Schizophrenia as a Disorder of Communication

Guest Editors: Margaret A. Niznikiewicz, Marek Kubicki, Christoph Mulert, and Ruth Condray
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The first characterizations of schizophrenia invoked the concept of disordered thought and broken mind as central to its clinical presentation [1, 2]. Interestingly, Bleuler's characterization of schizophrenia was couched in terms of four A's association, with its focus on disordered language, affectivity, ambivalence, and autism, all of which implicate different aspects of social function [3]. Bleuler captured much that is still relevant to the study of cognitive dysfunction in schizophrenia and, in fact, covers quite well the topic of social communication dysfunction highlighted in this issue. The research that followed these early characterizations firmly established the link between abnormal brain structure and function, mediated by genetics, and many clinical and cognitive manifestations of this devastating disease [4–6].

Over the last several years, great progress has been achieved in the understanding of mechanisms of schizophrenia [7–10]. And while a comprehensive theory of schizophrenia is still elusive, many compelling accounts of schizophrenia pathology have been put forward and generated valuable insights [8, 9, 11–15].

Within the field of study of the cognitive dysfunction in schizophrenia, research has focused on different aspects of what was described recently as “cold cognition” and included attention, memory systems that vary in duration, capacity, and operations, as well as language and perceptual mechanisms [9]. The last few years brought a welcome broadening of this field of study as it has been noted that abnormalities in “hot cognition” including abnormalities in emotion and affect processing from both face and voice are an important component of schizophrenia pathology [16, 17]. Social cognition, whose functions draw on both processes of “cold” and “hot” cognition, has become a focus of intense interest with studies addressing the ability to convey one’s attitudes and intentions and adaptively predict and interpret the attitudes and intentions of others. Finally and importantly, it has been increasingly recognized that impairments in social cognition contribute to both clinical and functional outcomes in schizophrenia [18, 19].

The aim of the current issue is to broaden the discourse on the nature of cognitive dysfunction in schizophrenia. We propose that the cognitive dysfunction in schizophrenia should be conceptualized as a disorder of communication rather that of language itself and that communication disorder is the core clinical deficit of schizophrenia. We believe that an array of sensory and cognitive processes and their interactions enable human beings to enter into meaningful social communication. Thus, communication in a human society involves a complex set of behaviors that include both formal languages embodied in the rules of phonology, grammar, syntax, and semantics, as well as behaviors that allow conveying emotional states and attitudes, and finally and importantly successful interpretation of these behaviors in others. They depend on effective perceptual processes on one hand and on the successful recruitment of intact
higher order processes such as working memory, attention, inhibition, and response selection on the other hand. We would like to argue that neither the focus on the study of language nor the study of social cognition fully captures the communicative difficulties that patients with schizophrenia encounter. Rather, a schizophrenia sufferer is confronted with a poor ability to effectively use language and a poor ability to deploy other communicative devices to achieve successful functioning in a society, both in social and professional settings. Given the complexity of the behaviors under consideration, most studies on cognitive impairment in schizophrenia tend to adopt one of the two perspectives. Thus, the studies are conducted either within the framework of “cold cognition” and focus on the study of language, executive function, and perception or within the framework of “hot cognition” and focus on the study of emotion, theory of mind, and agency, to name a few topics.

Articles in this issue reflect both perspectives: the focus on abnormal language function as a central characteristic of schizophrenia pathology on one hand and the conceptualization of impairment in schizophrenia as a result of abnormal processes of social cognition on the other. M. A. Boudewyn and colleagues examine language impairment in schizophrenia in a review paper and argue that the extent of language processing difficulties is a function of the complexity of a linguistic message: the more complex the message, the more impairment will be observed. According to this conceptualization, schizophrenia patients should be most impaired in the processing of discourse that calls for the manipulation and reconciling of multiple sources of information. Conversely, they should be least impaired in the processing of single words and word pairs. The authors articulate their proposal of language impairment within the framework of domain general control mechanisms as mediated at the brain level by dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). They argue that it is these impaired mechanisms that mediate most severe language dysfunction in schizophrenia. This proposal is distinctly different from the hypothesis that language abnormality in schizophrenia is primarily rooted in abnormal processes within semantic memory [15]. As the authors suggest, the hypothesis of prefrontally mediated language dysfunction promises to be a rich source of experimental approaches that will test how different levels of language complexity map onto the degree of dysfunction in the prefrontal systems, how well the results of nonlinguistic tests of cognitive control correlate with the results of language tasks that purport to rely on cognitive control functions, how tests probing semantic memory processes integrity compared with language tests of context building in terms of observed effect sizes as tested in the same subject group and using the same methodology. It will be important to use approaches that include multiple methodologies as each one—behavioral, event related potential (ERP) and functional magnetic resonance imaging (fMRI)—offers unique and nonredundant pieces of evidence on how language processes are implemented in the living brain and what it means for the theory of schizophrenia.

