# Cerebral Asymmetry in Schizophrenia

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**Abstract**

The hemispheres of the human brain are anatomically and functionally asymmetric, and many cognitive and motor functions such as language and handedness are lateralized. This review examines anatomical, psychological, and physiological approaches to the understanding of separate hemispheric functions and their integration. The concept of hemispheric laterality plays a central role in current neuropsychological and pathophysiological models of schizophrenia. Reduced hemispheric asymmetry has also been reported for other mental disorders, for example, bipolar disorder. Recent research reflects an increasing interest in the molecular and population genetics of laterality and its potential link with animal models of schizophrenia. The authors review the principles of laterality and brain asymmetry and discuss the evidence for changes in asymmetry in schizophrenia and other mental disorders.

**Keywords**

lateralization, planum temporale, corpus callosum, hemispheres, handedness

## Introduction

### *Lateralization and Functional Asymmetry*

Functional and structural asymmetry of the human brain has been reported frequently since the middle of the 19th century. This asymmetry extends from the gross anatomical level to differences in columnar organization (Hutsler and Galuske 2002), dendritic structure, and possibly even neurotransmitter distribution (Misgeld, 2005). However, the basis of the specialization of the cerebral hemispheres is still not well understood (Andrew, 2009). Whitehouse and Bishop (2009) suggested that functional asymmetry was more likely to be a result of independent probabilistic allocation of functions to the two hemispheres, rather than an overarching organizational principle.

In this review on laterality and lateralization and their role in schizophrenia, we use the term *lateralization* to denote a function that is preferentially subserved by the right or the left side of the brain—for example, language, commonly lateralized to the left hemisphere. Laterality is the preference for one side of the body that can result from such lateralization of brain function, for example, right-handedness. It is often linked with the concept of "hemispheric dominance," although it is not clear whether there is such thing as a general dominance of one hemisphere. The hemispheres rarely operate in isolation because they are directly connected through the corpus callosum, which is the main interhemispheric commissure, and the smaller anterior and posterior commissures.

Our knowledge of hemispheric specialization has been built on cases of so-called split-brain patients. To treat intractable epilepsy, whole or parts of the interhemispheric connections we removed in these patients. Another approach is to study the isolated function of one hemisphere through rare cases of hemispheric agenesis (Muckli and others 2009) or hemispherectomies, where fully developed cerebral hemispheres are removed because of Rasmussen's encephalitis, Sturge-Weber syndrome, or other severe forms of epilepsy (Devlin and others 2003). Clinical observations show partial recovery of brain functions—for example, language, perception, and motor skills (Devlin and others 2003; Muckli and others 2009; Samargia and Kimberley, 2009; Winter, 2010)—for lesions occurring prenatally up to adolescence, which is in contrast to the far more limited recovery after adult

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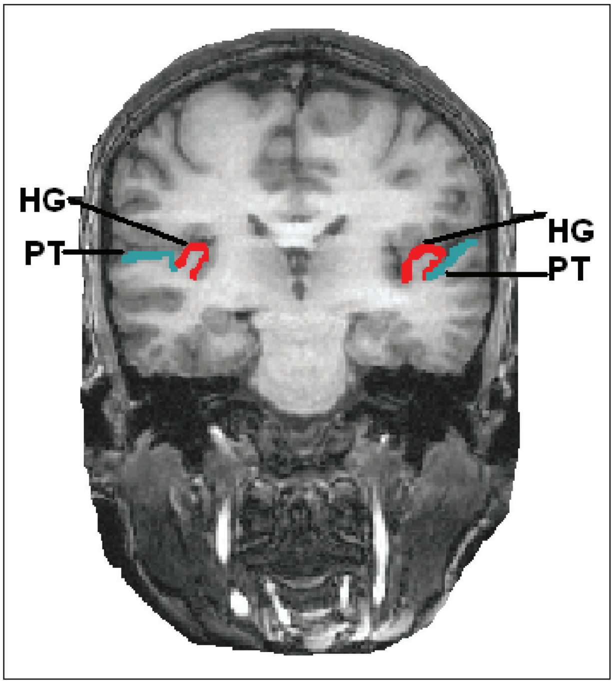


