parts. The first part outlines the theoretical framework under which the research in this thesis is carried out. The second part describes the neuroimaging methods used in this thesis (fMRI and ERPs) in connection with schizophrenia and describes Dynamical Causal Modeling (DCM), a novel connectivity tool which is used for hypothesis testing in subsequent chapters.

Chapters 2-4 – Results chapters – describe the experimental work: the aims, the hypothesis and the models tested the set up and the outcomes of three studies. The specific goals of each study are the following:

- To explain differences in both the perception of hollow faces and associated neural responses between schizophrenic patients and controls using effective connectivity measures by performing DCM on fMRI data (Chapter 2)
• To explore the time course of top-down processes in schizophrenia using ERPs (Chapter 3)

• To validate that schizophrenic patients fail to experience the hollow mask illusion due to a weakening of top-down processes, by performing DCM on ERP data (Chapter 4)

Chapter 5 – General Discussion – provides a synopsis and the conclusions of this work; it presents its contributions to the field and indicates directions for future research.
Chapter 1

1

Introduction
Schizophrenia

Schizophrenia strikes about 1% of the population worldwide, and it seems to affect men slightly more frequently and severely than it does women. Emil Kraeplin (1909), the director of the Psychiatry Clinic at the University of Heidelberg in Germany, was the first to recognize schizophrenia as a separate syndrome and called it *dementia praecox* (early deterioration of the intellect) because of its early age of onset. Eugen Bleuler (1911) objected to the term *dementia praecox* because he observed that some patients became ill in adulthood rather than adolescence whereas other patients occasionally experienced remission. He proposed that the disorder was a fragmentation of the mind, whereby the cognitive processes were split off the volition, behaviour and emotion. Therefore Bleuler called this group of illnesses *schizophrenia*, from the Greek roots *ζιζεῖν* (to split) and *φιλέν* (mind), which means a splitting of the mind.

Schizophrenia is characterized by psychotic episodes, discrete, often reversible mental states in which some of the patient’s thought processes are not able to test reality correctly. During a psychotic episode patients are unable to examine their beliefs and perceptions realistically and to compare them to what is actually happening in the world. This loss of reality testing is accompanied by other disturbances of higher mental functioning, especially the occurrence of delusions, hallucinations, incoherent thinking, disordered memory and sometimes confusion.

The first psychotic episode of schizophrenia is often preceded by prodromal signs. These include social isolation and withdrawal, impairment in the normal fulfillment of expected roles, odd behaviour and ideas, neglect of personal hygiene and blunted effect. The prodromal period is then followed by one or more psychotic
episodes. These episodes are sometimes separated by long periods during which the patient is not overtly psychotic but nonetheless behaves eccentrically maintaining a low level of emotional arousal (a flat affect), an impoverished social drive, poverty of speech, a poor attention span and lack of motivation. These symptoms of the nonpsychotic period are called negative symptoms. In contrast, the striking symptoms of psychotic episodes are called positive because they reflect the presence of distinctively abnormal behaviours. The negative symptoms are chronic features of the illness and they are still the most difficult to treat.

Schizophrenia is often divided into subtypes, three out of which are the most easily distinguished: a) paranoid schizophrenia, the most common type and more often found in men, in which systematic delusions of persecution predominate, b) disorganized schizophrenia, a form characterized by early age of onset, a wide range of symptoms and a profound impairment of personality, c) catatonic schizophrenia, a rare form in which mutism and abnormal postures dominate.

Identifying the causes of schizophrenia is one of the most challenging goals of psychiatric research; the only reliable finding to date is that schizophrenia is due in part to a genetic abnormality. Thus, until 1950 there was no effective treatment for schizophrenia. The first useful remedy employed was chlorpromazine, a drug originally thought to act as a tranquilizer. However, in 1964 it became clear that chlorpromazine and other related drugs of the phenothiazine class have specific effects on the psychotic symptoms of schizophrenia mitigating or abolishing delusions, hallucinations and some types of disordered thinking. These drugs are now called typical antipsychotics. These include not only the phenothiazines, but also the butyrophenones (haloperidol) and the thioanthenes. More recently a second group of
drugs, the atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone) have proved better in treating negative symptoms and cognitive defects in schizophrenia and produce fewer side effects on the extrapyramidal systems.

A three-component-system hypothesis of psychosis

Perception involves active processing of the continuous torrent of sensations. This processing comprises many successive and interactive stages. Those that deal with the simplest physical or sensory characteristics, such as colour, shape or tone, come first in the processing sequence and serve as foundations for the more complex, ‘higher’ levels of semantic and visuoconceptual processing that successively integrate sensory stimuli with one another and with the organism’s past experience. In other words, perception occurs when the information from our senses meets our knowledge, expectations and past experience, and thus gives meaning to the world around. Normal perception in the healthy organism is a complex process engaging many different aspects of brain functioning. Like other cognitive functions, the excessive cortical distribution and the complexity of perceptual activities make them highly vulnerable to any brain disease like schizophrenia.

In 1989 H.M. Emrich proposed the three-component model of psychosis. According to this theory, perception is principally made up of three components: firstly, sensory input (“sensualistic” component, bottom-up process); secondly, the internal production of concepts (“constructivistic” component, top-down process); and thirdly, control (“censor” component). The third component is identified as the interaction between the other two components and it is not attributed to a specific
spatial area in the brain. Emrich (1989) proposed that ‘the special interaction between these three components is responsible for the biologically fruitful and efficacious conscious internal representation of the external world during perception’ and suggested that the equilibrium between bottom-up and top-down components is disturbed during schizophrenia.

One instance that this becomes obvious is when an ambiguous situation like the hollow-mask illusion arises. Seen from a distance, the interior side of a mask will appear as a normal, nose-sticking-out face, even though it is hollow. If the mask is slowly rotated it looks as if it goes through astonishing transformations, reversing directions as the hollow back or the sticking-out front appears (Figure 1). Because the equilibrium between top-down and bottom-up processes is disturbed in psychosis, as suggested by Emrich, schizophrenia should likewise impair the correction of preconceptions. Thus, patients suffering from schizophrenia should not be fooled by the hollow mask illusion. Indeed, studies have shown that patients suffering from schizophrenia are not subject to the illusion as experienced by normal controls (Schneider et al., 1996a, 2002; Emrich et al., 1997). Similar results have also been found in other ‘pro-psychotic’ conditions such as cannabinoid-intoxicated states (Emrich et al., 1991, 1997; Leweke et al., 1999, 2000; Semple et al., 2003), alcohol withdrawal (Schneider et al., 1996b; 1998) and sleep deprivation (Sternemann et al., 1997), where it is not unusual for individuals to report psychotic symptoms such as delusional ideas or misperceptions.
Figure 1. Photographs of a rotated hollow mask:
A and B show the inside of the mask; it appears convex although it is truly hollow.
C is curiously confusing as part of the hollow inside is seen as convex, combined with
the truly convex face. Top-down knowledge of faces is pitted against bottom-up
signalled information.

D and E show the side and front truly convex view.
Although the integration of top-down and bottom-up processes has been widely investigated, no study to our knowledge has yet investigated the neural mechanisms underlying the failure to perceive visual illusions in schizophrenia. Examining the interaction between top-down and bottom-up processes in schizophrenia is important to our further understanding of the pathology of schizophrenia. In this thesis we used the hollow-mask illusion, or else binocular depth inversion paradigm, to further understand the interaction between top-down and bottom-up processes in schizophrenia. We used two neuroimaging methods fMRI and ERPs, as well as a novel connectivity method which will be explained below.

*Functional magnetic resonance imaging and schizophrenia*

Before the rise of functional magnetic resonance imaging (fMRI) researchers were already using an invasive non-tomographic method to determine regional cerebral blood flow with Xenon 133 in the human brain (Ingvar and Lassen, 1961). The first to use this method in schizophrenia where Ingvar and Franzen (1974), who found relative frontal hypometabolism (hypofrontality) in schizophrenia. This technique was followed by positron emission tomography (PET), which played (Herholz et al., 1987) and plays a big role in psychiatric neuroimaging.

However, the first report of localized changes in cerebral blood oxygenation in the occipital cortex following visual stimulation in humans (Belliveau et al., 1991) was of seminal importance to neuropsychiatric research. Only three years following this technological development, which enabled non-invasive visualization of in vivo human brain function, the application of the technique to psychiatric patients was first reported (Renshaw et al., 1994; Wenz et al., 1994). This ushered in a new era in
functioning neuroimaging and provided a powerful tool in cognitive neuroscience to explore both normal and abnormal brain function, complementing earlier techniques such as positron emission tomography. Following the initial application of fMRI to schizophrenia research, the technique has been reported with increasing frequency over the past decade.

The most common form of fMRI data acquisition is blood oxygenation level dependent (BOLD) imaging, first reported in humans by Ogawa et al. (1990). This is based on the differential magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin (Pauling and Coryell, 1936), which accordingly have different MR signal decay rates (Thulborn et al., 1982). Oxyhaemoglobin is diamagnetic; that is, it does not greatly disturb local magnetic field gradients. In contrast, deoxyhaemoglobin is paramagnetic and will therefore affect the local magnetic field by increasing the magnetic susceptibility and causing a loss of image intensity. Deoxyhaemoglobin, present only in red blood cells, provides a particularly good paramagnetic endogenous contrast agent, since it is present in the bloodstream at high concentrations. Neuronal activity leads to an initial transient increase (100-200ms) in oxygen consumption and a concomitant increase of deoxyhaemoglobin concentration. This is followed by increased local capillary blood flow and oxygen delivery to the activated region lasting several seconds. However, oxygen consumption does not increase proportionately with hyperoxemia. This causes a marked decrease in the ratio of deoxyhaemoglobin compared to oxyhaemoglobin concentration in that region, and consequently produces an increase in the MR signal, due to an increased T2 relaxation time. With the use of ultra-imaging techniques such as echo-planar imaging (Mansfield, 1977), which are sensitive in T2, multiple slices covering the whole brain can be collected rapidly. A
vast range of physiological, sensory and cognitive stimuli have been used to examine the consequent changes in cerebral blood oxygenation and thus, indirectly, the brain functions.

fMRI research in schizophrenia has explored a broad range of cognitive functioning, concentrating primarily on executive functions, attention, working memory, psychomotor functions and basic sensory processing. In order to examine the neurobiological basis of top-down and bottom-up processes in schizophrenia we adopted a case-control study that involved comparing the patients-group with healthy volunteers. Furthermore, in our fMRI experiment (Chapter 2) we used an event-related design, which has the benefit of improved psychological validity (avoiding the need to artificially block similar trials together) and of examining the temporal dynamics of the BOLD response.

*Event related potentials and schizophrenia*

Neural activity is an electrochemical process. Although the electrical potential produced by a single neuron is minute, when large populations of neurons are active simultaneously they produce electrical potentials large enough to be measured by placing electrodes on the scalp. These surface electrodes are much larger than those used for single-cell recordings but they involve the same principles; what is measured is a change in voltage corresponding to the difference in potential between the signal at a recording electrode and that at a reference electrode. This potential can be recorded at the scalp because tissues of the brain, skull and scalp passively conduct the electrical currents produced by synaptic activity. The recording of the signals is referred to as the electroencephalogram (EEG) (Berger, 1929). However, EEG is
limited in providing insight to cognitive processes because the recording tends to reflect the brain’s global electrical activity. In our experiment we used a more powerful approach (Chapter 3), which focuses on how brain activity is modulated in response to a particular task. This method requires extracting an evoked response from the global EEG signal. The logic of this approach is straightforward: EEG traces from a series of trials are averaged together by aligning the records according to an external event such as the onset of a stimulus. This alignment washes out any variations in the brain’s electrical activity that are unrelated to the events of interest. The evoked response, or else event related potential (ERP), is a tiny signal embedded in the ongoing EEG. So, by averaging the traces, one can extract this signal, which reflects the neural activity that is specifically related to sensory, motor or cognitive events.

Most of the research on event related potentials (ERPs) has been motivated by the belief that schizophrenia is a disorder of cognition. Therefore, ERP methodology, with its excellent time resolution and sensitivity to cognitive manipulations, provides a useful index of abnormal cognitive processes. Over the years, researchers have studied abnormal processes of attention, sensory memory and sensory filtering, short-term and working memory as well as language processes with a variety of ERP components. In this thesis, we will discuss two ERP components that are associated with top-down processing: the P300 and P600.