The article by S. M. Arcuri and colleagues fits very nicely within the proposal of examining how complex linguistic messages are processed by brain systems. The authors explore language processing in the healthy comparison subjects and patients with and without a formal thought disorder. Drawing on the tradition of ERP studies of language processing in schizophrenia, the authors examine the processing of sentences with congruent and incongruent endings reasoning that the contrast between the sentences that require integration of context relative to those requiring the suppression of inappropriate semantic material will highlight a role of brain regions involved in the inhibition of automatically primed stimuli. The results suggest that the left middle frontal cortex is activated more in the incongruent relative to congruent sentences in the healthy comparison group. When the same incongruent/congruent contrast is analyzed in patients with the formal thought disorder, reduced activation in the left inferior/middle frontal gyr and in the anterior cingulate is reported. Thus, these results seem to support the idea that indeed the brain regions involved in context maintenance and manipulation and in the inhibition of inappropriate semantic entries are involved in the disordered language in schizophrenia.

Finally, D. Ketteler and colleagues present a new tool to assess the nature of compromised language function in schizophrenia: higher order linguistic function test (HOLF). They also adopt the premise that more complex language forms will create special difficulties for schizophrenia sufferers. However, in contrast to M. A. Boudewyn and S. M. Acruri proposals, the authors focus on ambiguity in language as brought about by single words such as antonyms, synonyms, homonymy, and as well as on interpreting popular adages. While easier operations such as interpreting adages and antonyms were not impaired in the patient group, tasks associated with more complex forms distinguished between the two groups and were correlated with symptom ratings as measured by PANSS scores. These results suggest that complexity of linguistic material does not have to be related to discourse or sentence structure but can be also related to conceptual ambiguity in order to tap into linguistic difficulties in schizophrenia patients.

The articles by A. P. Pinheiro, H. Fatouros-Bergman, and C. G. Wible are conceived within the framework of conceptualizing schizophrenia as a disorder of social cognition. H. Fatouros-Bergman and colleagues describe a negative facial affectivity bias in patients with schizophrenia that seems to persist across several temporal measuring points. A. P. Pinheiro and colleagues draw attention to the fact that in spite of evidence of affect processing difficulties in schizophrenia, the conscious ratings of emotional valence seem to be intact. The review paper by C. G. Wible advances an argument on the centrality of social communication abnormality in schizophrenia. Rather than focusing on language as a disembodied communication devise, this approach situates language within the context of body-based gesture system whose communicative capabilities are richer than those possible to be achieved within language as a semantic and syntactic system only. As C. G. Wible points out, a live conversation involves not only parsing out words and paragraph meanings, but also relies on correct interpretation of facial expressions, and tone of voice, social salience, agency (who is doing
the talking), and intention. An ability to anticipate another person’s actions and represent another point of view, often referred to as a theory of mind, is also essential for successful communication. Finally, two major features of schizophrenia pathology, hallucinations and delusions, involve, in addition to abnormalities in cognitive control [20, 21] and in perceptual and attentional processes [22], also abnormalities in the sense of agency [23]. As the article argues, the brain region that supports most of these functions is the temporal parietal occipital junction (TPJ) with projections to inferior frontal regions, hippocampus, and insular regions. Like the proposal put forth by M. A. Boudewyn et al., the hypothesis formulated by C. G. Wible has a promise of generating interesting experimental paradigms to test the role of TPJ in mediating different aspects of social communication abnormality in schizophrenia. Given the differences in the emphasis between the two proposals, the importance of temporoparietal regions articulated by Wible, and the importance of prefrontal regions articulated in the theory of domain general control impairment, these two conceptualizations may be viewed as two competing views of schizophrenia dysfunction. However, they can be also viewed as two complementary views that together describe the phenomenology of schizophrenia better than each of these theories alone. The theory of abnormal control mechanisms provides a compelling account of how a complex message system with its symbolic and multilayered semantics and syntax can be affected by impaired capacity to manipulate its different elements. The theory of abnormal social communication provides a novel perspective on how a formal language may interface with social communicative devices (gestures, emotional facial expressions, tone of voice (prosody)) and faculties (theory of mind, sense of agency, and intention). Thus, together with the already existing theories of abnormal processes within semantic memory largely borne out of priming studies [15] and a theory of perceptual dysfunction in schizophrenia relying on evidence derived from studying sensory auditory and visual processes [11], the theoretical perspectives espoused in the two review papers add to the richness of theoretical conceptualizations of cognitive dysfunction in schizophrenia.

