From Semantic to Social Deficits: Dysfunction of the Nondominant Posterior Perisylvian Area in Schizophrenia

Salvador M. Guinjoan, M.D., Ph.D., Delfina de Achával, Ph.D., Mirta F. Villarreal, Ph.D., Valeria Abusamra, Ph.D., Charles B. Nemeroff, M.D., Ph.D.

Schizophrenia is characterized by profound deficits in social competence and functioning, independent from active psychotic symptoms at different stages of the disease. Social deficits in schizophrenia are clinically well characterized, but their neurobiological underpinnings are undetermined. This article reviews recent evidence supporting heritable deficits in a circuit necessary for appropriate naming of emotions and mental states in others, centered at the temporoparietal junction of the nondominant hemisphere. The clinical implications of this model are discussed, including the potential use of rehabilitation techniques oriented to recognition and naming of emotions and mental states as a necessary step for social rehabilitation.

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Mental health disorders are the main cause of years lived with disability worldwide; among these disorders, schizophrenia accounts for 7.4% of all years lived with disability despite a lifetime prevalence of <1%.[1] Loss of social abilities is a hallmark of the disorder, preceding the onset of positive symptoms and persisting after their successful treatment with a variety of available antipsychotic medications; compromised social competence is a major determinant of disability in this disorder.[2] Unfortunately, the neurobiological mechanisms of social dysfunction in schizophrenia are largely undetermined, although a combination of neurocognitive and social cognitive deficits is usually considered an important contributing factor. In this review, we summarize evidence by our group and others that social disability in schizophrenia is related to disturbed activity of the right, nondominant hemisphere, resulting in a sensory aphasia specific for emotionally laden nouns and adjectives, which might occur independently from, but could contribute to, general cognition and especially to social cognition. We commence with a description of linguistic functions of the nondominant hemisphere, and we review evidence germane to right hemisphere dysfunction as well as social cognition in schizophrenia. We then describe relevant work that has attempted to characterize neurobiological underpinnings of such abnormalities. We conclude by proposing a hypothesis of nondominant posterior perisylvian area dysfunction in schizophrenia and discussing the clinical implications of such a hypothesis.

LINGUISTIC FUNCTIONS OF THE NONDOMINANT HEMISPHERE

The classic model of language connectivity, formulated in the 19th century but summarized by Geschwind,[3] posits that Broca's area (posterior section of the left inferior frontal gyrus) and Wernicke's area (posterior middle and superior temporal gyrus, inferior parietal lobule, superior temporal sulcus in the left hemisphere) deal with speech production and comprehension/lexical access, respectively, connected by means of the arcuate fasciculus. Despite its relative simplicity, the model has shown remarkable resilience, probably due in part to its utility in the diagnosis of acquired language disorders.[4] More recent models of brain connectivity subserving language in humans postulate the presence of dorsal and ventral "streams" concerned with mapping of speech sounds to motor representation and to meaning, respectively.[4,5] However, it remains well recognized that the right hemisphere is not primarily involved with basic levels of language such as phonology, morphology, and syntax.[4,5] However, there is consensus based on diverse sources of evidence that the right hemisphere is involved in pragmatic aspects of language that are critical for understanding the speaker's intention. Thus, lexical semantic processing is currently considered to occur bilaterally.[5] Linguistic functions of the right hemisphere have been inferred from both lesion and functional neuroimaging studies and were extensively summarized by Mitchell and Crow[6] in their seminal review of this topic. In brief, such

abnormalities involve not only prosody (traditionally considered a language function regulated by the right hemisphere) but also comprehension of the main or central theme of discourse, as well as pragmatic aspects of linguistic social communication, including slights, metaphor, humor, and irony. Patients with right hemisphere damage generally understand the literal meaning of utterances well, but comprehension of the main theme of a topic of conversation or reading is usually impaired.[7,8] In addition, understanding of metaphors, indirect requests, humor, sarcasm, and irony is almost uniformly impaired in patients with schizophrenia in most studies.[9–11] Of note, whereas active psychotic symptoms have been found to have a definite role in deficits in these areas, a significant part of the impairment does not depend on symptoms but is considered to constitute a trait inherent to the disease.[12,13]