The P300 component is an endogenous component of the ERP that is elicited by events that call for a revision or updating of the representation of individuals’ environment in working memory (Donchin and Coles, 1988). This large positive wave with a centro-parietal topography reflects a higher-level, post-perceptual analysis that is based on the relevance of the stimulus to the task at hand. As such, the amplitude of
the P300 reflects demands on central attentional resources (Wickens et al., 1983). Since its first demonstration by Sutton et al. (1965), the P300 has been researched extensively in both normal and clinical populations and it has been of special interest to investigators studying cognitive dysfunction in schizophrenia. Ever since the original report of Roth and Cannon (1972) of reduced P300 amplitude over midline electrode sites in schizophrenia patients, numerous studies have used the P300 paradigm to assess different aspects of schizophrenia pathology (Polish, 2007). The P600 component of the ERPs is also a late positive wave that peaks usually between 600-800ms and has been shown to constitute a distinct component from the P300 (Friederici, 2002; Frisch et al., 2003). P600 generators have been identified in several regions (i.e., hippocampus, entorhinal, cingulate, and ventral prefrontal cortex) that are considered important for episodic/declarative memory (Fernandez et al., 1999; Guillem et al., 1999; Halgren et al., 1994). Furthermore, psychophysiological research suggests that the P600 component indexes the completion of any synchronized operation immediately following target detection; in other words, it signals the second pass paring processes of information processing; and it is impaired in schizophrenia (Papageorgiou et al., 2001; Ruchsov, et al., 2003).

Dynamic causal modelling

In this thesis we have used fMRI to identify which areas of the brain are active during the perception of the hollow mask in healthy controls and in patients suffering from schizophrenia, (Chapter 2) and ERPs to identify the time course of this process (Chapter 3). These techniques are important for understanding where and when in the
brain a neuronal process occurs; but it is the study of connectivity, as described below, that is crucial for understanding how this processing is coordinated.

Dynamic causal modelling (DCM) is a generative or forward model which assumes that changes in cortico-cortical coupling are responsible for event-related potential genesis. Additionally, it sheds light to the construction of plausible connectivity models for hierarchical cortical organization. These models embody bottom-up and top-down connections among distant regions. With DCM it is possible to assess how a given experimental manipulation activates a cortical pathway rather than a cortical area or source.

That the brain is highly interconnected is critical for understanding its function. The notion that the brain might be organized hierarchically was originally put forward by Hubel and Wiesel (1962) with regard to the visual domain. This notion, of course, also extends to other sensory modalities and to the integration between different modalities. A general rule of cortico-cortical connections is reciprocity, meaning that two areas are linked in bidirectional pathways. Felleman and Van Essen (1991) described a set of connectivity rules and provided a critical assessment of the principle of hierarchical organization in light of the available data. These rules relate to extrinsic connections, i.e., excitatory connections that cross the white matter. In contrast, intrinsic connections are confined to an area within the cortical sheet and can be either excitatory or inhibitory in nature. According to these rules, forward or ascending connections originate in agranular layers (I-III, V and VI) and terminate in the granular layer (layer IV). Backwards or descending connections link agranular layers together and lateral connections originate in agranular layers and target all layers. Forward and backwards connections mediate bottom-up and top-down processing respectively.
Mumford (1991, 1992), among others, has put forward ideas about the computational architecture of the neocortex that are in agreement with the view that the brain is hierarchically organized. Specifically, with respect to two reciprocally connected areas, the ‘lower’ area deals with more sensory or concrete information, whereas the ‘higher’ area is concerned with more abstract information. The descending pathways carry patterns which try to fit the information arriving via the senses. If the fitting is not perfect the residuals are sent upstream until top-down predictions and bottom-up constructions reach convergence.

Thus, the brain can be seen as an empirical Bayesian device. Bayesian models have been employed in neuroscience and cognition for the understanding of visual perception (Kersten et al., 2004; Yuille and Kersten, 2006). Hierarchical Bayes offers a good analogy for what may be happening in the brain: the prior probability of the causes \( p(\theta) \) formulated in higher hierarchical levels, flows down to be combined with the likelihoods of the data given the causes, \( p(y|\theta) \) in the lower hierarchical levels in order to compute the posterior probability \( p(\theta|y) \) which is then passed upstream to enter the following loop. According to the Bayes rule:

\[
p(\theta|y) \propto p(\theta) p(y|\theta)
\]

This is a recursive process that stops once reconciliation is reached, namely, as soon as the inputs no longer cause updates to the posteriors of the generative model or to our recreation of what caused the sensory input.

In order to address connectivity the majority of studies use functional connectivity measures such as coherence, phase-synchronisation or temporal correlations between the activities of two areas at the scalp or source level. Functional connectivity is used to establish statistical dependencies between time series and it is
useful because it does not require an underlying model or knowledge of the causal nature of the interactions. However, these are circumstances where the focus of interest is the causal architecture of the interactions. As opposed to functional connectivity, DCM is based on the concept of effective connectivity, which refers explicitly to the influences that one neuronal system exerts over another. This influence is parameterized in a causal or an explicit generative model, which can then be estimated using model inversion. In DCM the brain is regarded as a deterministic nonlinear dynamic system that is subject to inputs and produces outputs (Friston et al., 2003b). Effective connectivity is estimated by perturbing the system and measuring the response using Bayesian model inversion.

In our study we performed DCM on fMRI data (Chapter 2) and on ERP data (Chapter 4) in order to find out the connectivity pattern differences between healthy controls and patients suffering from schizophrenia.
Understanding why patients with schizophrenia do not perceive the hollow mask illusion using dynamic causal modelling.

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Abstract

Patients suffering from schizophrenia are less susceptible to various visual illusions. For example, healthy participants perceive a hollow mask as a normal face, presumably due to the strength of constraining top-down influences, while patients with schizophrenia do not (Schneider et al., 1996, 2002; Emrich et al., 1997). However the neural mechanisms underpinning this effect remain poorly understood. We used functional magnetic resonance imaging to investigate the hollow-mask illusion in schizophrenic patients and healthy controls. The primary aim of this study was to use measures of effective connectivity arising from dynamic causal modelling (DCM) to explain differences in both the perception of the hollow mask illusion and associated differences in neural responses between patients with schizophrenia and controls, which we hypothesised would be associated with difference in the influences of top-down and bottom-up processes between the groups. Consistent with this explanation, we identified differences between the two groups in effective connectivity. In particular, there was a strengthening of bottom-up processes, and weakening of top-down ones, during the presentation of ‘hollow’ faces for the patients. In contrast, the controls exhibited a strengthening of top-down processes when perceiving the same stimuli. These findings suggest that schizophrenic patients rely on stimulus-driven processing and are less able to employ conceptually-driven top-down strategies during perception, where incoming sensory data are constrained with reference to a generative model that entails stored information from past experience.
Introduction

In order to perceive the environment as meaningful the interaction between bottom-up and top-down processing has to be intact (Wallbott and Ricci-Bitti, 1993; Cauller, 1995). Visual illusions provide a useful tool to study the mechanisms by which top-down and bottom-up process interact in perception; they can occur when the brain interprets sensory information on the basis of contextual information and previous experience, resulting in a percept that diverges substantially from the true sensory input. In this study we used the ‘hollow-mask illusion’ (Gregory, 1973) to investigate such an interaction. The hollow-mask illusion occurs when a hollow mask is perceived (incorrectly) as a normal face. It is understood to be a process that involves the generation of hypotheses about the three-dimensional shape of faces by interpreting the bottom-up signals received from the eyes using conceptual and perceptual knowledge (top-down processing), as well as general rules of perception, such as Gestalt laws of organisation and perspective (Yellot, 1981; Ramachandran, 1988; Hill and Bruce, 1993; Gregory, 1998).

Almost a century ago Bleuler (1911) coined the term schizophrenia to represent the ‘splitting’ of different mental domains. This idea is still influential, but in recent years has been recast in terms of pathological connectivity between brain areas. In this framework, the symptoms of schizophrenia are not considered as a single deficit but can be seen as ‘resulting form the abnormal integration of two or more processes…and are expressed when two or more regions interact.’ (Friston, 1998). Similarly, Emrich (1989) proposed that the pathogenesis of schizophrenia can be described as a functional disequilibrium within the human brain, and that an impairment of the
bottom-up and top-down interaction may be a plausible explanation for the disintegrative and reality-impairing properties of psychotic disorders. Frith and Done (1988, 1989) and Malenka (1982) suggested that internal correcting systems may be deficient in psychotic states, and that an imbalance occurs in systems responsible for concept formation, suggesting that schizophrenics are forced to rely on stimulus-driven processing, whereby fragments of stimuli are pieced together without reference to an expected or stored model (Hemsley, 1987). The insusceptibility of patients with schizophrenia to visual illusions is consistent with such theories. For example, it has been demonstrated that patients suffering from schizophrenia do not experience the hollow-mask illusion, i.e. the hollow stimulus is correctly perceived as hollow (Schneider et al., 1996, 2002; Emrich et al., 1997), consistent with weakened top-down influences in schizophrenia.

While clear hypotheses relating to the integration of top-down and bottom-up processes arise from the theoretical positions discussed above, no study to date has investigated the neural mechanisms underpinning the failure to perceive visual illusions in schizophrenia. Understanding the interaction between top-down and bottom-up processes in schizophrenic patients is important in further understanding the pathology of schizophrenia. The primary aim of this study was therefore to use measures of effective connectivity arising from dynamic causal modelling (DCM) to explain differences in both the perception of hollow faces and associated neural responses between patients with schizophrenia and controls. We hypothesised that top-down influences from the fronto-parietal network give rise to the hollow-mask illusion in controls, and that normal or strengthened bottom-up influences from visual areas in
the absence of top-down input from the fronto-parietal network prevent the patients from experiencing the illusion.

**Materials and Methods**

*Subjects*

Thirteen patients and 16 healthy controls matched for age, gender and educational level participated in the study (See Table 1). All schizophrenic patients fulfilled DSM-IV and ICD-10 criteria for schizophrenia and were taking atypical antipsychotic medication. Schizophrenic patients with other psychiatric disorders, including drug and or alcohol abuse and neurological disorders, were excluded. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the current symptomatology of the patients. Educational level was quantified using a scale from 1 to 5 coding different levels from high school to graduate university studies according to the German educational system. All subjects underwent an ophthalmological examination before the study. Subjects were included in the study only if their vision was normal or corrected to normal and all had normal colour vision. Stereoscopic vision was tested using the Netherlands Organisation for Applied Scientific Research TNO test (Lameris, Utrecht, Netherlands). All participants were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects provided written informed consent prior to their inclusion in the study, and the study was approved by the local ethics committee.
Table 1. Demographic, psychopathological and behavioural data. Figures represent the mean (SD) or median (range)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Schizophrenic patients</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (male)</td>
<td>16 (13)</td>
<td>13 (11)</td>
<td>Fisher's exact test, p=1</td>
</tr>
<tr>
<td>Age</td>
<td>32 (9.7)</td>
<td>33 (10.5)</td>
<td>t(29)=0.25, p=0.826</td>
</tr>
<tr>
<td>Educational level</td>
<td>4.1 (0.7)</td>
<td>3.8 (0.7)</td>
<td>t(29)=0.60, p=0.722</td>
</tr>
<tr>
<td>Negative PANSS</td>
<td>–</td>
<td>19.7 (8.8)</td>
<td>–</td>
</tr>
<tr>
<td>Positive PANSS</td>
<td>–</td>
<td>18.5 (5.9)</td>
<td>–</td>
</tr>
<tr>
<td>Total PANSS</td>
<td>–</td>
<td>78.9 (23.9)</td>
<td>–</td>
</tr>
<tr>
<td>Misclassification of 3D normal faces as 3D inverted*</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
<td>-</td>
</tr>
<tr>
<td>Misclassification of 3D inverted faces as 3D normal*</td>
<td>71 (67-72)</td>
<td>4 (2-7)</td>
<td>-</td>
</tr>
</tbody>
</table>

* These data were collected as part of a separate experiment, outside the scanner.

Experimental design

We employed an event-related functional magnetic resonance imaging (fMRI) design with three experimental conditions (3D normal faces, 3D depth-inverted faces, 2D faces). Under laboratory conditions, it is possible to create a strong impression of three-dimensionality by presenting each eye with a separate image of the same face, with each photo taken at slightly different angle towards the displayed face (Wheatstone, 1838). To produce this effect, the following technique was used:
stimulus pairs were projected via a NEC 2001 colour projector onto the window that separates the MRI chamber from the operating room. On this window white paper was placed that afforded a high resolution display for the stimulus-pairs (see Figure 1A). Inside the MRI chamber a custom-made prism stereoscope was placed on the head coil that ensured that the left picture was projected to the left eye of the subject and the right picture to the right eye. The result was that the subject perceived a single 3D face in the middle of the display. Pseudoscopy, or binocular depth inversion, was induced by exchanging the pictures from the left and right sides (see Figure 1B). 2D faces were presented by showing the same picture to both eyes.

Before the main experiment started subjects, completed a practice session to verify that they were able to perceive 3D images in the scanner using our custom-made prism stereoscope. Subjects viewed stereoscopic pictures of an elephant and of faces (3D normal and 3D inverted) while lying in the scanner. None of the controls could distinguish between the 3D normal and 3D inverted conditions, while all the patients classified the 3D inverted face as hollow.