**Figure 1.** Delineation of planum temporale (PT) and Heschl's gyrus (HG) in an example of a healthy control subject. The brain image is shown in the sagittal view. Red = Heschl's gyrus; blue = planum temporale.

lesions (Vining and others 1997). Thus, different levels of neural plasticity need to be considered when studying large or complete hemispheric lesions at different points in development.

Hemispheric specialization is not limited to the human brain but also exists in animals, including fish, frogs, reptiles, birds, and mammals. In many animals, both hemispheres are specialized for different functions—for example, the left hemisphere is thought to be specialized for routine behavior, feeding, control of everyday tasks, and categorization of information (Vallortigara and Rogers 2005), and the right hemisphere may be responsible for detecting and answering to novel events, expressing intense emotion, and inducing emergency mechanisms (Walker 1980).

Although left-right asymmetries of the temporal cortex had already been proposed by neuroanatomists in the early 20th century, Geschwind and Levitsky (1968) were the first to demonstrate a leftward asymmetry of the planum temporale (PT; Fig. 1) quantitatively. The PT is known to be involved in speech sound processing. These postmortem findings were supported by further studies in healthy subjects, and evidence for related temporal lobe asymmetries was also found in nonhuman primates (Geschwind and Galaburda, 1985). Furthermore, Steinmetz and others (1991) showed smaller leftward asymmetry of the planum temporale in left-handers. Such findings were the basis for theories of a causal relationship between anatomical asymmetry of the temporal lobe and functional lateralization of the human brain.

## *Evolutionary and Genetic Theories of Lateralization and Laterality*

Some authors (Annett 2002; Vallortigara and Rogers 2005) suggest that lateralized behaviors either arose in early humans or evolved from behavioral asymmetries in ancestral species. Some authors suggest that lateralization of specific functions can be thought of as an evolutionary strategy to use cortical tissue efficiently in the sense that lateralization to one hemisphere increases space in the other (Cohen and Levy 1988). It may be necessary to preserve symmetric representations particularly for functions where fast reaction to environmental changes on either side of peripersonal space is required. Corballis (2009) argued that speech, skilled manual performance, or other complex motor patterns are relatively independent of such a need, and thus bilateral symmetry need not be as stringent.

Archaeological studies of cultural and skeletal remains report population-level biases toward right-handedness in early humans (Steele 2000; Toth 1985). Supporting genetic theories, Hepper and others (1998) suggested that behavioral laterality develops prenatally. For example, between 9 and 10 weeks' gestation, when embryos begin to make single arm movements, handedness is first shown (Hepper and others 1998). However, the nature of the genetics of handedness is not yet clear. More than 30 years ago, Annett (2002) introduced the idea of a "right-shift" factor, which may be present in an individual, contributing to right-handedness or not. Laland and others (1995) proposed a single dextral gene specifying right-handedness. The models implicating single dextrality genes mainly differ in the assumptions about the contributions of environmental influences. Corballis (2009) proposed that the presence versus the absence of asymmetry, rather than its direction, may be influenced by specific genes.

Functional asymmetry for language has been associated with the structural asymmetry of two perisylvian regions, anteriorly the pars triangularis (inferior frontal gyrus; Broca's area) and posteriorly the planum temporale (superior temporal lobe; Wernicke's area) (Foundas 1996; Foundas and others 1998; Galaburda and others 1991; Galaburda and others 1995). In a large MRI study of young right-handers, the left PT was on average about one-third larger than the right (Steinmetz 1996), which approximately matches the estimates obtained from postmortem studies (Geschwind and Levitsky 1968).