Overall, this selection of papers is a good representation of the richness of approaches applied to the study of communication dysfunction in schizophrenia. They illustrate the centrality of language dysfunction in schizophrenia as well as the importance of abnormalities in nonlanguage-based semiotic systems as contributors to the schizophrenia sufferers’ inability to effectively engage with the world in an act of communication.

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References


Clinical Study
High Order Linguistic Features Such as Ambiguity Processing as Relevant Diagnostic Markers for Schizophrenia

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Due to the deficits of schizophrenic patients regarding the understanding of vague meanings (D. Ketteler and S. Ketteler (2010)) we develop a special test battery called HOLF (high order linguistic function test), which should be able to detect subtle linguistic performance deficits in schizophrenic patients. HOLF was presented to 40 schizophrenic patients and controls, focussing on linguistic features such as ambiguity, synonymy, hypero-/hyponymy, antinomy, and adages. Using the HOLF test battery we found that schizophrenic patients showed significant difficulties in discriminating ambiguities, hypero- and hyponymy, or synonymy compared to healthy controls. Antonyms and adages showed less significant results in comparing both groups. The more difficult a linguistic task was, the more confusion was measured in the schizophrenic group while healthy controls did not show significant problems in processing high order language tasks.

1. Introduction

Regarding the history of diagnostic classification of schizophrenia, diagnostic tools and catalogues focussed on different symptoms to describe a complex syndrome called schizophrenia. On the one hand, Bleuler [1] had concentrated on the phenomenon of loosening of association to classify and explain schizophrenic symptoms. According to Bleuler, language-based “loosening of association” is pathognomonic for the so-called “schizophrenic symptoms complex.” On the other hand, Schneider [2] drew attention to the significance of “core” or “first rank” symptoms first outlined by Kraepelin (specific types of hallucination and thought disorder [3]). To overcome the at least obscure relationship between thought and association disorder of Bleuler’s approach, Andreasen [4, 5] shifted the focus of investigation from “thought” to the more objectively measurable “language behaviour.” Language impairment indeed seems to be one of the “core” phenomenological characteristics of patients with schizophrenia [6, 7]. It seems to be clear that there are deficits in the neural organisation of language in schizophrenic patients [6, 8].

There is only a small number of studies focussing on high order linguistic features and particularly on the phenomenon of ambiguity. Salisbury et al. [9] described a model of initial hyperpriming and subsequent decay of information by using ERP data investigating patients with schizophrenia. Using event related brain potentials and an ambiguity processing paradigm, Salisbury [10] found that schizophrenia patients showed the largest N400 effect to subordinate associates, with less activity to dominant meaning associates and unrelated words. These findings suggest a neural correlate for the difficulties in suppressing correct word alternatives.

Several other aspects of language comprehension and production have been found to be abnormal in patients with schizophrenia: comprehension, attention, semantic organisation, reference failures, paucity of speech, or fluency [11]. Covington et al. [12] discussed that thought disorder might reflect a disruption of executive function and pragmatics. Although normal with regard to segmental phonology and morphological organisation [13], there are obvious word-finding difficulties in patients with schizophrenia [4, 14]. Disturbed language production often includes deixtic terms.
with no clear referents and verbs which lead to a vague and ambiguous discourse. Difficulties in dealing with nonliteral expressions were found by Corcoran and Frith [15] and Langdon et al. [16]. Particularly vague and ambiguous terms seem to irritate patients with schizophrenia. Some studies investigating comprehension deficits attributed reduced comprehension to deficient working memory [17], and some found deficits in semantic processing [18].

Beside behavioural difficulties in solving high order language tasks there are neuroanatomic and neurofunctional changes, especially regarding language pathways, in patients with schizophrenia [19–25].

Regarding the aetiology of schizophrenia from a neurolinguistic point of view, there might be hemispheric interaction difficulties particularly in processing high order linguistic features such as semantic ambiguities. Besides cortical abnormalities, the subcortical role of language processing was underestimated for a long time.