The task included 24 trials in each of the 3D conditions and 27 in the 2D condition. Conditions were presented in a random order with a constant inter-trial interval (ITI) of 15 s. Each stimulus-pair was displayed for 6 s, with a 9 s blank-screen rest period between stimulus pairs. During the rest period 3 s before the stimulus-pair was displayed, a preparatory tone was played via headphones. Subjects were instructed to decide whether the face they saw was 3D or 2D and to answer, after the face had disappeared (i.e. during the rest period), by pressing a key using their forefinger or middle finger on an MRI-compatible response-pad. The subjects’ responses and reaction times were recorded. After scanning, subjects completed questionnaires to
ascertain whether they perceived any of the faces as ‘hollow’ (i.e. inverted). Subjects were explicitly asked if they experienced during the experiment a face as hollow and were instructed to answer with yes or no.

Note that our subjects were not asked to distinguish faces between normal and inverted faces during the task, but instead classified faces as either 2D or 3D. This incidental task design was chosen for three reasons. Firstly, it ensured that responding was sufficiently straightforward for our subjects, especially the patients, while inside the MRI scanner. Secondly it directed subjects’ attention while not confounding the interpretation of neural effects with their explicit knowledge about the possibility of inverted and non-inverted faces. Thirdly, several studies have shown that schizophrenic patients are insusceptible to the hollow-mask illusion, and we had no reason to expect that this group of patients would be any different (Schneider et al., 1996, 2002; Emrich et al., 1997); indeed, behavioural data collected during the scan and post-scan questionnaires confirmed that this was the case (see Results).

A. Stereoscopic pictures of a female human face.

B. Graphic representation of binocular depth and binocular depth inversion.

Figure 1A. Stereoscopic pictures of a female human face.

Figure 1B. Graphic representation of binocular depth and binocular depth inversion.
fMRI acquisition

Structural and functional images were acquired on a GE Signa 1.5-T Horizon LX System (General Electric, Milwaukee) at the Institute of Diagnostic and Interventional Neuroradiology, Medical School Hannover. A standard head coil was used for radiofrequency transmission and reception. A series of 26 axial (i.e. parallel to the bicommissural plane) spin echo T1-weighted structural images were obtained (TR=24 ms, TE=8 ms, slice thickness=1.5 mm, spacing=1.5 mm, field of view=26 cm and matrix 256*256 pixels). T2* functional scans covering the whole brain were acquired at the same locations as the structural scans by using a multislice two dimensional echo planar imaging (EPI) sequence depicting the blood-oxygenation level dependent (BOLD) signal (26 contiguous slices, TR=3000 ms, TE=40 ms, flip angle=90°, slice thickness=5.0 mm, spacing=0.5 mm, in-plane resolution=3.125×3.125 mm, field of view=26 cm and matrix 64*64 pixels). Each fMRI time series consisted of 454 images, the first 4 of which were discarded to allow the scanner to reach a steady state in T1 contrast. Overall the paradigm lasted 22 minutes and 30 seconds.

Image processing

For image pre-processing, analysis and DCM, we used the SPM5 software package (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London, http://www.fil.ion.ucl.ac.uk). The BOLD images were realigned to the fifth volume to correct for interscan movements by means of a rigid body transformation with three rotation and three translation parameters. Subsequently, the 450 EPI volumes were spatially normalized to the standard template of the Montreal Neurological Institute (MNI, Canada) and resampled to a voxel size of 2×2×2 mm.
Finally, the images were smoothed using a 6 mm full width half maximum Gaussian kernel.

The smoothed, normalized single-subject images were analyzed via multiple regression using the linear convolution model and an AR(1) model of serial correlations. Specifically, event-related responses to face displays were examined, with the design including regressors representing (i) all faces, (ii) 3D faces and (iii) 3D face inversion. Regressors were created by convolving a 6 s boxcar function coinciding with the presentation of each stimulus pair with a set of temporal basis functions. Blank-screen periods were modelled as an implicit baseline. To account for inter-regional and inter-subject variability in the shape of the hemodynamic response function (HRF), we used a set of temporal basis functions that included a canonical HRF as well as its temporal and dispersion derivatives. Six vectors representing the parameters from the realignment procedure were included as regressors of no interest. The model additionally included drift terms up to 1/128 Hz to remove low-frequency components, and global confounds were removed using global normalization. Contrast images representing the effects of (i) all faces relative to rest, (ii) 3D faces relative to 2D faces, and (iii) 3D inverted faces relative to 3D normal faces were created by linear combination of the resulting beta images.

Group-level analyses were based on random-effects analyses of the single-subject contrast images using the summary-statistic approach. Regions showing significant main effects across all subjects were identified using one-sample t-tests against zero. Regions showing significant interactions with group were identified using independent-samples t-tests between the patient and control groups. The statistical threshold was set to $p < 0.001$ (uncorrected), minimum cluster size 5 voxels.
Having said this, the inference reported in this paper pertains to the DCMs, not the regional effects. Parameter estimates for the interactions of interest were extracted for post-hoc analysis. Coordinates were transformed from the MNI spatial array to the stereotaxic array of Talairach and Tournoux (1988) (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Anatomical localization was performed with reference to the atlas of Mai et al (2003).

**Regions of Interest (ROIs) for DCM**

The primary aim of the present study was to explain the interactions arising from the basic SPM analysis by estimating connectivity among areas of the visual system and fronto-parietal network, and how this connectivity was modulated by the presentation of normal and inverted faces (i.e. DCM). Three ROIs were selected according to the results of the group x inversion interaction analysis, which showed significant effects in the supramarginal gyrus (SMG) (x= 28, y= -31, z= 33), intraparietal sulcus (IPS) (x= 22, y= -73, z= 52) and inferior frontal gyrus (IFG) (x= 46, y= 8, z= 9) (see Figure 2 and Table 2). We also selected V1 from the contrast of all faces with rest (x= -32, y= -92, z= -8), z score = 7.73) as an input region (direct input of ‘all faces’ on V1). Finally, the lateral occipital cortex (LOC) (x= -34, y= -90, z= 6) was chosen as an area demonstrating a main effect of inversion across all subjects (see Table 2).

We defined the individual ROIs for every subject according to the group coordinates. Hence for each subject the time-series of all ROIs were extracted for the same voxel using the effects of interest F-contrast. We adopted this approach to circumvent any possible bias in choosing ROIs introduced by a failure to activate a
particular brain region of interest in some subjects. Note such a failure was expected for some contrasts, since we were attempting to explain group x inversion interactions, in which one group may show a significant effect across subjects while the other does not.

**DCM**

We used DCM to assess effective connectivity between our ROIs and its modulation by our visual task. Before specifying the models we examined the literature to assess the evidence for anatomical connections between the ROIs as listed above (V1, LOC, SMG, IPS, and IFG). Connections between IPS and IFG (Kim et al., 2003), between SMG and IFG (Stoeckel et al., 2003), between LOC and SMG (Behrmann et al., 2004) and LOC and IPS (Grefkes and Fink, 2005) have all been established, suggesting that the models we chose were credible.

We constructed 2 models with different modulation of effective connectivity but the same endogenous connectivity (see Figure 3), and used Bayesian model selection (Penny et al., 2004) to identify the model showing the highest evidence in the applied Bayesian framework. So, the best model is the one with the highest log-Bayes Factor (log-BF, or ‘evidence’: $\ln(p(y|I_m))$). Since DCM is a hypothesis-driven technique, we constructed two models that allowed us to test our hypotheses, namely that (i) in controls, top-down influences from the fronto-parietal attention network result in the illusory perception of inverted faces as normal (see Figure 3A), while (ii) in patients, an impairment in the modulation of effective connectivity in this network produces a percept driven by bottom-up influences, preventing them from experiencing the illusion (see Figure 3B).
To compare the models we computed their relative log-BF (\(\ln(p(y|m_1)) - \ln(p(y|m_2))\)) for each subject. In order to obtain the evidence for a given model over the others across subjects we added the log-BF from each subject (Garrido et al., 2007b). Additionally, the endogenous connections and modulatory influences were extracted from the subject-specific DCMs, but only the modulatory influences were analyzed further.

Behavioural and demographic data and parameter estimates from the SPM and DCM analyses were analyzed using SPSS 15 (SPSS Inc, Chicago, IL, USA) using t-tests, or appropriate non-parametric tests if data were not normally distributed, with alpha = 0.05. For SPM and DCM analyses, one-tailed p-values are reported by convention, while two-tailed p-values were employed for behavioural and demographic data.

**Results**

**Behavioural data**

We initially established that, as expected, patients and controls differed in terms of the susceptibility to the inverted-face illusion. Post-scan questionnaires revealed that none from the controls reported seeing a face as ‘hollow’, while all patients did (Fisher's exact test, \(p < 0.0001\)). Analysis of the response data collected during the task revealed that, due to the illusion, controls occasionally erroneously classified a 3D inverted face as flat (2D) (mean = 8.3% and std = 6.8%). Notably, the patients almost never classified a 3D inverted face as 2D (mean = 0.3% and std = 1.2%). This difference between the groups was highly significant (\(Z = 3.6, p = 0.0006\)), again suggesting that the patients were insusceptible to the illusion. Analysis of reaction time
data revealed no significant differences between the two groups ($F (1, 27) = 1.557; p = 0.297$; patients: 1260 msec +/- 412ms; controls: 1092 msec +/- 435m).

In a separate experiment performed outside the scanner, we collected behavioural data from the same subjects using the same 3D face stimuli and same experimental setup as employed in the fMRI task. These data were collected within 2 weeks of fMRI data acquisition. Subjects were asked to classify faces as 3D normal or 3D inverted (72 of each type). Controls were clearly highly susceptible to the illusion, classifying almost all 3D inverted faces as 3D normal; by contrast, patients very rarely made such misclassification errors, confirming their lack of susceptibility to the illusion (see Table 1).

**Table 2.** Regions showing significant main effects and group interactions in terms of hemodynamic responses to the presentation of 3D inverted relative to 3D normal faces.

<table>
<thead>
<tr>
<th>Region</th>
<th>Laterality</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Cluster size</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3D inverted minus 3D normal faces (all subjects)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>R</td>
<td>28</td>
<td>-33</td>
<td>32</td>
<td>37</td>
<td>3.96</td>
</tr>
<tr>
<td>Pulvinar nucleus, thalamus</td>
<td>R</td>
<td>12</td>
<td>-32</td>
<td>14</td>
<td>12</td>
<td>3.87</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>L</td>
<td>-30</td>
<td>-47</td>
<td>26</td>
<td>13</td>
<td>3.65</td>
</tr>
<tr>
<td>Lateral occipital cortex</td>
<td>L</td>
<td>-34</td>
<td>-90</td>
<td>6</td>
<td>6</td>
<td>3.27</td>
</tr>
<tr>
<td>Occipital gyrus</td>
<td>L</td>
<td>-26</td>
<td>-87</td>
<td>4</td>
<td>5</td>
<td>3.18</td>
</tr>
<tr>
<td><strong>3D inverted faces - 3D normal faces patients&gt;controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>R</td>
<td>28</td>
<td>-31</td>
<td>33</td>
<td>12</td>
<td>3.6</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>-6</td>
<td>-39</td>
<td>-11</td>
<td>17</td>
<td>3.59</td>
</tr>
<tr>
<td>Intraparietal sulcus</td>
<td>R</td>
<td>22</td>
<td>-73</td>
<td>52</td>
<td>7</td>
<td>3.48</td>
</tr>
<tr>
<td>Putamen</td>
<td>R</td>
<td>24</td>
<td>-14</td>
<td>23</td>
<td>8</td>
<td>3.39</td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td>R</td>
<td>16</td>
<td>-40</td>
<td>-13</td>
<td>5</td>
<td>3.28</td>
</tr>
<tr>
<td><strong>3D inverted faces - 3D normal faces controls&gt;patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>R</td>
<td>46</td>
<td>8</td>
<td>9</td>
<td>15</td>
<td>3.48</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>R</td>
<td>18</td>
<td>-5</td>
<td>57</td>
<td>6</td>
<td>3.37</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; R, right.
Coordinates correspond to the stereotaxic array of Talairach and Tournoux (1988) and denote the distance in mm from the anterior commissure, with positive X=right of midline, positive Y=anterior to the anterior commissure, and positive Z=dorsal to a plane containing both the anterior and the posterior commissures. **Bold** text indicates that the maximum formed one of our regions of interest.
Figure 2. Differences between the groups in neural responses to 3D inverted faces relative to 3D normal faces. A. Increased responses to 3D inverted faces relative to 3D normal faces, in the patients relative to the controls, in the intraparietal sulcus (IPS) ([x = 22, y = -73, z = 52], peak Z-score = 3.6). B. Plots of parameter estimates to 3D inverted faces relative to 3D normal faces in the IPS in the two groups. C. Increased responses to 3D inverted faces relative to 3D normal faces, in the controls relative to the patients, in the inferior frontal gyrus (IFG) ([x = 46, y = 8, z = 9], peak Z-score = 3.48). D. Plots of parameter estimates to 3D inverted faces relative to 3D normal faces in the IFG in the two groups.
SPM analysis

First, we identified brain regions exhibiting significant group x inversion interactions; that is increased BOLD responses to 3D inverted faces relative to 3D normal faces, in the patients relative to the controls. These areas included the SMG and the IPS (see Figure 2 A & B and Table 2).