## Review of Empirical Research on Hemispheric Specialization

### Approaches of Experimental Psychology

Cognitive psychology provides several approaches to investigate the specialization of the hemispheres. The Wada test (Rasmussen and Milner 1977) uses selective anesthesia of one hemisphere to perform a neuropsychological examination of language comprehension, language production, verbal memory, and visual memory functions. Hugdahl (1988) used so-called dichotic listening tasks in order to evaluate selective attention in the auditory system. This approach originated in a phenomenon called Rand effect or "dichotic release from masking" (Rand 1974). During dichoting listening tasks, participants are asked to listen to two different auditory stimuli (usually speech), which are presented to either ear simultaneously. During the stimulation, participants are asked to attend to one or, in a divided-attention experiment, both of the messages. After the stimulation, individuals are asked about the content of either message. Bryden (1988) suggested that both structural and attentional components seem to be relevant for the dichotic laterality effect. This conclusion comes from the observation that, although there are ipsilateral projections from the inner ear to auditory cortex, a dichotic listening performance advantage for one ear may indicate a processing advantage in the contralateral hemisphere.

Most dichotic listening studies with speech or nonspeech sounds indicated that the majority of people have a left ear advantage for tasks involving the recognition of music or environmental sounds (Bryden 1988) and a right ear advantage for language sounds. With the help of this technique, it is possible to demonstrate the dissociation of phonetic (speech) and auditory (nonspeech) perception.

Similar techniques can be applied in the visual domain. It is possible to stimulate both visual cortices with different or the same (redundant target effects) material (Mohr and others 2002). The comparison of unilateral versus bilateral conditions provides a measure of hemispheric interaction. This paradigm has been tested for letters, patterns, numbers, symbols, and objects (Brown and others 1999; Koivisto 2000; Liederman and others 1985; Weissman and Banich 2000). Several authors reported mostly bilateral advantages (Liederman and others 1985; Koivisto 2000; Mohr and others 2002) and concluded that bilateral presentation of stimuli, where the participants have to match relevant information or to categorize across hemispheres, leads to better performance compared to unilateral presentation of the necessary information. This advantage may occur more in complex and less in simple matching tasks and would indicate hemispheric cooperation (Weissman and Banich 2000; Mohr and others 2002). A number of studies indicated a left hemisphere advantage for recognition of abstract words and low-frequency words but no clear advantage for concrete words (Lindell 2006).

### Functional Specialization of Hemispheres

Hemispheric specialization of cognitive functions, including attention, emotion, motor control, and language (e.g., Bryden 1988; Corballis 1993; Hellige 1993; Galaburda and others 1995; Ivry and Robertson 1998; Toga and Thompson 2003; Dien 2009; Brancucci and others 2009), has been reported frequently. Models of functional hemispheric specialization are based on convergence of experimental, neuropsychological (human lesion studies), brain imaging, and electrophysiology work. For example, linear reasoning, numeric and arithmetic skills (Lewy and others 1999), and language functions such as grammar and vocabulary are often lateralized to the left hemisphere of the brain, whereas prosodic language functions, such as intonation and accentuation, are controlled by the right hemisphere (Ross and Monnot 2008; George and others 1996). According to Goldberg (2009), the left hemisphere is most involved when routine or well-rehearsed processing is required, whereas the right hemisphere is more called on for processing novel situations. Dehaene and others (1999) reported that other integrative functions, including binaural sound localization, arithmetic, and emotions, are more bilaterally controlled.

However, some emotional and evaluative processes in the visual domain may be lateralized as well. For example, face recognition seems to be right lateralized (Sackeim and Gur 1978; Sergent and others 1992). Hellige (1993) reported that patients suffering from right hemisphere damage have greater difficulty in interpreting emotion in speech than patients with left hemisphere damage. Borod and others (1990) suggested the same effect for recognizing emotional words and Bowers and others (1995) for identifying emotion in faces.