An additional source of evidence underscoring linguistic functions of the nondominant hemisphere comes from patients with "disconnection syndromes," either with sections or agenesia of the corpus callosum. These studies suggest that left hemispheric structures involved in language comprehension and production necessitate input from the nondominant hemisphere to appropriately and accurately label emotions. In classic studies, commissurotomized patients can show nonverbal indications that they understand emotion but are unable to verbalize these feelings.[14] Patients with agenesia of the corpus callosum use less emotional words in the Thematic Apperception Test descriptions.[15] Buchanan et al.[16] described these patients as having difficulties verbalizing feelings. These findings point to the fact that the right hemisphere must not only be intact for these linguistic functions to be accomplished, but it must also be appropriately connected to structures of the left, dominant hemisphere if the understanding and production of speech conveying emotional meaning are to occur normally (see below).

This and other evidence led to the idea that the left hemisphere has no direct access to the emotional aspects of language, necessitating an intact input from the right hemisphere if emotionally laden words are to be used effectively (reviewed by Shobe[17]).

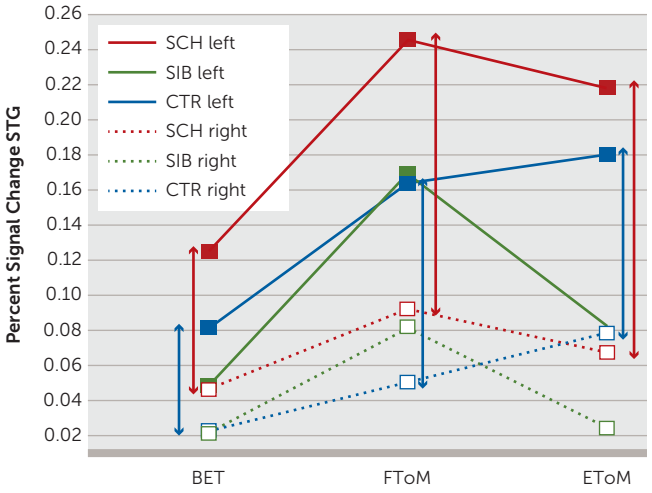
LINGUISTIC AND SOCIAL COGNITIVE ALTERATIONS IN SCHIZOPHRENIA

As summarized by Mitchell and Crow,[6] dysfunction of the right hemisphere during the production and interpretation of speech in schizophrenia can also be inferred from a variety of studies. In general, patients with schizophrenia have repeatedly been found to display deficits while understanding others' speech and producing a coherent discourse, processing meaning alternative to the literal interpretation of speech, and understanding/producing emotional prosody associated with uttered language. Studies documenting these deficits span several decades, and speech abnormalities are in fact considered a core feature of schizophrenia. Bleuler[18] described "looseness of associations" in patients with dementia praecox, and this observation has been extensively studied in the following decades. For example, Noël-Jorand et al.[19] used computer-assisted discourse analysis to conclude that patients with schizophrenia display a lack of logical cohesion in speech, with use of "language satellites" (i.e., short stretches of speech having no clear relevance to the main topic of conversation). Metaphor comprehension has long been found to be impaired in schizophrenia.[20,21] Patients with schizophrenia also fail in the processing of indirect requests, as evidenced by Corcoran et al.[22] in the "hinting task." Humor and sarcasm are also a type of verbal communication that necessitates the evaluation of multiple possible, nonliteral meanings, which is also disrupted in schizophrenia. Corcoran et al.[13] suggested that impaired humor comprehension and production in schizophrenia are in turn related to impaired theory of mind abilities, because humor usually requires the observer to discern the character's true intention in a social situation (see below). In fact, we and others have documented different theory-of-mind deficits in patients with schizophrenia and their unaffected first-degree relatives. Such observations suggest that these deficits are not dependent on active symptoms and might well constitute an endophenotype of this syndrome.[23,24]