Deficits of schizophrenic patients in resolving vague meaning probably enable test batteries for the early detection of psychosis and might lead to a better understanding in the aetiology of schizophrenia in general. Ceccherini-Nelli and Crow [26] used a psychometric test (CLANG) to evaluate language disturbances and found that language symptoms like semantic/phonemic paraphasias or poverty of speech were superior to nuclear symptoms in discriminating ICD-10 schizophrenia from other psychoses. CLANG was originally developed by Chen et al. [27]. This task highly depends on the experience of the examiner and is not appropriate to detect subtle language symptoms. We argue that the CLANG test focuses on symptoms that are more commonly seen during episodes of acute illness. We tried to develop a more elaborated test battery which is able to detect more subtle language deficits in well-medicated patients with low symptom load. The so-called HOLF (high order linguistic function test) was presented to 40 schizophrenic patients and controls focusing on linguistic features. HOLF is a pilot test battery created by our group containing different high order language features such as antonyms, homonyms, synonyms versus hyponyms, and adages. This experiment is the first attempt to introduce our test design to the scientific community. It has not been published before; however, there was one study by Ketteler et al. [24] regarding the homonym part using fMRI with healthy individuals.

2. Method and Subjects
40 schizophrenic patients (27 male, 13 female) with a mean age of 31.54 (sd = 10.834) and 40 controls (27 male, 13 female) with a mean age of 32.48 (sd = 9.081) participated in the study. All participants were monolingual German native speakers and had no history of neurological disorder or a history of head trauma. Schizophrenia was diagnosed by an experienced clinician using the ICD-10 criteria. To determine the symptom load of the schizophrenic patients we used PANSS [26] as a well-established diagnostic instrument. For the language symptoms CLANG [28] was rated by an experienced examiner. Furthermore, age, gender, and CGI (Clinical Global Impression Score [27]) were registered in all participants and number of previous hospitalizations in the clinical subsample.

3. Experimental Design and Procedure
A linguistic task (HOLF) was presented to 40 patients with schizophrenia and 40 controls. The first task was a warm-up task consisting of 20 antonym relation pairs, while half of them were distractors. The second task represented other, mixed high order linguistic features, including synonymy, homonymy, and hyperonymy versus hyponymy. Each item group included 20 items while 10 of them were correct, and 10 of them were distractors. Individuals were instructed by the examiner: “Please mark if the first words correlate with the last word in the line” (for details see HOLF test in German language attached in supplementary material available online at doi:10.1155/2012/825050).

Example (regarding the ambiguity task):

River Money Bank [X].

Distractors were arranged by using one or two distractors on position one or two:

River Wind Bank [ ].

or

Door Wind Bank [ ].

Example (regarding the hyperonymy/hyponomy task).

Water Juice Drink [X].

Additionally, three classical adages were tested by giving three answer alternatives for each wording. HOLF has not been published before, and this is the first attempt to test the effect of high order language tasks with schizophrenic patients using a very simple design. HOLF uses German language items and has not been translated to the English language until now. HOLF is in an early stage of development, and further data concerning validity and reliability has to be collected in future studies.

4. Statistic Analysis
Anonymised data was analysed with SPSS 15.0 for Windows (Statistical Package for the Social Sciences, Inc., Chicago, 2006). HOLF was analysed descriptively with regard to the number of items that were processed adequately. The sum score of correct answers were calculated on total HOLF scale as well as on the five subscales antonyms, homonyms, hyperonyms, synonyms, and adages. Since the distribution of raw scores was highly skewed with a large proportion of subjects delivering high sum scores, nonparametric tests (Mann-Whitney U test, Wilcoxon rank order test) were performed in order to compare the two subsamples (clinical population and healthy controls).

5. Results
The sample comprised 40 patients diagnosed with schizophrenia according to ICD-10, F20, and 40 healthy controls.
There were no significant differences in age and gender. The clinical subsample had a history of 4.1 previous hospitalisations on average and a severity-of-illness-score of 4.4 (moderately ill) according to Clinical Global Impression Scale (CGI) at the time of the investigation.

Statistical measurements of the HOLF scale and subscales as well as CLANG and PANSS are shown in Table 1. The internal consistency measured by Cronbach’s alpha of HOLF total scale and subscales was high.

Healthy controls answered the items on HOLF and CLANG mostly without mistakes, whereas patients had significant problems with the task. The differences between the two groups on almost all subscales were highly significant with the exception if the adages scale. HOLF total scale showed a significant correlation with CLANG even if controlled for psychopathology as measured by PANSS ($r = -0.396, P < 0.001, df = 76$). HOLF subscales correlated significantly with CLANG with the exception of adages scale. Correlation coefficients are shown in Table 2.