### Handedness

The distribution of handedness among humans is asymmetric. Several theoretical models (Hardyck and Petrinovich 1977; Annett 2002) have been proposed. There are three possible types of hand dominance: left-handed, right-handed, or mixed-handed. Only 7% to 10% of the population is left-hand dominant. Mixed-handedness, which most commonly denotes the use of one hand for a number of tasks and the other for other tasks (e.g., writing with the right hand but throwing with the left), is found in 25% to 33% of the population (Annett 2002). Mixed-handedness may also reflect mixed laterality in other domains where eyes, ears, feet, and hands are favored on different sides (Porac and Coren 1981). However, Guiard (1987) suggested that handedness is not a simple matter of genetically transmitted preference but the expression of a more complex collaboration of both hands, in which the right hand appears specialized for finer movements and the left for broader contextual activities. An example would be a right-handed person whose left hand orients and grips the paper and provides the context from which the right hand operates, whereas the right hand writes on the paper.

Several authors (e.g., Corballis 1993; Annett 2002) believe that a number of characteristics such as language, cerebral asymmetry, and handedness were developed parallel to the development of *Homo sapiens*. Furthermore, studies on left-handedness have shown that the handedness of a child is strongly related to that of his or her biological parents (Hicks and Kinsbourne 1976; Carter-Saltzman 1980), and left-handedness is often thoroughly maintained in families (familial sinistrality; Coren 1994). Tzourio-Mazoyer and others (2010) examined the impact of left-handers in healthy families on planum temporale volume and found reduced size of the left PT in subjects with left-handers among their close relatives. The results indicate that laterality may depend on genetic influence on the brain and additional environmental factors.

Studies investigating the association between handedness and language dominance using different methodological approaches (e.g., electroconvulsive therapy [Warrington and Pratt, 1973], brain imaging [Pujol and others 1999; Knecht and others 2000]; Whitehouse and Bishop 2009) show that in more than 95% of right-handed men and more than 90% of right-handed women, articulate language is subserved by the brain's left hemisphere. The incidence of left hemisphere language dominance in left-handed people has been reported at between 61% (Taylor and Taylor 1990) and 73% (Knecht and others 2000). Taylor and Taylor (1990) reported that 19% of left-handed people have bilateral language functions. Further studies with Doppler ultrasonography (Flöel and others 2005) showed that atypical patterns of asymmetry for verbal production and spatial attention are more common in left- than in right-handers.

## Cerebral Asymmetry in Schizophrenia

Disturbed hemispheric lateralization, including structural and functional asymmetries, is one of the central areas of schizophrenia research and may be helpful in understanding the etiology of the disorder (e.g., Løberg and others 1999; Mitchell and Crow 2005; Paul and others 2007; Hugdahl and others 2008). For example, several studies investigating PT volume in schizophrenia reported reduced PT lateralization (Fallgatter and Strik 2000; Hori and others 2008; Petty and others 1995; Barta and others 1997; Hirayasu and others 2000; Kasai and others 2003). Angrilli and others (2009) and Spironelli and others (2008) proposed a neuropsychological link between reduced language lateralization and the psychopathology of schizophrenia. The most influential theory about lateralization in schizophrenia is the one proposed by Crow (Crow and others 1989), who introduced the idea that schizophrenia results from a failure of normal cerebral lateralization and that this failure is genetically determined. Following up on this, twin studies (Niethammer and others 2000), molecular genetic studies (e.g., Leonard and Freedman 2006; Francks and others 2007; Crow 2008), and animal models (Morice and others 2005; Vallortigara and Rogers 2005) have been applied to study cerebral asymmetry in schizophrenia. One important point is whether reduced asymmetry is specifically associated with schizophrenia or rather with cognitive impairment, as suggested by Leonard and others (2008). The findings by Oertel and others (2010) of reduced PT asymmetry in cognitively unimpaired relatives of schizophrenia patients support a specific association between reduced laterality and the risk of schizophrenia, although they do not rule out altered asymmetry as an independent risk factor for cognitive impairment.