Ross et al.[25] and Ross and Monnot [26] demonstrated that linguistic abnormalities in patients with schizophrenia are indistinguishable from those of patients with right hemisphere lesions and are distinct from speech disorders characteristic of a variety of dominant hemisphere lesions. They used an aprosodia paradigm and showed that schizophrenia is characterized by an asymmetric process, whereby language deficits in this disorder are referred to linguistic functions of the right hemisphere. In fact, in the studies by Ross,[25,26] patients displayed not only aprosodia (output of nonverbal indications of emotional state) but also deficits in the processing of facial affect, ultimately interfering with interpersonal relations and resulting in social isolation. On the basis of these observations, Ross et al.[25] predicted that patients with schizophrenia would display faulty functioning of right posterior perisylvian structures. As reviewed below, our group and others have provided evidence supporting this hypothesis, following observations that schizophrenic patients and at-risk individuals display semantic deficits that are specifically applicable to words denoting emotions and socially salient meaning.

Emotion processing and theory of mind are consistently altered not only in patients with schizophrenia but also in their unaffected first-degree relatives, as extensively documented in the available literature by our group[23] and others (Lavoie et al.[27] and Martin et al.[24] provide recent reviews of available evidence). Emotional processing and theory of mind are usually tested with verbal instruments in which the participant is requested to choose the appropriate word naming an emotion, intention, or mental state, or to interpret the verbal description of a social situation.[23] This function can be presumed to depend on intact linguistic functions of the nondominant hemisphere, given the fact that language is an essential part of these tests.

FIGURE 1. Brain Activation in the Superior Temporal Gyri Bilaterally, Induced by Social Cognitive Tasks in Siblings Discordant for Schizophrenia and Healthy Comparison Subjects[a]



[a] Social cognitive tasks tend to evoke a more asymmetrical response (due to lesser right hemisphere activation and greater left hemisphere activation) in patients with schizophrenia (red arrows) compared with healthy controls (blue arrows). Details are available in the text and in our previous work.[28] Reproduced from de Achával et al.,[28] with permission. BET, basic emotions task; EToM, theory of mind in eyes; FToM, theory of mind in faces; STG, superior temporal gyrus.

RIGHT HEMISPHERIC DYSFUNCTION DURING PROCESSING OF SOCIAL COGNITIVE INFORMATION IN PATIENTS WITH SCHIZOPHRENIA AND AT-RISK SUBJECTS

We studied siblings who are discordant for schizophrenia, and we found evidence that supports the predictions by Ross et al.[25] regarding dysfunctional right perisylvian structures in schizophrenia. We used a functional MRI paradigm that employed emotion processing and theory-of-mind stimuli in these groups. We found that compared with healthy individuals, siblings who are discordant for schizophrenia display a specific deficit of activation of right hemisphere structures during these paradigms. Figure 1 shows deficits at the temporoparietal junction/superior temporal sulcus, although the inferior and middle frontal gyri were also compromised in the original study.[28]

Given the fact that unaffected siblings of patients with schizophrenia partially shared the pattern of right hemisphere dysfunction, we sought to determine whether subclinical traits were associated with this finding. Relatives of patients with schizophrenia are known to exhibit an increased risk for personality disorders, classically cluster A (odd, paranoid, eccentric, or autistic behavior), although some epidemiologic studies show an excess prevalence of cluster B personality disorders (attention-seeking behavior, impulsivity, deceitfulness, and even self-directed aggression). We observed that deficit activation of the right temporoparietal junction is related to altered social competence in at-risk individuals with cluster B personality traits (Figure 2).[29] This observation provides a parsimonious association of clinical traits with social deficits and a neurobiological signature characteristic of schizophrenia—namely, deficit activation of the right temporoparietal junction.