The reverse interaction revealed brain regions exhibiting significantly increased BOLD responses to 3D inversed faces relative to 3D normal faces in the controls relative to the patients. These areas included the IFG and other frontal areas (see Figure 2 C & D and Table 2).

We also identified brain regions exhibiting significantly increased BOLD responses to 3D inverted faces relative to 3D normal faces across all subjects. These areas included the LOC (see Table 2).

Figure 3. Model specification. The models have the same endogenous connectivity, but different modulation of effective connectivity according to face-type (3D inverted or 3D normal). The sources comprising the models were: V1: primary visual cortex; LOC: Lateral occipital cortex; SMG: supramarginal gyrus; IPS: intraparietal sulcus; and IFG: inferior frontal gyrus. A. Model 1, where the modulation is place on the backwards connection from the IPS to LOC. B. Model 2, where the modulation is place on the forwards connection from V1 to LOC.
**DCM analysis – Model Comparison**

Having summarised the regional activity in our distributed network of face processing, we then made inferences about this network using DCM. By convention, our inference strategy followed two steps. First, we identified the best model for each group, using Bayesian model comparison. Second, using the best model we then examined the parameter estimates of coupling strengths qualitatively; again using the summary statistic approach. In this instance, the subject-specific summary statistics were the estimates of coupling strength for each connection. These were compared within and between groups using simple $t$-tests.

We constructed two models (see Figure 3). The first (Model 1) modelled the effect of depth-inversion in terms of an enabling or modulation of the top-down connection to LOC from the IPS. Conversely, the second model (Model 2) tried to explain the same data using a modulation of the bottom-up connection to the LOC from V1. We compared the evidence for both models (in both groups) in terms of their
log-evidence. To ensure that this evidence was expressed consistently over subjects we also applied t-tests to the log evidences.

Comparing the two models using Bayesian model comparison revealed that Model 1 best explained the data (group log-BF = 3.653; BF = 38.5903). Raftery (1995) suggested an interpretation of BF as providing weak (BF<3), positive (3≤BF<20), strong (20≤BF<150), or very strong (BF≥150) evidence for one model over another. In this case we have strong evidence in favour of Model 1 relative to model 2 at the group level.

The above analysis is equivalent to a fixed-effects analysis. We also performed random-effects analyses to be able to extend our inferences to individuals not included in the present study. However the groups differed in terms of their preference for Model 1 (t(27) = 1.9, p = 0.03). The patients actually weakly favoured Model 2 (BF = 3.0), though the random-effects analysis was non-significant (t(12) = 0.52, p = 0.32). By contrast the control group strongly favoured Model 1 (BF = 117.7) and the random-effects analysis was significant (t(15) = 2.5, p = 0.01).

**DCM - endogenous connectivity and modulatory influences**

Endogenous connectivity refers to effective connectivity between brain areas independent of any task (Friston et al., 2003b). However, we were most interested in the extent to which endogenous connections were modulated by depth-inversion. By assessing the modulation we can effectively estimate and quantify synaptic plasticity on a macroscopic scale, and determine how it differs between schizophrenic patients and controls (Stephan et al., 2006). In Model 1 (best model), where the modulation was placed on the backwards connection from the IPS to LOC we identified
significantly increased modulation in the controls compared to the patients ($t(27) = 2.7; p = 0.0065$). Post-hoc analysis revealed that the controls significantly increased effective connectivity from IPS to LOC when presented with 3D inverted faces ($t(15) = 2.7, p = 0.008$), while the patients did not ($t(12) = -1.2, p = 0.13$). In contrast, in Model 2, where the modulation was placed on the forwards connection from V1 to LOC, we found significantly increased modulation in the patients compared to the controls ($t(27) = 1.7; p = 0.048$). Post-hoc analysis revealed that while both groups significantly increased effective connectivity from V1 to LOC when presented with 3D inverted faces, this effect was much stronger in the patients ($t(12)=4.4, p = 0.0005$) than the controls ($t(15) = 2.2, p = 0.02$).

**Relationship between neural responses, connectivity and symptoms**

We identified no significant relationship between equivalent chlorpromazine dose, the severity of hallucinations and delusions and the modulation of connectivity with the LOC ($p>0.05$ for all correlations), or with neural responses in any of our ROIs ($p>0.001$ for all correlations).

**Discussion**

In this study we demonstrated that schizophrenic patients and healthy controls differ in terms of the modulation of neural connectivity during the presentation of illusory stimuli. More precisely, the data of the control group were best explained by a model where the dynamic modulation of connectivity according to face-type (normal or inverted) was placed on the backwards connections from IPS to LOC. This finding
is consistent with the hypothesis that top-down influences from the fronto-parietal network contribute to the perception of the hollow-mask illusion in controls. By contrast, the data of the patients with schizophrenia were, if anything, explained better by a model where the modulation was placed on the forward connection between V1 and LOC, consistent with a lack of modulatory top-down control in this group. Furthermore, directly comparing the strength of the modulatory effect of face-type in the context of the two models revealed, as expected, a significantly stronger modulation of the backward connection from IPS to LOC in the controls than the patients in the context of Model 1, but a significantly stronger modulation of the forward connection from V1 to LOC in the patients than the controls in the context of Model 2.

We assessed changes in connectivity using DCM because it is the most sensitive method currently available to quantify synaptic coupling at a macroscopic level with fMRI (Stephan et al., 2006). We were particularly interested in changes in coupling associated with the perceptual processing of normal and depth-inverted 3D faces. This was modelled in terms of an inversion-specific modulation of either forward or backward connections to LOC. The group-specific differences in these changes are entirely consistent with the dysconnection hypothesis of schizophrenia (Friston, 2005a) and current models of perceptual inference based on hierarchical Bayes and predictive coding (Garrido et al., 2007a). The dysconnection hypothesis states that schizophrenia is caused by an abnormal modulation of synaptic plasticity resulting in abnormal procedural and perceptual learning. The failure of our schizophrenic subjects to experience the illusion rests, we suppose, on a failure to invoke top-down prior expectations during perceptual inference on the sensory stimuli.
This failure may be due to sub-optimal perceptual learning during neurodevelopment and beyond. Alternatively, it could reflect an abnormal modulation of synaptic efficacy and a sub-optimal balance between bottom-up sensory information and top-down priors. Both explanations rest on classical neuromodulatory systems that regulate synaptic efficacy in the short-term (through classical neuromodulatory actions) or in the long-time (by enabling associative plasticity).

Stephan et al. (2006) propose that hallucinations may be related to impairments in synaptic plasticity during perceptual learning, while delusions may be related to impairments during stimulus-response learning. In support of this hypothesis, it has recently been demonstrated that aberrant learning of stimulus-reinforcement associations was related specifically to delusions, but not to hallucinations (Roiser et al, in press). However, in the present study we were unable to establish a relationship between hallucination severity and responses to 3D-inverted faces in our ROIs, or with the modulation of connectivity with the LOC during the processing of 3D-inverted faces. This negative result is not definitive, though, since we were only able to include 13 patients, who varied little in positive symptom scores as assessed by the PANSS, both of which make the likelihood of Type II error relatively high. Future studies investigating the hollow mask illusion in schizophrenia should employ larger samples and more sophisticated assessments of positive symptoms, perhaps including subgroups of patients based on symptom type, in order to further investigate this important question.

Quantitatively speaking, our results are also consistent with a failure of hierarchical inference in the visual cortex. This is because, for both groups, depth-inversion produced greater activation in the lateral occipital area. This is consistent
with a greater degree of prediction error, reflecting the mismatch between the depth-inverted face and the predictions afforded by a normal face. We hypothesise that, in controls, these prediction errors are not sufficient to outweigh the influences of top-down priors, suggesting an increased sensitivity of LOC populations to top-down inferences. This is exactly what we saw in the DCM analyses. Conversely, in schizophrenic patients, the synaptic efficacy of top-down connections may be engaged to a lesser degree, allowing bottom-up connections to supervene; again, this explanation is corroborated by the DCM results. In short, our findings indicate that the modulation of synaptic efficacy in schizophrenia is altered compared to healthy controls.

Elaborating on this argument, the three-component-model of psychosis proposed by Emrich (1989) is also supported by our data. This theory assumes that perception principally comprises three components: firstly, sensory input (bottom-up); secondly, the internal production of concepts (top-down); and thirdly, control (a ‘censor’ component). The third component is identified as the interaction between the two first components and is not attributed to a specific spatial area in the brain, but characterized as the interaction between top-down and bottom-up processing (Emrich, 2006). Emrich’s theory proposed that the equilibrium between these three components is disturbed in psychosis, and most specifically when an ambiguous situation arises, such the illusion employed in this study.

Our data also shed light on pharmacological studies of visual illusions, for example those using psychomimetics. Studies that used Δ9-tetrahydrocannabinol, the major psychoactive compound of cannabis resin (Gaoni and Mechoulam, 1964), found that subjects under the influence of cannabis did not experience the hollow-mask
illusion (Emrich et al., 1991, 1997; Semple et al., 2003); similar results were obtained in studies using synthetic Δ9-tetrahydrocannabinol (Leweke et al., 1999) and nabilone, a synthetic cannabinoid (Leweke et al., 2000), while a study using cannabidiol, a non-psychoactive cannabinoid, did not find any effects on illusion perception (Leweke et al., 2000). Our study suggests that the psychomimetic effects of these substances might be understood in terms of their effects on neural connectivity, though this hypothesis requires verification in studies using pharmacological fMRI.

A feature of our experimental design merits comment. We deliberately employed an incidental task to direct attention to ensure both that the patients could easily perform the task in the scanner, and that any neural effects identified were unconfounded by the explicit knowledge about the possibility of inverted or non-inverted faces. However, this design also precluded the possibility of comparing neural responses between trials on which patients experienced the illusion and those on which they did not. Future studies investigating binocular depth inversion may wish to employ tasks that permit such analysis. Furthermore, all patients included in the present study were taking atypical antipsychotics, meaning that we were unable to assess the impact of different types of medication on susceptibility to the hollow-mask illusion and associated neural responses. Future studies may also wish to include patients taking both typical and atypical antipsychotics to investigate this question.

In summary, schizophrenic patients exhibited changes in connectivity, in particular a strengthening of bottom-up processes and weakening of top-down ones, during the presentation of ‘hollow’ faces; by contrast, the controls exhibited a strengthening of top-down processes when perceiving the same stimuli. These findings suggest that schizophrenic patients rely on stimulus-driven processing and are less
constrained by top-down processes during perception, where incoming sensory data are interpreted with reference to a model composed of stored information of past experiences and knowledge.
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We thank our colleagues for helpful discussions, the Institute of Diagnostic and Interventional Neuroradiology, Medical School Hannover, for using their facilities to perform the fMRI scans, and Karl Friston for valuable comments on the manuscript as well as guidance in statistical and fMRI analysis.
Reduced P300 and P600 amplitude in the hollow-mask illusion in patients with schizophrenia

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Submitted
Abstract

Illusions provide a useful tool to study the mechanisms by which top-down and bottom-up process interact in perception. Patients suffering from schizophrenia are not as subject to illusions as normal controls indicating a weakened top-down processing in schizophrenia. Little is understood about the neurobiology of this partial failure to experience illusions in schizophrenia. We used event-related potentials to investigate the hollow-mask illusion in patients with schizophrenia and healthy controls, since it has been shown that healthy participants perceive a hollow mask as a normal face, while patients with schizophrenia do not. We hypothesized that there will be a visible reduction of top-down processing in the patients’ group and that this reduction will occur in the late stages of processing. We found significantly decreased amplitudes in the P300 and P600 in the patients’ group, indicating that visual information does not benefit from frontal, parietal or temporal activity for perceiving incoming stimuli. We propose that a deficit in functional connectivity may be responsible for impaired top-down visual processing in schizophrenia. These data further the understanding of the time course of top-down processing in patients with schizophrenia.
Introduction

Visual illusions can reveal the mechanisms of perception which attach meaning to the world around us. In order to perceive the environment around us as meaningful, the interaction between bottom-up and top-down processing has to be intact (Wallbott and Ricci-Bitti, 1993; Cauller, 1995). There are two kinds of visual illusion: physiological illusions that occur naturally (such as afterimages), and cognitive illusions which demonstrate how human perceptual systems work (Gregory, 1997). Cognitive visual illusions occur because the brain interprets any incoming sensory information on the basis of knowledge and tries to add sense to the stimulus. In this study we use the principles of the ‘hollow-mask illusion’ (Gregory, 1973). The hollow-mask illusion occurs when a hollow mask is perceived (incorrectly) as a normal face. It is thought to be a process that involves the generation of hypotheses about the three-dimensional shape of faces by interpreting bottom-up signals received from the eyes using conceptual and perceptual knowledge (top-down processing), as well as general rules of perception, such as Gestalt laws of organisation and perspective (Yellot, 1981; Ramachandran, 1988; Hill and Bruce, 1993; Gregory, 1998).