### *Functional Specialization of the Hemispheres in Schizophrenia*

Several authors have found that schizophrenia patients are more often left-handed than people without schizophrenia (7%–31% vs. 1%–20% of the healthy population; Shukla and others 1993; Green and others 1994; Hugdahl and others 2008). Interestingly, several authors (e.g., Satz and Green, 1999; Sommer and others 2001) suggested that schizophrenia patients are more likely to be mixed-handed. Observations in nonclinical populations (Nicholls and others 2005) indicate that mixed-handedness is associated with an increase in magical thinking. Furthermore, dichotic listening tasks (Shukla and others 1993; Green and others 1994; Hugdahl and others 2008) showed no right ear advantage in hallucinating schizophrenia patients (Green and others 1994; Hugdahl and others 2008), whereas nonhallucinating patients showed the normal right ear advantage. This indicates that auditory hallucinations may be associated with abnormalities in left hemisphere functioning.

The search for causes of reduced lateralization in schizophrenia is ongoing (Shenton and others 2001). Genetic mechanisms (Annett 2002; Crow 2002), prenatal selective hemispheric damage (Witelson and Nowakowski 1991), and neurodevelopmental abnormalities (Rapoport and

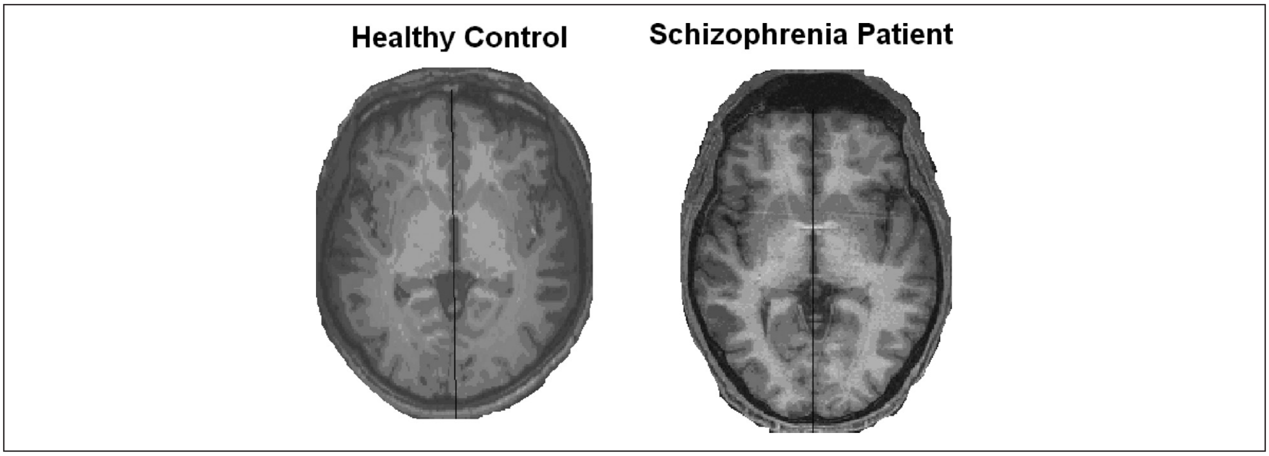


**Figure 2.** Examples of torque in a healthy control and its absence in a schizophrenia patient. The brain images are shown in transversal view and radiological convention (right side of image is left side of brain).

others 2005) have all been implicated. Witelson and Nowakowski (1991) suggested that prenatal hemispheric insult contributes to the loss of hemispheric lateralization (e.g., of the hand preference). They furthermore suggested that a loss of axons of the corpus callosum may be one mechanism underlying the embryological development of hand preference and hemispheric anatomical and functional asymmetries.