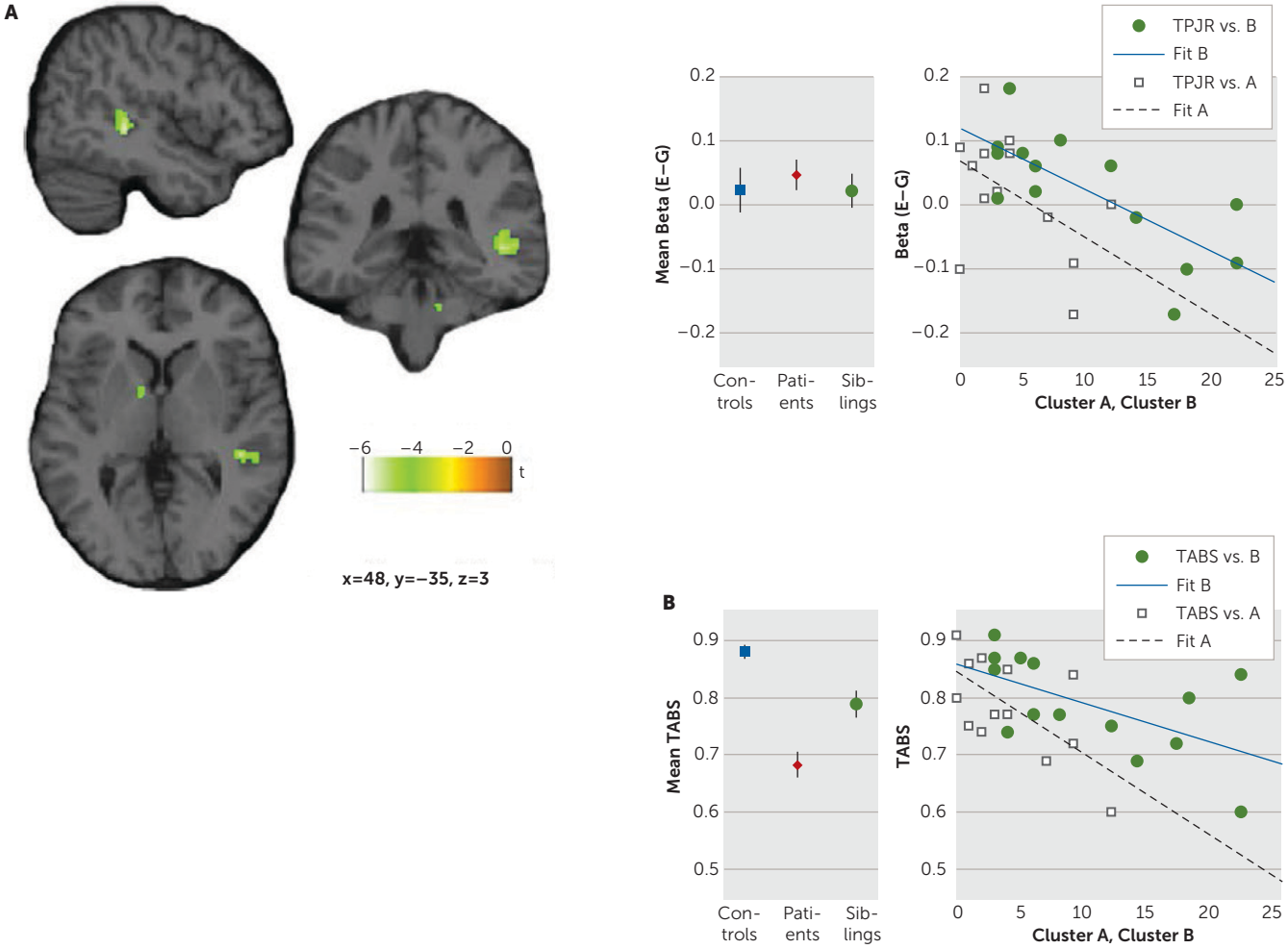
We also attempted to determine whether the observed abnormality in right hemisphere activation induced by social cognitive tasks was relevant to actual social functioning in schizophrenia. For this purpose, we studied social competence tasks in this group. We observed a "right-to-left gradient" in brain activity related to social competence in healthy persons, unaffected siblings, and patients, such that activation of right hemisphere structures correlated with social competence in controls, left hemisphere structures were related to competence in patients, and siblings occupied an intermediate position (Figure 3).[30]

SEMANTIC APHASIA FOR MENTAL AND EMOTIONAL STATES IN SCHIZOPHRENIA IS DUE TO DYSFUNCTION OF A COMPLEX CIRCUIT CENTERED AT THE RIGHT TEMPOROPARIETAL JUNCTION