In 1989 Emrich proposed that the pathogenesis of schizophrenia can be described as a functional dysequilibrium within the human brain, and that an impairment of the top-down processes may be a plausible explanation for the disintegrative and reality-impairing properties of psychotic disorders. Using the hollow-mask illusion, various studies have shown that patients suffering from schizophrenia are not subject to the illusion experienced by normal controls, meaning
that they perceived the ‘hollow’ face as being hollow (Schneider et al., 1996a, 2002; Emrich et al., 1997). These results indicate that weakened top-down processing in schizophrenia is unable to ‘correct’ incoming sensory data. Frith and Done (1988, 1989) and Malenka (1982) also suggested that internal correcting systems may be deficient in psychotic states and that an imbalance occurs in systems responsible for conceptual formation. Therefore, it has been suggested that patients with schizophrenia are forced to rely on stimulus-driven processing, wherein fragments of the stimulus are pieced together without reference to an expected or stored model (Hemsley, 1987, 2005). Similar results have also been found in other ‘pro-psychotic’ conditions such as cannabinoid-intoxicated states (Emrich et al., 1991, 1997; Leweke et al., 1999, 2000; Semple et al., 2003), alcohol withdrawal (Schneider et al., 1996b; 1998) and sleep deprivation (Sternemann et al., 1997).

We have previously used effective connectivity measures in functional magnetic resonance imaging (fMRI) data to demonstrate that in schizophrenic patients weakened top-down processing is accompanied by strengthened bottom-up processes (Dima et al., 2009). Our previous study employed fMRI data providing an excellent spatial resolution, but did not specify the temporal course of these findings. The electroencephalogram provides a direct and ‘real-time’ index of neuronal activities at a millisecond scale of resolution and is ideally suited to examine the rapidly changing patterns of brain activities that underlie human cognitive function and dysfunction (van der Stelt and Belger, 2007). Thus, in this study we used event-related potentials (ERPs) to explore top-down processes in the hollow mask illusion in schizophrenia.

Two ERP-components were of special interest regarding our experiment. The P300 component of the ERPs is a late positive wave that peaks approximately 300-
600ms after the presentation of an informative task-relevant stimulus and reflects higher level information processing functions (Knott et al., 1999). It most likely reflects brain processes functionally linked to attention allocation and memory updating operations in the brain (Polish and Kok, 1995). It has been shown to be impaired in schizophrenia in various studies (van der Stelt and Belger, 2007). The P600 component of the ERPs is also a late positive wave that peaks usually between 600-800ms which has been shown to be a distinct component from the P300 (Friederici, 2002; Frisch et al., 2003). P600 generators have been identified in several regions considered (i.e., hippocampus, entorhinal, cingulate, and ventral prefrontal cortex) important for episodic/declarative memory (Fernandez et al., 1999; Guillem et al., 1999; Halgren et al., 1994). Furthermore psychophysiological research suggested that the P600 component indexes the completion of any synchronized operation immediately following target detection, in other words, signals the second pass paring processes of information processing and is impaired in schizophrenia (Papageorgiou et al., 2001; Ruchsow, et al., 2003).

We used three kinds of stimuli in this experiment (faces, objects and the mask) that differed in their everyday familiarity (Hill and Bruce, 1994). Previous studies have shown that objects with a higher degree of everyday familiarity, i.e. faces, tend to evoke a more pronounced binocular depth inversion (Yellott, 1981; van den Enden and Spekreijse, 1989; Hill and Bruce, 1994). Thus, we hypothesized the illusion to be stronger in the face and mask condition for the controls and that in the object condition there will be no illusion for both groups. Furthermore, we expected to find disrupted top-down cognitive processes in the face and mask condition in schizophrenia, as reflected by a reduction of the amplitudes of the P300 and P600.
Methods

Subjects

Twenty patients (16 male, 4 women) suffering from schizophrenia and twenty age matched healthy subjects (16 male, 4 women) participated in the study (see Table 1). All patients fulfilled DSM-IV and ICD-10 criteria for schizophrenia and received antipsychotic medication which was stable for at least 10 days (15 patients were taking older and 5 patients second generation antipsychotic medication). Schizophrenic patients with other psychiatric disorders, including, e.g. personality disorders, drug and or alcohol abuse and neurological disorders, were excluded. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the current symptomatology of the patients. The level of educational was quantified using a scale from 1 to 5 coding different levels from high school to graduate university studies, according to the German educational system. All subjects underwent an ophthalmological examination before the study. Subjects were included in the study only if their vision was normal or corrected to normal, and all had normal colour vision. Stereoscopic vision was tested using the Netherlands Organisation for Applied Scientific Research TNO test (Lameris, Utrecht, Netherlands). All participants were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects provided written informed consent prior to their inclusion in the study, and the study was approved by the local ethics committee.
Table 1. Demographic and psychopathological data: Mean (SD)

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Stimuli and design

In order to test binocular depth inversion, stereoscopic pictures were taken (at a slightly different angle towards the displayed object) from three groups of different natural objects: ordinary objects (e.g. a chair), a mask (see Figure 1), and faces of men and women. Faces were photographed as frontal views. The pictures of the mask were taken from the rear, looking into the concavity of the shape (primary concave view), and also from the frontal view (convex view). The stereoscopic pictures were presented on a computer monitor with high resolution (overall stimulus size 800 × 600 points, 30.0 × 22.5 cm) and color depth (16 bits) for a maximum of 5 s. A Wheatstone mirror stereoscope (Wheatstone 1838) was used to achieve stereoscopic vision. Under laboratory conditions, it is possible to create a strong impression of three-dimensionality by presenting each eye with the corresponding stereoscopic image of the same face or object. The mirror stereoscope used four semi silvered trapezoid mirrors with two central right and left eye display mirrors (25 cm²),
and two larger lateral right and left mirrors (160 cm$^2$), each with a vertical axis of rotation. The distance between the presentation unit and the mirror stereoscope in front of it was 80 cm. The lateral mirrors reflected the corresponding part of the stereoscopic to the corresponding central mirror. The ability to rotate the lateral mirrors enabled the adjustment of the stereoscope to the individual intraocular distance of each volunteer. The mirror stereoscope ensured that the left picture was projected to the left eye of the subject and the right picture to the right eye. The result was that the subject perceived a single three-dimensional (3D) face or object in the middle of the display. Pseudoscopy, or binocular depth inversion, was induced by exchanging the pictures from the left and right sides. The volunteers were told that the presented objects might either have a convex (3D normal) or a concave (3D inverted) shape. Each inverted image displayed was presented also in a non-inverted way.

Twelve blocks were performed, each containing 36 stimuli (12 objects, 12 images of the mask, 12 faces), half concave and half convex, which were presented in a random order for 5 s each. Each block lasted 4.5 min and the blocks were separated with 2 min breaks. The volunteers were told that depth perception of each stimulus may vary, and were instructed to decide whether the face or object they saw was concave or convex. Participants had to answer after the image had disappeared (i.e. during the inter-item period that lasted 2.5 s), by pressing one of two buttons with the left or right index finger. The subjects were told that accuracy was the most important criterion, whereas speed of response was not important. Hence only the subjects’ correct responses will be analyzed.
**ERP acquisition and analysis**

EEG recordings were acquired with the Scan 4.0 software (NeuroScan Labs) and obtained from 31 scalp locations, including all standard sites of the International 10/20 system (Jasper, 1958). The horizontal electro-oculogram (EOG) was recorded with bipolar electrodes at the outer ocular canthi, and the vertical EOG was recorded using an electrode below the right eye referenced to the right outer ocular canthus. All electrodes were referenced to the right mastoid and electrode impedance was maintained below 5 kΩ. The biosignals were amplified using a 1.6 s time constant and processed with a band pass filter between 0.1 and 30 Hz (half amplitude low and high frequency cut-offs) and digitized at a rate of 250 Hz (AD resolution 12 bit, 4 ms). Automated artifact rejection was performed off-line to eliminate data epochs.

*Figure 1. Stereoscopic pictures of the mask (primary concave view).*
contaminated by blinks, saccades, and muscle activity and amplifier saturation (amplitude > 100 µV).

The ERP analysis was computed with the factors group (schizophrenia group vs. control group) and 3D inversion (where for each stimulus type separate analyses were performed: 3D normal faces vs. 3D inverted faces, 3D normal mask vs. 3D inverted mask and 3D normal objects vs. 3D inverted objects). The factor group was treated as a between-subject variable, whereas the 3D inversion factor was treated as a within-subject factor. The mean amplitudes of the ERPs were separately analyzed in a 300-600 ms time window (P300) and in the 600-800ms time interval (P600) for five electrode groups; frontal (Fp1-Fp2-F7-F3-Fz-F4-F8), temporal (T3-T5-T4-T6), parietal (P3-Pz-P4), central (C3-Cz-C4) and occipital (O1-Oz-O2). The ERPs and behavioral data were analyzed using repeated measures analysis of variance (ANOVAs) with a 5% confidence level (SPSS 16 Inc, Chicago, IL, USA).

Results

Behavioural data

We initially established that, as expected, patients and controls differed in terms of the susceptibility to the inverted-face illusion. Analysis of the response data collected during the task revealed that, due to the illusion, controls erroneously classified a 3D inverted face as 3D normal (mean = 91.9% +/- 14.3%). Notably, the patients classified a 3D inverted face as 3D normal to a much lesser extent (mean = 22.6% +/- 16.2%). This difference between the groups was highly significant ($F (1, 38) = 106.27, p < 0.001$), again suggesting that the patients were insusceptible to the illusion.
No significant differences were found between the two groups for the object and mask condition. More specifically, for the mask condition the patients almost never misclassified the 3D inverted mask as 3D normal (mean = 2.8% +/- 1.8%) as well as the controls (mean = 2.9% +/- 1.5 %), clearly showing that both groups were immune to the illusion and did not differ significantly \( (F (1, 38) = 0.67, p = 0.3) \). The same effect is also seen in the object condition. Again the patients almost never misclassified a 3D inverted object as 3D normal (mean = 1.6% +/- 0.7%) neither did the controls (mean = 2% +/- 1.1%).

**ERP results-face condition**

The grand average ERPs to 3D normal and 3D inverted faces for the patients’ group and the control group are illustrated in Figure 2 and Figure 3 respectively. As predicted, a significant difference was found between the two groups in the face condition. In the control group, the ERPs for the 3D normal faces did not differ from the ERPs for the 3D inverted faces. On the contrary, in the patients’ group, ERPs were more negative for the 3D inverted faces than for the 3D normal faces with an onset of about 300ms after stimulus presentation. In the P300 time window a significant group difference was found for three electrode groups (T3-T5-T4-T6; P3-Pz-P4; O1-Oz-O2) in interaction with the 3D inversion factor (group x 3D inversion). More precisely, for the temporal electrodes the groups differed significantly \( (F (1, 38) = 6.983, p = 0.012) \) and post-hoc analysis revealed that this effect was caused by the patients’ group \( (F (1, 38) = 6.160, p = 0.023) \), which differed significantly for the 3D inversion factor, and not by the control group \( (F (1, 38) = 0.956, p = 0.340) \). Similar significant differences were found for the parietal electrodes [group x 3D inversion: \( (F (1, 38) = 6.66, p = \)
3D inversion: patients’ group: \((F (1, 38) = 9.605, p = 0.006);\) control group: \((F (1, 38) = 0.002, p = 0.962)\) and for the occipital electrodes \([\text{group x 3D inversion: } (F (1, 38) = 7.697, p = 0.009); 3D inversion: \text{patients’ group: } (F (1, 38) = 11.030, p = 0.004); \text{control group: } (F (1, 38) = 0.063, p = 0.804)]\). No significant group-differences were found for the frontal and central electrodes (\([\text{group x 3D inversion: } p > 0.05])\).

Furthermore, ANOVA revealed the same pattern also for the P600 time-window. A difference between the groups (\([\text{group x 3D inversion: }])\) was found at the frontal electrodes \((F (1, 38) = 6.107, p = 0.018).\) Post-hoc analysis indicated that the patients’ group again differed significantly for the 3D inversion factor \((F (1, 38) = 10.208, p = 0.005),\) while the control group \((F (1, 38) = 0.059, p = 0.81)\) did not. Significant differences were also found for the temporal electrodes \([\text{group x 3D inversion: } (F (1, 38) = 8.317, p = 0.006); 3D inversion: \text{patients’ group: } (F (1, 38) = 15.104, p = 0.001); \text{control group: } (F (1, 38) = 0.608, p = 0.445)]\), for the central electrodes \([\text{group x 3D inversion: } (F (1, 38) = 6.125 , p = 0.018); 3D inversion factor: \text{patients’ group: } (F (1, 38) = 21.3, p = 0.000); \text{control group: } (F (1, 38) = 2.05, p = 0.168)]\) and for the occipital ones \([\text{group x 3D inversion: } (F (1, 38) = 4.474, p = 0.041); 3D inversion: \text{patients’ group: } (F (1, 38) = 17.269, p = 0.001); \text{control group: } (F (1, 38) = 1.847, p = 0.19)]\). There was a tendency \([\text{group x 3D inversion: }])\) between the two groups at the parietal electrodes \((F (1, 38) = 3.495, p = 0.069)\).