Crow (2002) suggested a disruption of hemispheric lateralization in schizophrenia due to mutation of the right-shift gene (Annett, 1999, 2002), which would lead to loss of neurons in the left hemisphere (Hugdahl and others 2008). Reduced asymmetry (driven by left hemispheric volume reductions) of the temporal lobe in relatives of schizophrenia patients supports Crow's hypothesis (e.g., Oertel and others 2010). Many genes that have been tentatively implicated in schizophrenia have a direct influence on brain development, regulating such processes as neuronal migration, axonal guidance, myelination, neurotransmission, and synaptic plasticity (Owen and others 2004; Harrison and Weinberger 2005). Some of these genes have been associated with anatomical brain abnormalities in schizophrenia patients and their first-degree unaffected relatives (Addington and others 2007; Gruber and others 2008; Winterer and others 2008; Van Haren and others 2008; Zinkstok and others 2008). Many researchers now agree that genetic abnormalities observed in schizophrenia further predispose and sensitize the brain to environmental stresses, resulting in a lifelong dysregulation of brain development and plasticity that predisposes the subject to schizophrenia (Bartzokis 2000; Pantelis and others 2005). This may explain why some structural and functional changes are found in relatives as well but are then more pronounced and widespread in patients.

## *Evidence from Neuroimaging and Postmortem Studies*

Postmortem and MRI studies of gray matter volume asymmetry in schizophrenia reveal reduced or reversed asymmetry of the planum temporale (Kwon and others 1999; Hirayasu and others 2000) and a reduction or absence of normal torque (i.e., the right frontal and left occipital petalias [Bilder and others 1994; Kwon and others 1999]; see Fig. 2 for an example). There is also a considerable amount of evidence for altered interhemispheric connections.

*Corpus Callosum.* Both the varied clinical presentation and the neurophysiological and neuroanatomical findings (Shenton and others 2001) have led to the assumption that schizophrenia is brought about by distributed changes in and faulty connections between multiple brain areas (Friston 1998) rather than a lesion to a single brain region or functional system. Smaller volumes of the corpus callosum or its subregions in schizophrenia patients have been found in most of the relevant MRI studies (Downhill and others 2000; Goghari and others 2005; Rotarska-Jagiela and others 2008). In addition, postmortem studies have shown an association between reduced numbers of pyramidal cells and disturbances in the cortico-cortical connectivity (Crow and others 1989; Pierri and others 2001), whereas diffusion tensor imaging studies have mostly shown decreased fiber integrity for schizophrenia patients in the whole or parts of the corpus callosum (Agartz and others 2001; Ardekani and others 2003; Hubl and others 2004; Buchsbaum and others 2006; Rotarska-Jagiela and others 2008; Rotarska-Jagiela and others 2009).

*Planum Temporale.* The predominant opinion in the literature is that the reduced cerebral asymmetry indicates genetic abnormalities responsible for cerebral lateralization. Further investigations showed that these structural changes correlate with clinical (Oertel and others 2010) and cognitive parameters, for example, executive and memory functions (Toga and Thompson 2003). However, the structural imaging literature and postmortem literature on temporal lobe asymmetry changes in schizophrenia have been inconsistent, with only half of the published MRI studies reporting changes in patient groups (Chance and others 2008). However, some of this inconsistency could be attributable to methodological differences in the measurement of the cortical regions of interest and sample selection (Oertel and others 2010).

*Brain Function.* Reduced functional asymmetry in schizophrenia has been reported frequently (Sommer and others 2001; Spaniel and others 2007; Bleich-Cohen and others 2009; Oertel and others 2010). For some language-mediated cognitive and psychopathological symptoms in schizophrenia, altered interaction between regions within the superior temporal gyrus and across hemispheres was found to be at least partially responsible for reduced asymmetry (Lennox and others 2000; Dierks and others 1999; van de Ven and others 2005; Ishii and others 2000; Kircher and others 2004). Some functional imaging studies of neural correlates of psychopathological symptoms report predominantly right hemispheric activation even in left-handed patients during task performance (Geschwind and others 2002)—for example, for auditory hallucinations (Sommer and others 2001)—but results have been inconsistent (see Dierks and others 1999; van de Ven and others 2005).