On the basis of these observations, we propose that social deficits in schizophrenia are the manifestation of deficits in linguistic functions of the right, nondominant hemisphere—specifically, in the form of a sensory or comprehension aphasia that originates in faulty function of right posterior perisylvian structures traditionally associated with theory of mind, affecting speech output through extensive connections with Wernicke's area in the left hemisphere. Wible[31,32] extensively reviewed the role of the right temporoparietal junction. Whereas implicit recognition of the emotion and intention experienced by another member of the group relies on motor and limbic activity in other species, language is probably the "final common pathway" for theory of mind and empathy in humans. Ultimately, the capacity for precise recognition of what another member of the group is feeling or thinking depends on being able to produce the word that most accurately describes such a state. The right temporoparietal junction and right superior temporal sulcus are the contralateral homologue areas of Wernicke's area of the dominant hemisphere, and they display extensive connections with the latter through fibers that cross the corpus callosum[33] and are anatomically located in the tapetum. It is not surprising that the temporoparietal junction is involved in an integrative function such as theory of mind, because it is a true anatomical "crossroad" linking areas in all cerebral lobes. In addition to the tapetum and arcuate fasciculus, white matter tracts underlying the temporoparietal junction area include the horizontal portion of the superior longitudinal fasciculus, the middle longitudinal fasciculus, the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, and optic radiations; hence, the known clinical finding of the temporoparietal junction is known as one of the most "eloquent" areas of the human brain in neurosurgical studies.[33]

In relationship to its anatomical position, the temporoparietal junction/superior temporal sulcus integrates motor information about others' gaze and arm movements, possibly subserving intention detection in other members of

FIGURE 2. Brain Activation Induced by the Basic Emotion Task and Personality Traits in Nonpsychotic Siblings of Patients With Schizophrenia[a]