6. Discussion

The aim of the current study was to explore in how far schizophrenic symptoms are correlated with difficulties in high order linguistic processing. By testing high order language performance using the HOLF battery we found that schizophrenic patients showed significant difficulties in discriminating ambiguities, hypero- and hyponymy, and synonymy compared to healthy controls. Antonyms and adages showed less significant results comparing both groups. The group differences observed for antonyms and adages were weaker than the effects obtained for the other types of linguistic ambiguities. If this pattern is determined to be reliable, these latter linguistic features may have less pathognomonic value for schizophrenia. The more difficult a linguistic operation was the more confusion was measured within the schizophrenic group while healthy controls did not show significant problems solving high order language tasks. Age correlated slightly with general performance in HOLF, but there were more significant effects regarding the severity of illness and times of hospitalization. One might assume that age and times of hospitalization correlate with the chronicity of illness.

HOLF highly correlated with the standard instrument for scoring symptom load in schizophrenia called PANSS. We conclude that disturbed (high order) language function might be pathognomonic for schizophrenia. As already mentioned by Bleuler, “loosening of association” might be the core symptom regarding psychotic syndromes. Focussing on the correct word alternative while discriminating ambiguous meanings seems to be deeply disturbed in our patient group. According to our data, homonymy detection was highly impaired in patients with schizophrenia.

In further studies, patients with schizophrenia showed problems in selecting context-related ambiguous meanings. They have been shown to be impaired in using the context of sentences to determine an appropriate meaning of a homographic word [29, 30]. Cohen and Servan-Schreiber [31] showed that schizophrenic patients have difficulties in processing multimeaning words, but only when disambiguating context precedes the target homograph. Previous research has suggested that a failure in processing contextual information may account for the heterogenous clinical manifestations and cognitive impairments observed in schizophrenia.
### Table 2: Correlation coefficients (patients N = 40; controls N = 40).

<table>
<thead>
<tr>
<th>Spearman-Rho</th>
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<th>Correlation coefficient</th>
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<td>.004</td>
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**Note:** Sig. (2 sides) indicates significance at the two-tailed level.
**Table 2: Continued.**

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<th>Spearman-Rho</th>
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**The correlation is significant on a 0.01 niveau (2 sides).**

**The correlation is significant on a 0.05 niveau (2 sides).**
Our data suggests difficulties of schizophrenic patients in processing multimeaning words such as ambiguities and synonyms but also suggests difficulties in solving semantic taxonomies such as hypero- and hyponymies. Antonyms were not presented in a randomised order but in a block design with several distractors. The antonym task within our experiment might have been too simple to solve, so these items did not show any differences between patient and control group. Therefore, we used the antonym task as a warm-up and to motivate patients to carry on with the more difficult tasks.

CLANG [32] was a first and important step in reactivating the Bleulerian idea of underlying language disturbance in schizophrenia but seems to be much too unspecific for detecting high order language dysfunction. CLANG has to be rated by the examiner who is always subjectively biased by the personal impressions and diagnostic data concerning his patient. HOLF now offers a more objective method which is highly significantly correlated with CLANG and PANSS. PANSS indeed is a well known and established diagnostic tool regarding schizophrenic symptoms.

Delusions can be considered as deviations in the capacity to attach significance to the phonological representations that are the primary building blocks of words. Disruptions such as clause boundaries or sentence endings occur generally, particularly at points of attentional focus fluctuation [11, 33]. As a consequence, coherence of speech breaks down, which is fundamental for the development of formal thought disorder. According to our data one might assume that the more vague or ambiguous a semantic correlation is presented, the more effort has to be made by the neural system in processing these items.

According to connectionist network models [34], each component of an utterance activates associated semantic units which remain activated for a finite period of time [35]. In schizophrenia, the speed of decay which is following the spread of activation seems prolonged. If such an inhibitory process becomes impaired, patients have a greater potential for intrusion into later thought and speech. Although context information is important for almost all cognitive tasks, the domain of language is ideally suited for the study of contextual processing. Homonyms and synonyms highly depend on correct contextual priming, so deficits in processing these features lead to massive linguistic irritation in the schizophrenic brain as seen in our experiment.