### *Altered Asymmetry in Relatives*

The investigation of unaffected individuals who carry a genetic risk of schizophrenia has contributed to the debate of cerebral asymmetry in schizophrenia. In general, family, twin, and adoption studies suggest an important genetic role in the etiology of schizophrenia (McGuffin and others 1995; Cardno and others 1999; Bediou and others 2007; Crow 2008; Whalley and others 2007). Hemispheric laterality in relatives of schizophrenia patients has mainly been investigated with functional imaging during language tasks. Sommer and others (2004), Whyte and others (2006), and Li and others (2007) reported significantly decreased lateralization of activity in the inferior frontal gyrus, caused by relatively higher right hemisphere activation (Sommer and others 2004; Whyte and others 2006) or lower left frontal activation (Li and others 2007). A genetic predisposition may increase sensitivity to environmental triggers. Currently, the only study investigating both structural and functional asymmetry of the auditory cortex in relatives is that of Oertel and others (2010). In this study, we showed that relatives had intermediate asymmetry measures between patients and controls on both structural and functional measures. This study also suggested associations between reduced asymmetry in these areas and the severity of positive symptoms, including auditory hallucinations in the patient group.

## Altered Brain Asymmetry in Other Mental Disorders

To address the question of diagnostic specificity, several authors have investigated altered asymmetry in other mental disorders. Evidence for reduced cerebral asymmetry in affective disorders, especially in bipolar patients and anxiety disorder, has frequently been reported (Bruder and others 1992; Bruder 1993; Kato and others 1995; Bruder and others 1997). Bruder (1993) reviewed the evidence from dichotic listening tasks in schizophrenia and affective disorders and reported an association between clinical state and ear asymmetry. Overall, greater severity of illness in schizophrenia and depressed patients appeared to be associated with reduced laterality, whereas clinical remission was accompanied by a normalization of laterality. In 1991, Wexler and Gille asked schizophrenia, schizoaffective, and depressed patients to perform a dichotic nonsense test and a dichotic word test. The results showed significantly lower right ear advantages for schizophrenia, depressed, manic, and schizoaffective patients in comparison with controls. However, they found an interesting syndromal differentiation. Manic patients with lower right ear advantages were likely to have more symptoms of thought disorder than of mood disturbance, whereas the reverse was found for manic patients with higher right ear advantages.

Bruder and others (1992) used visual half-field, visuospatial tests, and dichotic listening measurements of perceptual asymmetry to investigate cerebral laterality in bipolar and unipolar major depression. Whereas both unipolar patients and healthy controls displayed the left visual field (right hemisphere) advantage for dot enumeration, bipolar patients failed to do so. Brain event-related potentials recorded during audiospatial and temporal discrimination tasks revealed an electrophysiological correlate of abnormal visual field asymmetry in bipolar depression. Bipolar patients had reduced event-related responses to test stimuli in the left compared to the right hemifield, which was not the case for patients with unipolar depression and controls. The origins of left hemifield deficits in bipolar depression have been sought in right-sided dysfunction of an arousal/attentional system involving temporoparietal and possibly frontal regions (Bruder and others 1992).

## Discussion

The human cerebral hemispheres are anatomically and functionally asymmetric. Many cognitive and motor functions, such as handedness, language, linear reasoning, and numeric and arithmetic skills (Lewy and others 1999), are often lateralized to one hemisphere. Alterations of this structural and functional asymmetry feature prominently in current models of schizophrenia. Postmortem and MRI studies of gray matter volume asymmetry in schizophrenia have revealed reduced or reversed asymmetry of the planum temporale and a reduction or absence of the brain's normal anticlockwise torque (i.e., the right frontal and left occipital petalias). Reduced hemispheric asymmetry has also been reported in affective disorders.