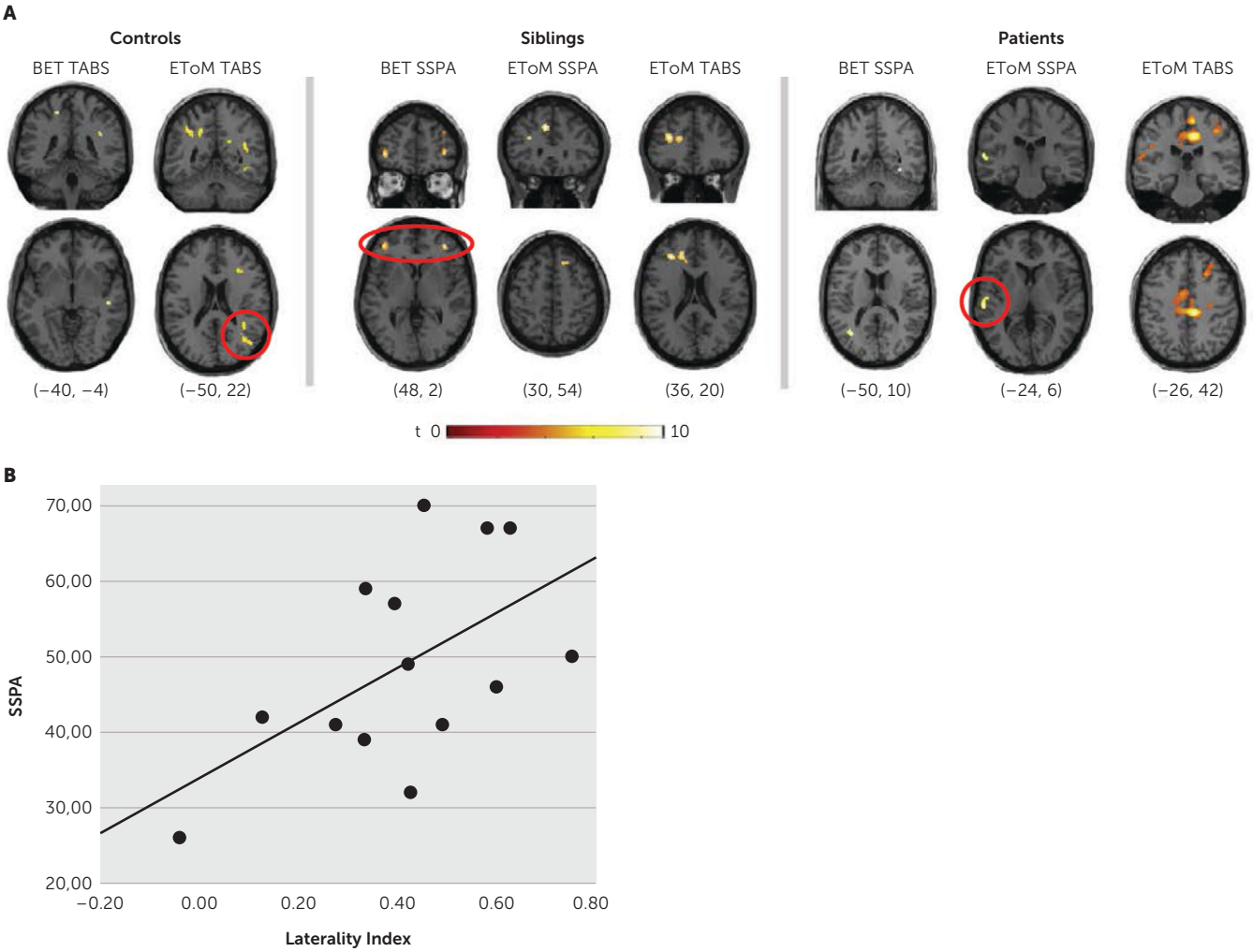


[a] (A) Brain activation correlates with the degree of cluster B symptomatology at the level of the right temporoparietal junction. (B) There is an inverse correlation between cluster B symptom severity and both (a) right temporoparietal junction activity and (b) social competence measured with the Test of Adaptive Behavior in Schizophrenia. Details are available in the text. Reproduced from Goldschimidt et al.,[29] with permission. Ctrols, controls; Pat, paternal; Sib, sibling; TABS, Test of Adaptive Behavior in Schizophrenia; TPJR, right temporoparietal junction.

the species.[34,35] This is likely accomplished by comparing one's own intentions, as inferred from motor behavior, with the intention of others (i.e., regions used to represent the self overlap with those used to represent others).[36–38] Presumably, activity in this area in humans informs its analogue in the dominant hemisphere (i.e., Wernicke's area) to allow identification of the right word to describe the other person's mental state.[34,35] Whereas most data point to dysfunction of the right posterior perisylvian area during cognitive tasks in patients with schizophrenia and in individuals at genetic risk, it is not possible to rule out that the latter is primarily due to frontal/motor alterations in the same hemisphere or to a more general brain lateralization abnormality (see below).[28]

In this view, appropriate social functioning ultimately depends on an adequate recognition of emotions and intentions in other members of the species, which manifests with the precise naming of such mental states in humans (Figure 4). The naming process begins with identification of facial expression, which is a particular case of motor behavior. Presumably, such identification depends on intact bilateral mirror neuron systems located in prefrontal areas, especially the inferior frontal gyri and operculum. Motor information should then reach the right temporoparietal junction, which is identified as a critical node for theory of mind. Indeed, the right temporoparietal junction is the homologue of Wernicke's area in the nondominant hemisphere, informing the latter through extensive callosal connections across hemispheres. Only then can the appropriate noun or adjective designating an emotion or mental state be chosen. In experimental paradigms, the appropriate concept is uttered after Broca's area receives this information through the arcuate fasciculus. In day-to-day social interactions, the word is not pronounced but still informs the person about the other subject's intentions or emotional state, permitting the planning and elaboration of the context-appropriate social behavior. As predicted by Ross et al.,[25] in this scheme, schizophrenia would be characterized by failed

FIGURE 3. Brain Activity Induced by Social Cognitive Tasks Shows a Distinct Correlation With Actual Social Competence in Healthy Controls and Siblings Discordant for Schizophrenia[a]