Titone et al. [36] used a priming task by presenting sentences containing homonyms. Eighteen schizophrenic patients were asked on lexical decisions about visual targets related to the homonyms’ subordinate, respectively, dominant meaning. When sentences biased subordinate meaning, patients showed priming of dominant targets. The results also suggest that contextual strength is an important determinant of when schizophrenia patients fail to inhibit contextually irrelevant meanings. Wentura et al. [37] investigated priming by using a masked repetition task and compared formal thought-disordered patients, nonthought disordered patients, and healthy controls. For thought-disordered patients they found “hyperpriming,” whereas the other groups showed regular priming. This result yields evidence for a lack of inhibitory function in thought- (and therefore language-) disordered patients. Furthermore, Sitnikova et al. [38] found that the N400 ERP component that is known to be sensitive to contextual effects was attenuated in patients with schizophrenia. This is potentially due to inadequate contextual suppression mechanisms and/or due to increased levels of word-meaning activation.

“Hyperpriming” was detected in our data too while there were many false-positive errors in the schizophrenia group. As already mentioned above, Salisbury [9, 10] described a model of initial hyper-priming by using ERP data investigating patients with schizophrenia. These findings suggest a neural correlate for the difficulties in suppressing correct word alternatives.

In summary, using the HOLF test battery we found that schizophrenic patients showed significant difficulties in discriminating ambiguities, hypero- and hyponymy, or synonymy compared to healthy controls. Antonyms and adages showed rather significant results in comparing both groups, so these features seem to have a less specific pathognomonic and diagnostic value regarding schizophrenia or were too simple to solve. The more difficult a linguistic operation was, the more confusion was measured in the schizophrenic group while healthy controls did not show significant problems in solving higher order language tasks.

One limitation of our study might be a very low error rate in healthy individuals. Therefore, very few errors cause a highly significant difference in performance between both groups. On the other hand, HOLF was able to detect schizophrenic symptoms on a very subtle level which might be an indicator for underlying language problems, although the patient group presented a low level of symptoms, and all patients have been well medicated. By revitalising the Bleulerian focus on thought, respectively, language disorder the almost chaotic mechanisms of psychotic experience might become more understandable. Our findings might inspire the development of early detection test batteries which include high order language functions in order to detect subtle and underlying language deficits in schizophrenic patients. HOLF is in a very early stage of development, and more data is needed especially regarding psychometric properties such as test-retest reliability and validity.

References

Schizophrenia Research and Treatment


Clinical Study

From Semantics to Feelings: How Do Individuals with Schizophrenia Rate the Emotional Valence of Words?

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Schizophrenia is characterized by both emotional and language abnormalities. However, in spite of reports of preserved evaluation of valence of affective stimuli, such as pictures, it is less clear how individuals with schizophrenia assess verbal material with emotional valence, for example, the overall unpleasantness/displeasure relative to pleasantness/attraction of a word. This study aimed to investigate how schizophrenic individuals rate the emotional valence of adjectives, when compared with a group of healthy controls. One hundred and eighty-four adjectives differing in valence were presented. These adjectives were previously categorized as “neutral,” “positive” (pleasant), or “negative” (unpleasant) by five judges not participating in the current experiment. Adjectives from the three categories were matched on word length, frequency, and familiarity. Sixteen individuals with schizophrenia diagnosis and seventeen healthy controls were asked to rate the valence of each word, by using a computerized version of the Self-Assessment Manikin (Bradley and Lang, 1994). Results demonstrated similar ratings of emotional valence of words, suggesting a similar representation of affective knowledge in schizophrenia, at least in terms of the valence dimension.

1. Introduction

Emotional abnormalities are a hallmark of schizophrenia [1–4] and are often evident in prodromal stages of this disorder [1, 5]. Recent years have seen a rapid increase in interest in emotion processing in schizophrenia. Stimuli with emotional salience have particular relevance for the individual and, thus, abnormalities in their processing have important consequences for social functioning and functional outcomes for individuals with schizophrenia [6]. The existing studies have explored different aspects of emotion processing in this disorder (see [7] for a review) including the study of (a) emotional perception (e.g., [8]); (b) emotional experience (e.g., assessment of self-reported affect through the presentation of emotionally evocative stimuli; assessment of trait differences in emotion components) (e.g., [9]); (c) emotional expression [10]; (d) effects of emotion on cognitive processes, such as working memory [11, 12]; (e) evaluation of the affective properties of stimuli varying in valence and arousal. In terms of the conceptual framework, the latter studies represent a dimensional approach to emotion. Dimensional theories of emotion propose that emotions can be characterized along a small number of underlying and separable dimensions, such as valence (the overall unpleasantness/displeasure relative to pleasantness/attraction of a stimulus) and arousal (the intensity of motivational mobilization—appetitive or defensive) [13–15]. This assumption is supported by brain functional imaging (e.g., [16]) and event-related potential (ERP) studies (e.g., [17]) indicating differential effects of valence and arousal on brain activation and function. In contrast, a discrete emotions approach holds that emotions may be distinguished from one another according to a set of features [18].