The topographic maps (Fig. 4) for the ERP difference waves (3D normal faces minus 3D inverted faces) showed more positive difference potentials at almost all electrodes sites during 300-900ms after stimulus onset in the patients’ group than in the control group \((p< 0.05)\).
Figure 2A. Grand average ERP waveforms for 3D normal faces and 3D inverted faces in the patients group (n = 20). Figure 2B. Grand average ERP waveforms for 3D normal mask and 3D inverted mask in the patients group. Figure 2C. Grand average ERP waveforms for 3D normal objects and 3D inverted objects in the patients group. Figure 2D. A scalp-map of the electrodes presented.
Figure 3A. Grand average ERP waveforms for 3D normal faces and 3D inverted faces in the controls group (n = 20). Figure 3B. Grand average ERP waveforms for 3D normal mask and 3D inverted mask in the controls group. Figure 3C. Grand average ERP waveforms for 3D normal objects and 3D inverted objects in the controls group. Figure 3D. A scalp-map of the electrodes presented.
A quite similar pattern can be seen in the mask condition for the patients where ERPs were more negative for the 3D inverted mask than for the 3D normal mask with an onset of about 300ms after stimulus presentation (Figure 2B). Nevertheless, this difference did not reach significance level compared to the controls (Figure 3B) for any electrode group (group x 3D inversion: p > 0.05). The same results were present for the object condition (Figure 2C; Figure 3C), where again no significant differences
where found between the two groups for any electrode group (group x 3D inversion: $p > 0.05$).

4. Discussion

In the current study, we established that patients with schizophrenia and healthy controls differ in terms of their susceptibility to the hollow-face illusion, and that this phenomenon is reflected by significant differences in their ERPs. More precisely, we showed that although the control group ERPs did not differ according to face-type presented (normal or inverted), it evoked a large discrepancy in the patients’ group. This discrepancy started in the late stages of visual processing, with the ERPs demonstrating a more negative course for the inverted faces. For the P300 the difference was more pronounced in occipital areas, whereas for the P600 the discrepancy lay in the frontal and temporal regions.

The interesting finding of this study is that when the controls fail to discriminate between the concave and the convex face we have no ERP difference. On the other hand, patients are not fooled by the illusion. The reduction of the P300 and P600 when patients with schizophrenia perceive the inverted face is consistent with the hypothesis that top-down input contributes to the perception of the hollow-face illusion. Due to the reduced amplitude of the P300 and P600 which are considered to be a measure of attentional resource allocation when memory updating is engaged (Polish and Kok, 1995; Papageorgiou et al., 2001; 2004) we can assume that these brain processes are constrained in patients in schizophrenia.
Although we expected that our control group would be susceptible to the hollow mask illusion when the stimulus would be a mask, this was not the case. The controls were able to distinguish between the concave and the convex view of the mask. One explanation we could offer for this is the fact that the mask used in this experiment is not based on a real face and thus we could assume that the degree of familiarity with this kind of mask is not high enough in order to create a strong effect of the illusion (Yellott, 1981; van den Enden and Spekreijse, 1989; Hill and Bruce, 1994). Moreover, in the patients group we have again a reduction in the P300 and P600 when the presented stimulus is the hollow mask, but the difference did not reach a significant level when compared to the controls.

In the last years several theories have been proposed that suggest that cognitive deficits associated in schizophrenia can be attributed to an impaired ability to use information (context) to interpret incoming stimuli (Silverstein and Schenkel, 1997; Hemsley, 2005). One such study used the ‘contrast-contrast’ illusion and showed that patients with schizophrenia are more accurate at judging contrast and thus less vulnerable to the illusion due to weaker contextual suppression (Dakin et al., 2005). Also, studies that used ERPs during linguistic processing by patients with schizophrenia have shown that P300 and N400 abnormalities appear to index failure to utilize preceding context, either semantic or probabilistic, to modulate stimulus processing (Nestor et al., 1997; Nestor and O’Donnell, 1998). Furthermore, Vianin and colleagues found a reduced P300 amplitude in a visual recognition task in patients with schizophrenia and concluded that this was due to reduced frontal/prefrontal activity when discriminating stimuli (Vianin et al., 2002). Our results are also
consistent with the above studies and suggest that contextual suppression also takes place during the hollow-mask illusion, occurring in the late stages of processing.

Contextual suppression or constrained top-down input on incoming stimuli accords with what Bleuler (1911) described as schizophrenia almost a century ago, as the ‘splitting’ of different domains. A number of theories have come forward based on the idea that the biological basis of schizophrenia is a disruption of particular neural circuits, most prominently the dysconnection hypothesis of schizophrenia (Friston and Frith, 1995; Friston, 1998). A study that used the rubber-hand illusion paradigm showed that patients with schizophrenia had significant alterations in long latency evoked responses during the illusion (Peled et al, 2003). In our fMRI study (Dima et al., 2009) it was shown that top-down influences from the fronto-parietal network contribute to the perception of the hollow-mask illusion in controls. By contrast, patients with schizophrenia did not seem to benefit from this top-down control. These findings as well as the current study support the hypothesis of alterations in associate higher-level activity in schizophrenia.

Looking in the neurobiology of schizophrenia our study also gives new insights on pharmacological studies of visual illusion. Studies that used Δ9-tetrahydrocannabinol, the major psychoactive compound of cannabis resin (Gaoni and Mechoulam, 1964), showed that subjects under the influence of cannabis are less able to experience the hollow-mask illusion (Emrich et al., 1991, 1997; Semple et al., 2003). Furthermore, the identification of a central nervous cannabinoid receptor (Devane et al., 1988) and of the endogenous cannabinoid receptor ligands, anandamide and 2-arachidonylglycerol (Devane et al. 1992; Stella et al. 1997), gave rise to investigations of the specific actions of naturally and synthetically obtained
cannabinoids. Studies using synthetic cannabinoids, Dronabinol (Leweke et al., 1999) and nabilone (Leweke et al., 2000) also showed that cannabis-intoxicated subjects were impaired in the perception of the hollow mask illusion. One study using cannabidiol, a nonpsychoactive cannabinoid, showed that subjects under the influence of cannabidiol experience the illusion in a normal fashion (Leweke et al., 2000). All the above studies implicate a functional disturbance in the endogenous cannabinoid system can be related with the pathology of schizophrenia.

In summary, we have shown that there is an increased number of correct responses in patients performing the hollow-mask inversion task, compared to controls subjects. These results confirm that patients with schizophrenia are greatly impaired in perceiving the hollow-mask illusion. The decreased amplitude of the ERP difference waveforms (3D inverted faces compared to 3D normal) in the time windows 300-600ms and 600-800ms in the patients’ group indicates that visual information in the pathological brain does not benefit from frontal, parietal or temporal activity when perceiving visual stimuli. This highlights the difficulty with which patients are able to refer to previous experience or knowledge in order to cope with incoming information. In line with our previous study (Dima et al., 2009), we propose that functionally deficient connectivity may be responsible for impaired top-down visual processing in schizophrenia.
Acknowledgements

We thank our colleagues for helpful discussions, and especially Jonathan Roiser and Ed Roberts for valuable comments on the manuscript. Finally, we would like to thank all the subjects who participated in this study.
4

Impaired top-down processes in schizophrenia: A DCM study of ERPs.

Danai Dima, Detlef E Dietrich, Wolfgang Dillo, Hinderk M Emrich

In preparation
Abstract

Perception is not simply based on a hierarchical organization of the brain; it arises from an interplay between inputs from the environment and internal predictions of these inputs. It is an active process which involves an interaction between bottom-up information coming from the senses and feedback connections coming from higher-order cortical areas. In our experiment we use the hollow-mask illusion to investigate the strength of top-down processes in schizophrenic patients and healthy controls. By using dynamic causal modelling (DCM) on functional magnetic resonance tomography (fMRI) data we have presented evidence to suggest that patients with schizophrenia are less constrained by top-down processes during perception (Dima et al., 2009). In this study we re-address this issue by using DCM on event-related potentials (ERPs) data. Our aim was to validate our previous findings by conducting the same connectivity method on data obtained from a different neuroimaging method. Our results confirm our initial hypothesis that top-down influences are constrained in schizophrenia, especially in perceptual tasks that require top-down control, like the hollow-mask illusion.
Introduction

Perception is the result of the interaction between information we receive from our senses and our existing knowledge, expectations and past experience. Perception in the healthy organism is a complex process involving many different aspects of brain functioning. The excessive cortical distribution and the complexity of activities that are needed for perception make it extremely vulnerable to any brain malfunctioning. In this paper our focus is on the impact of schizophrenia on perception. Schizophrenia is a chronic, severe and disabling brain disorder that affects about 1% percent of the population. In 1989 Emrich proposed that the equilibrium between sensory input (bottom-up processes), internal production of concepts (top-down processes) and control (decision making component) is disturbed in schizophrenia. He predicted that this functional disequilibrium will be more evident in the perception of ambiguous stimuli. An example of such an ambiguous stimulus is the hollow mask. Healthy individuals are prone to the ‘hollow mask illusion’ whereby a hollow mask is perceived (incorrectly) as a normal face. The face is perceived as convex because cognitive factors (top-down influences) override the binocular disparity cues of stereopsis (Gregory, 1973; 1998). It has been shown that, contrary to healthy participants, patients suffering from schizophrenia are less susceptible to the hollow mask illusion, thus perceiving the face as concave (Dima et al., 2009; Schneider et al., 1996; 2002).

The fact that schizophrenic patients are less susceptible to various visual illusions has been shown in a few studies (Dakin et al., 2005; Dima et al., 2009; Schneider et al., 1996; 2002; Uhlhaas et al., 2004). Recently we provided evidence
that schizophrenic patients exhibited changes in connectivity, in particular a weakening of top-down and a strengthening of bottom-up processes during the presentation of the hollow mask; by contrast, the controls exhibited a strengthening of top-down processes when perceiving the same stimulus (Dima et al., 2009). These findings suggest that schizophrenic patients are less constrained by top-down processes, where incoming sensory data are interpreted with reference to a model composed of stored information of past experiences and knowledge, during perception (Frith and Done, 1988; Malenka et al., 1982; Hemsley, 2005).

In our previous study (Dima et al., 2009) effective connectivity was measured with dynamic causal modelling (DCM) on functional magnetic resonance imaging (fMRI) data. In this study we employ the hollow mask illusion paradigm and conduct DCM on EEG (electroencephalography) data. This study aims firstly, to corroborate the validity of our previous findings that patients suffering from schizophrenia do not benefit from top-down processes, as controls do, and secondly, to further support these findings by conducting DCM on data obtained by using a different neuroimaging method on a larger sample size.

Materials and Methods

Subjects

Twenty patients (16 male, 4 women) suffering from schizophrenia and twenty age matched healthy subjects (16 male, 4 women) participated in the study (see Table 1). All patients fulfilled DSM-IV and ICD-10 criteria for schizophrenia and were taking antipsychotic medication (16 patients received atypical and 4 typical neuroleptica). Schizophrenic patients with other psychiatric disorders, including, e.g.
personality disorders, drug and or alcohol abuse and neurological disorders, were excluded. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the current stage of symptoms of the patients. The level of education was quantified using a scale from 1 to 5 coding different levels from high school to graduate university studies, according to the German educational system. All subjects underwent an ophthalmological examination before the study. Subjects were included in the study only if their vision was normal or corrected to normal, and all had normal colour vision. Stereoscopic vision was tested using the Netherlands Organisation for Applied Scientific Research TNO test (Lameris, Utrecht, Netherlands). All participants were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects provided written informed consent prior to their inclusion in the study, and the study was approved by the local ethics committee.

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data that corresponded to eight spatial modes. These were the eight principal modes of a singular value decomposition (SVD) of the channel data between 0 and 800 ms, over 3D inverted and 3D normal faces trials. The use of eight modes explained on average 88 % of the variance in the data across the group.

Table 2. Prior coordinates for the locations of the equivalent current dipoles in Montreal Neurological Institute (MNI) space (mm).

<table>
<thead>
<tr>
<th>Location</th>
<th>Coordinates</th>
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<tr>
<td>Left primary visual cortex (V1)</td>
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<tr>
<td>Left lateral occipital cortex (LOC)</td>
<td>-34, -93, 2</td>
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<td>Right supramarginal gyrus (SMG)</td>
<td>28, -34, 34</td>
</tr>
<tr>
<td>Right intraparietal sulcus (IPS)</td>
<td>22, -78, 52</td>
</tr>
<tr>
<td>Right inferior frontal gyrus (IFG)</td>
<td>46, 8, 10</td>
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</table>

Figure 2. Prior locations for the nodes in the models. Sources of activity were modeled as equivalent dipoles. Their prior mean locations in mm are superimposed in an MRI of a standard brain in MNI space.
DCM specification

In our previous study with fMRI data (Dima et al., 2009) we constructed 2 models with different modulation of effective connectivity but the same endogenous connectivity (see Figure 1). Three of the nodes where selected according to the results of the group x inversion interaction analysis, which showed significant effects in the supramarginal gyrus (SMG), intraparietal sulcus (IPS) and inferior frontal gyrus (IFG) (see Table 2; Figure 2). We also selected V1 from the contrast of all faces with rest as an input region (direct input of ‘all faces’ on V1). Finally, the lateral occipital cortex (LOC) was chosen as an area demonstrating a main effect of inversion across all subjects (see Table 2, for more details see Dima et al., 2009). All the coordinates used are in MNI space. Since DCM is a hypothesis-driven technique, the two constructed models allowed us to test our hypotheses, namely that (i) in controls, top-down influences from the fronto-parietal attention network result in the illusory perception of inverted faces as normal (see Figure 1A), while (ii) in patients, an impairment in the modulation of effective connectivity in this network produces a percept driven by bottom-up influences, preventing them from experiencing the illusion (see Figure 1B).