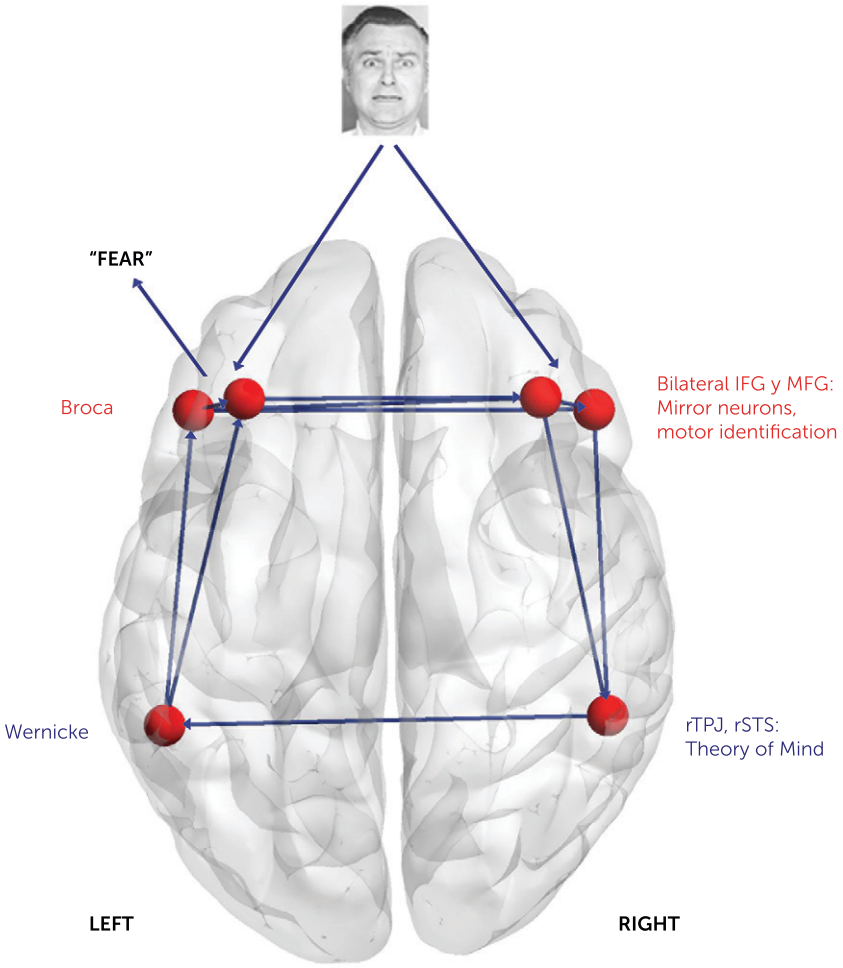
[a] (A) Brain activity induced by social cognitive tasks shows a distinct correlation with actual social competence (measured with the TABS and SSPA tests) in healthy controls and siblings discordant for schizophrenia (red circles). (B) There is a "gradient" of brain activation such that right hemisphere activation correlates with social performance in healthy individuals, left hemisphere activation is related to performance in patients with schizophrenia, and nonpsychotic siblings show areas of correlation on both sides of the brain. In patients with schizophrenia, left lateralization correlates with social competence. Details are available in the text. Reproduced from Villarreal et al.,[30] with permission. BET, basic emotions task; ETOM, theory of mind in eyes; SSPA, Social Skills Performance Assessment; TABS, Test of Adaptive Behavior in Schizophrenia.

social responses that originated in faulty identification of mental states in others due to nondominant hemisphere deficits specifically involving posterior perisylvian areas (Figure 4). This model would extend Crow's[6] proposal of abnormal brain lateralization resulting in symptoms that are originated in nondominant hemisphere linguistic functions (namely, positive symptoms, including Schneiderian first-rank symptoms, and symptoms considered as "negative," especially flatness of affect and social isolation).