The existing studies on emotion processing in schizophrenia suggest that the components of emotional processing
mentioned above are differentially affected by the disorder (see [7] for a review). For example, previous studies pointed to a dissociation between the subjective experience and the expression of emotion in schizophrenia [19], based on somewhat paradoxical findings revealing that these individuals show less emotional expression, even though they report momentary emotional experience similar to that of healthy controls (HC) in response to stimuli such as film clips, pictures, or emotional face expressions (e.g., [20, 21]). Studies using self-report measures of emotional experience have additionally demonstrated that individuals with schizophrenia report experiencing feelings in a way that is consistent with the valence of the presented evocative stimuli, that is, they report negative mood states in response to unpleasant stimuli or positive mood states in response to pleasant evocative stimuli ([22–27]; see also [28] for a review). Nonetheless, other studies found that individuals with schizophrenia diagnosis report experiencing less positive emotion in response to happy emotional face expressions, in comparison with HC [25].

In particular, most studies investigating the way schizophrenic individuals rate affective properties of stimuli have provided evidence for similar evaluation of valence of affective stimuli in schizophrenic patients and HC (pictures [4, 20, 23, 29–31], facial expressions [32] and odors [33, 34]). However, these results have not been always replicated. For example, some studies indicated that schizophrenic individuals tend to rate pleasant stimuli as being less pleasant [35, 36], and negative stimuli as being less unpleasant [35, 36] (in both studies, the stimuli used were emotional pictures, words, and faces). Differences in patients’ samples (e.g., gender [29]), including schizophrenia subtype, clinical symptoms (e.g., severity of negative symptoms and level of anhedonia) and functional outcome measures [36–38] as well as differences in stimuli (e.g., level of arousal) may account for the apparent discrepancies between studies.

Findings related to the assessment of arousal indicate either similarities [23] or differences [21, 36, 39] in the assessment of this dimension. For example, differences were observed in arousal ratings of aversive/unpleasant stimuli, with lower ratings indicated by individuals with schizophrenia relative to HC in response to different types of stimuli, such as pictures selected from the International Affective Pictures System dataset (IAPS [39]), words selected from the Affective Norms for English Words dataset (ANEW [40]), sounds selected from the International Affective Digitized Sounds dataset (IADS [41]), or emotional faces [35]. When compared with patients with bipolar disorder and HC, schizophrenia patients reported lower arousal for aversive stimuli with social content [39]. Also, heightened arousal ratings were found for pleasant pictures [21] and for neutral stimuli (pictures, words, and faces [36]). Discrepancies in these findings might be related to methodological differences, including sample differences (e.g., differences in anhedonia level or in neurocognitive measures such as working memory [35]). In spite of differences in ratings of valence and arousal in some of individuals with schizophrenia, the existing studies point to a representation of affective knowledge in schizophrenia similar to that found in HC, suggesting that valence and arousal are also two major features of this knowledge (see also [42]).

Besides affective abnormalities, disturbance of language processes has long been reported in schizophrenia. It includes deficits in declarative-episodic memory of verbal material [43], abnormal semantic priming effects [44, 45], and abnormal context processing [46]. Abnormalities were also found in the brain network involved in semantic processing [47]. Language abnormalities in schizophrenia were proposed to rely both on an initial overly activated semantic network and on later inhibition difficulties indicating abnormal context utilization [48, 49]. These semantic processing deficits do not seem to be dependent on grammatical category of a word, such as nouns, verbs, or adjectives [50]. However, it is less clear how individuals with schizophrenia process verbal material with emotional valence.

Studies with healthy populations have demonstrated a differential processing of neutral, pleasant and unpleasant verbal information [51–56] as well as an automatic processing of emotional word content in the sense that it is not dependent on the availability of attentional resources [57]. For example, pleasant adjectives tend to be better remembered than unpleasant or neutral adjectives, suggesting a preferential processing of pleasant words [55, 57]. Electrophysiologically, the prioritized processing of emotional verbal material is indexed by enhanced (i.e., more positive or more negative) ERP amplitude for emotional relative to neutral words [54, 57, 58].