We have modeled each area (each node of the model, Table 2, Figure 2) with a single equivalent current dipole (ECD), with a prior variance of 32 mm. The moment parameters had prior mean of 0 and a variance of 8 in each direction. We have used these parameters as priors to estimate, for each individual subject, the posterior locations and moments of the ECDs (Table 2).
**Figure 3.** Model specification. The models have the same endogenous connectivity, but different modulation of effective connectivity according to face-type (3D inverted or 3D normal). The sources comprising the models were: V1: primary visual cortex; LOC: Lateral occipital cortex; SMG: supramarginal gyrus; IPS: intraparietal sulcus; and IFG: inferior frontal gyrus. **A.** Model 1, where the modulation is place on the backwards connection from the IPS to LOC. **B.** Model 2, where the modulation is place on the forwards connection from V1 to LOC.
In order to compare the two models we used two different methods. The first called group Bayes factor (GBF) is a fixed-effect analysis and assumes that all subjects’ data are generated by the same model. The best model, given the data, is the one with the highest log-evidence, \( \ln(p(y|I_m)) \). For each subject we computed their relative log-BF, \( \ln(p(y|I_{m1})) - \ln(p(y|I_{m2})) \) - where \( m_1 \) is model 1 and \( m_2 \) is model 2. In order to obtain the evidence for a given model over the others across subjects we added the log-BF from each subject. Raftery (1995) suggested an interpretation of BF as providing weak (\( BF<3 \)), positive (\( 3 \leq BF<20 \)), strong (\( 20 \leq BF<150 \)), or very strong (\( BF \geq 150 \)) evidence for one model over another. Until now GBF was the most used method to compare models in EEG data (Garrido et al., 2007, 2008). To be able to extent our inferences to individuals not included in the present study we also performed random-effects analyses. We used classical inference, applying simple t-tests to the log-evidence of the two models within and between groups.

Additionally, the modulatory influences were extracted from the subject-specific DCMs and further were analyzed. Behavioural and demographic data and parameter estimates from the DCM analyses were analyzed using SPSS 16 (SPSS Inc, Chicago, IL, USA) using t-tests, or appropriate non-parametric tests if data were not normally distributed, with alpha = 0.05.

Results

Behavioural data

We initially established that, as expected, patients and controls differed in terms of the susceptibility to the inverted-face illusion. Analysis of the response data
collected during the task revealed that, due to the illusion, controls erroneously classified a 3D inverted face as 3D normal (mean = 91.9% +/- 14.3%). Notably, the patients classified a 3D inverted face as 3D normal to a much lesser extent (mean = 22.6% +/- 16.2%). This difference between the groups was highly significant (F (1, 38) = 106.27, p < 0.001), suggesting that the patients were insusceptible to the illusion.

**Event-related potentials**

The grand average ERPs to 3D normal and 3D inverted faces for the patients’ group and the control group are illustrated in Figure 3. A group difference was identified in the time window 300 to 800 ms.

**Figure 3.** A. Grand average ERP waveforms for 3D normal faces and 3D inverted faces in the patients group (n = 20) for channels F3, C3 and P3. B. Grand average ERP waveforms for 3D normal faces and 3D inverted faces in the controls group (n = 20) for channels F3, C3 and P3.
In the patients’ group, ERPs were more negative for the 3D inverted faces than for the 3D normal faces and the difference was more pronounced in occipital and parietal areas for the P300, whereas for the P600 the discrepancy lays in the frontal and temporal regions (for more details see Chapter 3).

**Model Comparison**

We have constructed two models (see Figure 1). Comparing the two models using GBF revealed for the patients that Model 2 best explained the data (group log-BF = 33.682; BF = 4.2453e+014), where the modulation was placed on the forward connection between V1 and LOC. According to Raftery (1995) we have very strong evidence that the patients prefer model 2. On the contrary, the controls very strongly preferred Model 1 (group log-BF = 347.347; BF = 7.0939e+150), where the modulation was placed on the backwards connection from IPS to LOC.

Using simple t-test we showed that the groups differed in terms of their preference for Model 1 (t(38) = 2.047, p = 0.048). The patients with this random-effects analysis did not significantly differ between the 2 models (p> 0.05). On the other hand the controls group showed a significant difference (t(19) = 2.864; p = 0.01), strongly favouring Model 1.
Figure 4. Bayesian model comparison for the two models tested. The graph shows the log-evidence at the group level, pooled over subjects, for the two models.

DCM - Modulatory Influences

We further analyzed the modulation because we were interested in the extent to which endogenous connections were modulated by depth-inversion. In model 1 where the modulation was placed on the backwards connection from IPS to LOC we found significantly increased modulation in the controls compared to the patients ($t(38) = -2.92, p = 0.039$). Post-hoc analysis revealed that while both groups significantly increased effective connectivity from IPS to LOC when presented with 3D inverted faces this effect was much stronger in the controls ($t(19) = 358.645, p = 0.000$) than the patients ($t(19) = 41.424, p = 0.000$). In model 2, where the modulation was placed on the forwards connections from V1 to LOC the groups did not differ significantly
Post-hoc analysis revealed that both groups significantly increased effective connectivity from V1 to LOC when presented with 3D inverted faces (patients: t(19) = 16.097, p = 0.000; controls: t(19) = 15.215, p = 0.000).

**Relationship between behavior, connectivity and symptoms**

We identified no significant relationship between behavior and the modulation of connectivity with the LOC or with symptoms and the modulation (p>0.05 for all correlations). We found one significant correlation between delusions and the misclassification of 3D inverted as 3D normal faces (r = -0.462, p<0.05).

**Discussion**

In this study we have presented further evidence to support our previous findings (Dima et al., 2009). Our results indicate that patients with schizophrenia have impaired top-down processes during the perception of the hollow mask. By contrast, healthy controls exhibit a strengthening of top-down processes when perceiving the same stimulus. Specifically, we showed that patients and controls differ in terms of the modulation of connectivity according to face type (normal or inverted). The patients group showed preference for the model where the modulation was placed on the forward connection between V1 and LOC. On the other hand, the control group preferred the model where the modulation was placed on the backwards connection from IPS to LOC. Furthermore, we directly compared the modulatory effect of face type and we found a stronger modulation in the controls than the patients when the modulation was placed in the backwards connection between IPS and LOC. This result
confirms that top-down control contributes to the perception of the hollow-mask illusion in controls (Yellott, 1981; Ramachandran, 1988; Hill and Bruce, 1993; Gregory, 1998).

The finding that patients suffering from schizophrenia are impaired in perceptual tasks which rely heavily on top-down influences has been supported by many studies (Gilbert and Sigman, 2007; Gold et al., 2007). One line of research has used the visual masking paradigm to test this. In this paradigm the visibility of a briefly presented target is reduced by a mask that is presented very shortly before or after the target (Breitmeyer, 1984). By changing the order of appearance of the mask, different levels of top-down processes emerge. Forward masking (when the mask precedes the stimulus) relies more on bottom-up processes from the retina, and backward masking (when the stimulus precedes the mask) is based on an active interaction between bottom-up and re-entering top-down processes of visual information (Enns, 2004). Studies have shown that schizophrenic patients are impaired in backward (Green et al., 1997, 1999; Miller et al., 1979) but not in forward masking (Saccuzo et al., 1996). These studies indicate that there is a bias performance deficit in schizophrenia, with patients showing normal behaviour in tasks that rely on bottom-up processes and impaired perception in tasks that require top-down control.

Our findings are also in accordance with the ‘dysconnection’ hypothesis of schizophrenia (Friston, 1998; Stephan et al., 2009). The hypothesis states that ‘there is abnormal functional integration among brain regions in schizophrenia’, with some functional interactions appearing to be reduced while others seem to be abnormally increased. Several studies using EEG have found abnormal functional connectivity in schizophrenia (Saito et al., 1998). Studies that used dimensional complexity
(dimensionality of single-channel EEG time series), which is thought to correlate with performance of higher brain functions (Mölle et al., 1996), have shown that there is increased dimensional complexity in schizophrenic patients in rest (Koukkou et al., 1993; Lutzenberger et al., 1995). Other studies that used EEG coherency between different scalp locations during perceptual activation reported decreased coherence in patients (Hoffman et al., 1991; Rappelsberger et al., 1994; Merrin and Floyd, 1996).

Our study also indicates that there is a disconnection between the parietal cortex and the lateral occipital cortex in schizophrenia. By measuring the modulation of connectivity according to face-type between the parietal cortex, involved in top-down control, and the lateral occipital cortex, involved in bottom-up processing of visual information, we have shown that there is a reduction in the top-down influences in the schizophrenic patients. The reduction of top-down processes in schizophrenic patients may be responsible for their failure to perceive the hollow face illusion, because in order to perceive the hollow face as convex top-down influences have to be intact.

One form of top-down control failure that has been implicated in schizophrenia is the corollary discharge; a mechanism for distinguishing self-generated percepts from externally generated ones (Feinberg, 1978; Frith, 1992). Failures of corollary discharge are thought to underlie certain positive symptoms in schizophrenia, such as hallucinations and self-monitoring deficits. Patients suffering from schizophrenia may attribute their thoughts and actions to external agents due to a dysfunction of corollary discharge. Several EEG studies by Ford et al. (2001a; 2001b; 2002; 2005) have shown that a reduced fronto-temporal functional connectivity may contribute to the misattribution of inner thoughts to external voices in schizophrenia which is consistent with the hypothesis that there is a defective corollary discharge mechanism in
schizophrenia. Ford and his colleagues have suggested that hallucinations are produced because of the low input from the frontal areas to the temporal lobes. In other words, the ‘higher’ areas do not inform the ‘lower’ areas what the inner speech is generating. Although this field of research has mostly focused on the auditory modality, several studies have shown that corollary discharge also occurs in the visuomotor control (Franck et al., 2001; Spence et al., 1997; Ford et al., 2008). This indicates that there is a cross-modality impairment in self-monitoring in schizophrenia. Our study has implications for this area of research. Using DCM we have shown that top-down processes are constrained in schizophrenia and that this deficit becomes more evident in perceptual tasks that require top-down control. Future studies investigating the modulation of corollary discharge and showing directly that a failure of corollary discharge correlates with reduced modulation of connectivity should consider our findings.
General discussion
Synopsis

Perception arises as a result of an interaction between the two components: sensory input and prior knowledge (Frith and Dolan, 1997). The hollow-mask illusion, or else binocular depth inversion paradigm, represents a well known model of illusionary perception (Gregory, 1998). Visual illusions have been used before in investigating into the psychopathology and abnormalities of perception in schizophrenic patients. The advantage of using the hollow-mask illusion is that it allows for testing directly the interaction between top-down and bottom-up processes. We were interested in examining how this interaction takes place in the healthy brain and how it differs in patients suffering from schizophrenia.

In chapters 2, 3 and 4 we initially established that, as expected, patients and controls differed in terms of their susceptibility to the inverted-face illusion. More precisely, patients suffering from schizophrenia were insusceptible to the illusion; by contrast, controls were highly susceptible to it. These results are in accordance with previous studies (Schneider et al., 1996a, 2002; Emrich et al., 1997).

The aim of this thesis was to demonstrate that the schizophrenic patients fail to perceive the hollow-mask illusion due to a deficient functional connectivity that results from a weakening of top-down processes and a strengthening of bottom-up processes, in contrast to controls. Thus, two different connectivity models were specified in order to evaluate these hypotheses and they were tested as shown in chapters 2 and 4. The two models we constructed state that (i) in controls, top-down influences from the fronto-parietal attention network result in the illusory perception of hollow faces as normal, while (ii) in patients, an impairment of the modulation of effective
connectivity in this network produces a percept driven by bottom-up influences, thus preventing them from experiencing the illusion. In chapter 2 we were able to show that, indeed, top-down influences from the fronto-parietal network contribute to the perception of the hollow-mask illusion by controls. By contrast, patients lack a modulatory top-down control. Furthermore, by directly comparing the strength of the modulatory effect of face-type (hollow or normal), we were able to exhibit that patients show a strengthening of bottom-up processes, while the controls show a strengthening of top-down processes. In chapter 4 we were able to further validate these results, however this time by performing connectivity analysis on EEG data. This study confirms our hypothesis that there is a top-down impairment in patients suffering from schizophrenia.