ABNORMAL BRAIN LATERALIZATION AND PREDISPOSITION TO SCHIZOPHRENIA

Abnormal brain lateralization in schizophrenia has been extensively addressed in the literature,[6,39] and most structural and functional findings in persons with schizophrenia and predisposed subjects are indeed lateralized. A recent meta-analysis of combined structural and functional MRI studies in persons with an increased genetic risk for schizophrenia detected a series of lateralized abnormalities, including functional alterations in the right anterior and posterior temporal gyri.[40] Recent preliminary findings by our group in a regional sample detected increased cortical thickness in the right supramarginal gyrus in patients and unaffected siblings,[41] in the vicinity of the right temporoparietal junction/superior temporal sulcus. The question arises regarding the mechanisms of abnormal brain lateralization in schizophrenia, which in turn is related to social disability. Recent research on the genetic basis of the psychoses[42,43] maintains that predisposition to schizophrenia is highly polygenic (likely involving single nucleotide polymorphisms in thousands of genes, each with a very small individual effect) and is highly prevalent in the

FIGURE 4. Model of Semantic Deficits for Naming of Emotions and Mental States in Schizophrenia[a]



[a] Naming fails when left hemisphere language structures do not receive appropriate input from the right temporoparietal junction, leading to faulty recognition of emotions and theory of mind. Ventral/dorsal streams of speech processing in the dominant hemisphere and anatomical right frontal to left occipital brain "torque" are not shown. Details are available in the text. IFG, inferior frontal gyrus; MFG, middle frontal gyrus; rSTS, right superior temporal sulcus; rTPJ, right temporoparietal junction.

general population. It is interesting to note that few genes have been observed to show a lateral bias in brain tissue expression.[44] Therefore, aspects of the disease that are highly relevant to the deficits seen in this disorder might be accounted for by the single genetic variable of laterality/asymmetry,[45] which acquires paramount importance in language development. In this regard, it is interesting that schizophrenia differentially affects males and females; there are data that primate brain lateralization is gender specific, as evidenced by the homology of X- and Y-linked protocadherins (PCDHX and PCDHY, respectively).[45–47] Inherited developmental deficits in areas of the nondominant hemisphere involved in language would thus have a significant explanatory value for symptoms of schizophrenia in the preclinical and premorbid phases, including social adjustment deficits.[48,49]

CLINICAL IMPLICATIONS

Attempts at ameliorating functional outcomes in schizophrenia have had limited success. Apart from administering standard pharmacologic interventions (e.g., antipsychotics and, when indicated, antidepressants) and intervening with the patients' families to reduce levels of expressed emotion,[50,51] current efforts aim to remediate cognitive deficits and further ameliorate positive symptoms with the help of cognitive-behavioral interventions. In this regard, it is worth considering rehabilitation techniques used with patients who have sustained right hemisphere lesions of a different nature, including those with traumatic brain injury. Recent attempts have been made at rehabilitating verbal communication deficits in these patients.[52–56] Such efforts are mostly addressed at ameliorating the aprosodia resulting from these lesions[57] as well as improving conversational capacity and knowledge of social rules, both of which are impaired in patients with right hemispheric lesions.[55,56,58] To our knowledge, no studies have aimed to improve identification and naming of emotional and mental states in other persons. On the basis of the evidence reviewed herein, we suggest that language rehabilitation should also be included and should specifically address improving the preciseness of the patients' lexicon to name

emotion and mental states in others by means of specific training. This training would focus on pragmatic aspects of verbal communication, possibly with correct semantic identification of emotions and intentions in faces and social situations, and this effort would include ecological training on the detection of irony and prosody during social interactions. Although our proposal is speculative at this time, it might be worth exploring as an addition to developing techniques of social rehabilitation in patients with schizophrenia.

AUTHOR AND ARTICLE INFORMATION

From the Dept. of Neurology & Psychiatry, Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI) Teaching Unit, FLENI Instituto de Investigaciones "Raúl Carrea," School of Medicine (SMG, DdA, MFV), and Consejo Nacional de Investigaciones Científicas y Técnicas, Cátedra de Psicolingüística, Facultad de Filosofía y Letras (VA), University of Buenos Aires, Buenos Aires, Argentina; and the Dept. of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine, University of Miami, Miami, FL (CBN).

Send correspondence to Salvador M. Guinjoan, M.D., Ph.D.; e-mail: sguinjoan@fleni.org.ar

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