Crow (Crow and others 1989) proposed that schizophrenia results from a failure of normal cerebral lateralization and that this failure is genetically determined. Abnormal hemispheric asymmetry may result in impaired speech processing, which has been proposed to be a key cognitive factor in the manifestation of schizophrenic symptoms (Stephane and others 2001; Frith 2005). Reduced asymmetry of the PT has considerable explanatory power for models linking neuroanatomy and phenomenology of schizophrenia, but findings have not been consistent. To advance our knowledge of reduced structural asymmetry of the PT and adjacent temporal lobe areas in schizophrenia, a large-scale study with a homogeneous, gender-matched, and handedness-matched patient group would be needed, using a combination of surface and volume measures. This might be combined with a genome-wide association study, looking for a potential genetic association with planum temporale asymmetry as a quantitative trait.

The reduction of cerebral asymmetry in temporal lobe structure and function in schizophrenia patients and relatives supports a continuum of schizophrenia-associated anatomical changes (Oertel and others 2010). Artiges and others (2000), Sommer and others (2001), Hubl and others (2010), and Oertel and others (2010) also reported that reduced temporal asymmetry was clinically relevant by contributing to hallucinations and other positive symptoms. These findings support the idea that changes in brain organization in schizophrenia strongly contribute to the psychopathological manifestation of the disease (Crow and others 1989; Friston 1998). Anatomical changes may underlie these functional connectivity abnormalities and contribute to the experience of positive symptoms, such as hallucinations and delusions (Gaser and others 2004; Levitan and others 1999; Sumich and others 2005). Theoretical models of the pathomechanism in schizophrenia now suggest that genetic abnormalities observed in schizophrenia further predispose and sensitize the brain to environmental insults, resulting in a lifelong dysregulation of brain development and plasticity (Bartzokis 2000; Pantelis and others 2005).

## Conclusions and Implications

The current update assesses the evidence for altered laterality and hemispheric asymmetry in schizophrenia and suggests avenues for further study. The reduction of left-right lateralization of temporal lobe structure and function supports a continuum of schizophrenia-associated anatomical changes along a putative genetic spectrum. In patients, the reduced temporal asymmetry may contribute to hallucinations and other positive symptoms. Changes in hemispheric asymmetry thus are promising parameters for pathophysiological and neuropsychological models of schizophrenia and warrant further investigation both in patients and people at genetic risk. One aim should be the identification of genes involved in the control of cerebral lateralization, which can then be explored for potential variants associated with schizophrenia. The study of asymmetry and laterality is also of interest for the discussion on the syndromal nature of schizophrenia and its potential overlap with other psychotic disorders.

Although some of the behavioral and biological indicators of altered laterality in schizophrenia are reasonably stable across studies, their sensitivity and specificity are insufficient to qualify as biological markers. Thus, we are still far from a diagnostic use of laterality parameters. However, apart from increasing our knowledge of the neurodevelopmental processes of schizophrenia, the study of functional and structural asymmetry may have therapeutic implications. For example, Gruzelier (1994) developed a theoretical model of hemispheric imbalance in schizophrenia. He proposed two syndromes of schizophrenia distinguished by opposite asymmetries in hemispheric activation: a florid syndrome that is coincidental with left hemisphere overactivation and a nonflorid syndrome with right hemispheric overactivation. If a hemispheric functional imbalance can indeed be established as being clinically significant in individual patients, suppression of the overactive hemisphere with transcranial magnetic stimulation (Sack and Linden 2003) may have some benefit.

Although the potential clinical benefits of laterality research in schizophrenia have not yet been harnessed, it has proven to be a fascinating field linking clinical psychiatry with evolutionary psychology and biology, and we are confident that it will provide further insights into the mechanisms of the disease.

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