In the work shown in chapter 3, we were interested in establishing the time course of this phenomenon. We were able to demonstrate that there is a reduction in P300 and P600 when patients with schizophrenia perceive a hollow face. This finding is consistent with the notion that top-down input contributes to the perception of the hollow-mask illusion, since both P300 and P600 are attributed to “higher” processes, such as the engagement of memory updating (Polish and Kok, 1995). Furthermore, the ERP differences found between controls and patients were located in the late time windows, thus providing with additional support the notion that top-down processing is disturbed in schizophrenia.
Implications of this work and directions for future research

I. The ‘cannabinoid hypothesis’ of schizophrenia

Our study also sheds light on the ‘cannabinoid hypothesis’ of schizophrenia (Emrich, 1996; Müller-Vahl and Emrich, 2008). Cannabis sativa is one of the oldest and most widely used drugs in cultural history. Delta-9-tetrahydrocannabinol (THC) has been identified as the major psychoactive constituent of cannabis sativa. THC and agonistic synthetic cannabinoids produce characteristic behavioral, cognitive and motor effects. The relationship between schizophrenia and the use of cannabinoids is complex and not fully understood. However, there is substantial evidence that heavy cannabis abuse is a risk factor for the clinical manifestation of schizophrenia and that it triggers both the onset of psychotic episodes in predisposed individuals and the relapse to schizophrenia in patients (Andréasson et al., 1987). The hypothesis that the consumption of exogenous cannabinoids may contribute to the pathophysiology of psychosis is additionally supported by the fact that the administration of intravenous THC to healthy volunteers may produce transient schizophrenia-like positive and negative symptoms (D’Souza et al., 2004; 2005; 2008). Investigating the hollow-mask illusion in THC-intoxicated normal volunteers compared to healthy controls revealed that the THC-intoxicated subjects were also immune to the illusion (Emrich et al., 1991, 1997; Semple et al., 2003). Similar results were obtained in studies using synthetic THC (Leweke et al., 1999) and nabilone, a synthetic cannabinoid (Leweke et al., 2000). Interestingly, a study that used cannabidiol, which is a non-psychoactive cannabinoid, did not find any effects on the perception of the illusion (Leweke et al.,
Emrich proposed that the central nervous endogenous cannabinoid system is involved in perceptual processes on a higher level of information processing and that this top-down processing is weakened under the influence of psychotropic cannabinoids. Indeed, the high receptor levels of the cannabinoid system in the limbic system suggest that. Our results point to some extent to similar disturbances of perceptual processes in schizophrenic patients and cannabis-intoxicated healthy volunteers. Moreover, our findings in this thesis suggest that the psychomimetic effects of these substances might be understood in terms of their effects on connectivity which result in a weakening of top-down processes, as was shown to be the case in schizophrenia. These hypotheses require verification in studies using pharmacological fMRI and EEG.

Elaborating on the “cannabinoid hypothesis” of schizophrenia, a large number of both animal and human studies support an interaction between the cannabinoid and the dopaminergic system. In the last decades, it has been largely suggested that psychosis is caused by an overactive dopaminergic system, the “dopamine hypothesis” of schizophrenia (Meltzer and Stahl, 1976). This is supported mostly by the capacity of dopaminergic drugs to cause paranoid psychoses and pharmacological studies show that antipsychotic drugs antagonize postsynaptic D2 receptors (Seeman and van Tol, 1994). Gardner and Lowinson (1991) found that THC acts as a dopamine agonist in dopaminergic projections of the medial forebrain bundles. Therefore, it has been speculated that cannabinoids cause or exacerbate psychoses by increasing the activity of the dopaminergic system. These findings indicate a tight link of the endogenous cannabinoid system to the dopaminergic system and point to an interaction linkage between these receptor systems in relation to schizophrenia.
II. The ‘dysconnection hypothesis’ of schizophrenia

In order to describe abnormal brain connectivity in schizophrenia two terms are most commonly used in literature: disconnectivity and dysconnectivity. These terms are frequently employed as if they are identical in meaning and interchangeable. Their different etymology, however, suggests otherwise. The Latin prefix *dis* means apart; thus “disconnection” refers to the breakdown of cognitive functions in schizophrenia. It implies that connectivity in schizophrenia is a priori reduced, with different brain areas communicating less than normal. On the other hand, the Greek prefix *dys* means bad or ill. This is exactly what the “dysconnection hypothesis” states; while some functional interactions appear to be reduced, other functional interactions may be abnormally increased. The term “dysconnection” ‘emphasizes the notion that ‘there is abnormal (rather than decreased) functional integration among brain regions in schizophrenia’ (Friston, 1998; Stephan et al., 2006; 2009). This statement is in total accordance with the findings presented in this thesis. The results of our studies in chapters 2 and 4 suggested that in healthy volunteers connectivity between two parts of the brain, the parietal cortex, involved in top-down control, particularly spatial attention, and the lateral occipital cortex, involved in bottom-up processing of visual information, increased when the hollow faces were presented. In patients with schizophrenia this increase did not occur. On the other hand, the patients showed an abnormal increase in connectivity between the primary visual area and the lateral occipital cortex, when presented with the hollow faces.
In the last twenty years, with the arrival of noninvasive neuroimaging techniques (fMRI, EEG and positron emission tomography, PET) many experiments have shown abnormally distributed activity and functional connectivity in schizophrenia. A PET study found that ‘schizophrenic subjects showed derangements in the pattern of interactions among brain areas’ (Volkow et al., 1988). Similar conclusions emerged from other studies based on PET; their findings were ‘consistent with the notion that schizophrenia involves pathology of and dysfunction within a widely distributed neocortical-limbic neural network’ (Weinberger et al., 1992). Moreover, many studies have found abnormal functional connectivity between temporal and frontal regions as measured by PET and fMRI (Friston et al., 1996; Lawrie et al., 2005; Meyer-Lindenberg et al., 2005). Similarly, analyses of cross-sectional studies suggested ‘disinhibition of left medial temporal lobe activity mediated by fronto-limbic connections’ (Friston et al., 1992). Furthermore, EEG studies have found abnormal functional connectivity patterns both during rest and during performance of various tasks (Breakspear et al., 2003; Hoffman et al., 1991; Koukkou et al., 1993; Saito et al., 1998). Finally, magnetoencephalography (MEG) and EEG studies have indicated abnormal beta and gamma band synchrony during sensory processing and cognitive tasks (Cho et al., 2006; Lee et al., 2003; Spencer et al., 2004; Symond et al., 2005; Uhlhaas et al., 2006).

How dysconnection arises in schizophrenia has been widely discussed in literature. The first explanation proposes that interregional functional coupling might be abnormal in schizophrenia because of impairments of structural (anatomical) connectivity, for example, due to aberrant wiring of association fibers during brain development (Bullmore et al., 1997). This explanation assumes that there is an
anatomical disconnection between brain areas and an abnormal operation of cellular processes like axons. The second explanation suggests that functional coupling could be disturbed due to impairments in synaptic plasticity (Friston, 1998). Synaptic plasticity indicates an experience-dependent change in synaptic strength (Zucker and Regehr, 2002). It has been proposed that plasticity is not abnormal per se in schizophrenia but that its modulation during reinforcement and perceptual learning may be (Friston, 2003a; 2005a). In this thesis we were able to quantify synaptic plasticity on a macroscopic level by assessing the dynamic modulation of connectivity using DCM. Furthermore, the hollow-face paradigm that was used throughout this thesis is related to the concept of perceptual learning; controls experience a 3D inverted face as a 3D normal face precisely because they have learned in the past that faces are convex and not concave. Our findings indicate that synaptic plasticity in schizophrenia is altered, since schizophrenic subjects fail to invoke top-down prior expectations while viewing the hollow face. This failure may be due to inferior perceptual learning during neurodevelopment and could reflect a sub-optimal balance between bottom-up sensory information and top-down prior expectations.

Of course, we do not wish to imply that dysconnectivity resulting from abnormal synaptic plasticity does not have structural substrates. On the contrary, there must be changes, for example, in the morphology of distribution of dendritic spines or in the numbers of transmitter receptors. Moreover, we should keep in mind that ‘any impairment in synaptic plasticity would affect the survival of long-range connections in the developing brain and thus the resulting pattern of anatomical connectivity in later life’ (Stephan at al., 2009). Indirect assessments of structural connectivity changes, such as multivariate analyses of covariations in regional brain volume or
morphometric analyses of white matter maps, have indicated disruptions of anatomical connectivity in schizophrenia (Kyriakopoulos et al., 2008). But for future research, we think the important question that needs to be answered in the field of connectivity in schizophrenia is whether disrupted axonal connectivity is secondary to or independent from synaptic plasticity.

Concluding remarks

Especially with regard to the visual system, the widespread view has been that lower regions start from the analysis of very simple characteristics of a stimulus and that the representation of this stimulus becomes progressively more complex as one moves up the hierarchy. However, the function of any cortical area is not fixed, but changes according to the current perceptual requirements. Perception is not simply based on a hierarchical organization of the brain; it arises from an interplay between inputs from the environment and predictions of these inputs. Moreover, these inputs and predictions travel across the different hierarchical levels of an interconnected cortical network. We know by now that even the primary visual cortex is subject to top-down influences of attention, expectation and perceptual task (Gilbert and Sigman, 2007). Thus, vision is an active process which involves an interaction between bottom-up information coming from the retina and feedback connections coming from the higher-order cortical areas.

In this thesis, our aim was to investigate this interaction between bottom-up and top-down processes in healthy volunteers and to understand how this interaction is
disturbed in schizophrenia. Our findings confirmed our initial hypothesis that top-down processes are constrained in schizophrenia. Furthermore, we were able to show that schizophrenic patients employ a stimulus-driven processing, whereby fragments of the stimulus are pieced together without reference to a model composed of stored information of past experiences and knowledge. Finally, we specified that the distortion of the balance between bottom-up and top-down processes in schizophrenia occurs in the late stages of sensory processing.
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Summary

Danai Dima

Investigation of neural correlates of bottom-up and top-down processing with functional magnetic resonance imaging and electroencephalogram. Exemplified by the binocular depth inversion-paradigm.

Perception is the result of interaction between sensory signals (bottom-up processing) and prior knowledge, predictions and models stored in memory (top-down processing). It is a crucial balance that has to be maintained in order to make sense of the environment around. Schizophrenia impacts on perception by creating an imbalance between top-down and bottom-up processes. This imbalance becomes more manifest when the percept is ambiguous like an illusion (Emrich, 1989). Illusions provide a useful tool for studying the impact of previous knowledge and contextual information on perception because the perceived stimulus diverges substantially from the real sensory input. In this research the binocular depth inversion paradigm, that is, the ‘hollow-mask illusion’, was used to investigate the interaction between top-down and bottom-up processing. The hollow mask illusion occurs when a hollow mask is erroneously perceived as a normal convex face. Studies so far have shown that patients suffering from schizophrenia do not perceive the illusion, but see the hollow mask as a hollow face (Schneider et al., 1996a, 2002; Emrich et al., 1997). Other studies have attributed this kind of findings to the impairment of the internal correcting systems (Frith and Dove, 1988; 1989; Malenka et al., 1982) and to an imbalance in systems responsible for concept formation in schizophrenia (Hemsley, 1987, Friston, 1998). In this research we hypothesized that the patients suffering from schizophrenia do not
perceive the hollow mask illusion because they rely more on stimulus-driven processing than on top-down processing.

The aim of this thesis was to test these hypotheses by using two complementing neuroimaging techniques, functional magnetic resonance tomography (fMRI) and electroencephalography (EEG). As anticipated, schizophrenic patients and controls differed in their susceptibility to the hollow face illusion. In contrast to control subjects, patients were immune to the illusion. In the fMRI study by using a novel connectivity tool dynamic causal modeling (DCM), we demonstrated that during the perception of the hollow faces schizophrenic patients exhibited changes in connectivity. In particular top-down processes were weakened and bottom-up processes were strengthened. On the contrary, when perceiving the same stimuli controls exhibited a strengthening of top-down influences. DCM analysis on EEG data verified these results. Furthermore, by using the event-related method we specified that the distortion in the balance between bottom-up and top-down processes occurs in the late stages of sensory processing in schizophrenia. These findings indicate that there is deficient functional connectivity in schizophrenia which constrains top-down control during perception.
Zusammenfassung

Danai Dima

Untersuchung der neuronalen Grundlagen der Interaktion von Top-down - und Bottom-up - Prozessen mittels funktioneller Magnetresonanztomographie und Elektroenzephalographie, anhand des Paradigmas der binokulären Tiefeninversion.


entstehen. Die Daten bestätigen, dass bei der Schizophrenie eine funktionelle Dyskonnektivität besteht, die die Wirksamkeit der Top-Down Komponente vermindert.
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Publications

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Conference Poster Presentations


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Publications


Talks

Dima D. Investigation of neural correlates of bottom-up and top-down processing with functional Magnetic Resonance Tomography und Electroencephalogram. Exemplified by the binocular depth inversion paradigm. Center for systems neuroscience, ZSN-Colloquium, Hanover, Germany, 3th November 2007.