Studies testing affective semantic priming (a variant of the semantic-priming paradigm consisting of the presentation of an emotional prime word before a target word with emotional meaning) reported similar affective and semantic priming in individuals with schizophrenia when compared with HC [59, 60]. However, other studies revealed that these individuals tend to show a facilitatory priming effect for neutral word stimuli, but not for positive or negative word stimuli; in addition, schizophrenic individuals’ reaction times tended to be slower for related negative word targets than to unrelated negative word targets [45].

Studies on sentence processing with affective semantic content showed abnormalities in the interaction between semantic networks and emotional processing in schizophrenia [61], as indexed by increased N400 for negative word endings relative to both depressed and HC groups. In addition, individuals with schizophrenia did not show memory enhancement for self-referenced adjectives, contrary to HC, which may be related to poor social outcomes in this disorder [62]. Interestingly, phenomenological studies on auditory verbal hallucinations show that these often have negative/derogatory semantic content [63–65], which may suggest a relationship between clinical symptoms and processing of verbal material with negative emotional valence.

In spite of evidence suggesting abnormalities in processing verbal affective stimuli, it is yet not clear if abnormalities are related to abnormal declarative knowledge about affect. A previous study [42] provided evidence for similar knowledge representations of verbal affective stimuli in 11 individuals with schizophrenia and 7 HC, in terms of their valence-based and arousal-based meaning. Differences were found
in the weighting of valence and arousal dimensions in a task of similarity assessment of affective word pairs: while participants with schizophrenia weighted the valence and arousal dimensions equally, HC weighted more the arousal than the valence dimension, suggesting that the relative importance of these dimensions may differ in individuals with schizophrenia and HC. However, in this study only 16 emotion terms were used (excited, lively, cheerful, pleased, calm, relaxed, idle, still, dulled, bored, unhappy, disappointed, nervous, fearful, alert, and aroused), and they were assessed on a 7-point Likert scale (1: extremely dissimilar; 7: extremely similar). Also, Burbridge and Barch [35] assessed emotional experience to pleasant, neutral and unpleasant stimuli in different modalities, including 75 words selected from the ANEW dataset [66], varying in valence (pleasant, unpleasant, and neutral) and arousal (low and high). Schizophrenic participants and HC were asked to rate their emotional experience to the stimuli, in terms of how pleasant-unpleasant and aroused-calm the stimuli made them feel. However, in this study a composite index was used that did not allow to investigate the separate processing of word stimuli with emotional valence.

In this study, we compared valence ratings of adjectives in individuals with schizophrenia and in HC. To our knowledge, only one previous study [42] has directly assessed how individuals with schizophrenia assess emotional adjectives, in spite of substantial research on how they assess other types of affective stimuli such as pictures or film clips [4, 21, 23, 31, 67, 68]. However, the study of Kring et al. [42] included a small number of adjectives that may not be representative of the vocabulary that depicts emotional situations in the daily life.

In our study, we have presented a list of 184 adjectives (previously assessed as “pleasant,” “unpleasant,” or “neutral” by a group of 5 judges) to a group of 16 individuals with schizophrenia diagnosis and to 17 HC. They were asked to assess the valence of the words on a 1–9 Likert scale [13]. We posited that individuals with schizophrenia and HC would show similar ratings of valence of adjectives, consistent with reports of preserved assessment of affective properties of stimuli differing in valence and similar representation of emotion in schizophrenia.

### 2. Materials and Methods

#### 2.1. Participants

Sixteen subjects diagnosed with schizophrenia (APA, 2002) and seventeen HC participated in the study (see Table 1). Inclusion criteria were (a) age between 18 and 50 years; (b) no history of neurological illness or traumatic head injury, defined as loss of consciousness for more than 5 minutes and/or structural sequelae following head trauma; (c) no history of alcohol or drug dependence in the past five years or abuse within the last year (DSM-IV-TR; APA-2002) with diagnoses determined by the Structured Clinical Interview for DSM-IV-TR (SCID) administration [69, 70]; (d) no hearing, vision, or upper body impairment; (e) estimated intelligence quotient (IQ) of above 80 [71]; (f) no alcohol use in the 24 hours before testing; (g) an ability and desire to participate in the experimental procedure, as demonstrated by given written informed consent, following Harvard Medical School (HMS) and Veterans Affairs Boston Healthcare System (VABHS) guidelines.

HC subjects were recruited from Internet and newspaper advertisements and matched to the patients on the basis of age, gender, parental socioeconomic status, and handedness (Table 1). For HC, additional inclusion criteria were no history of Axes I or II disorders as determined by SCID interview [69, 70]; no history of Axis I disorder in first or second degree family members, determined by the Family History-Research Diagnostic Criteria (FH-RDC) instrument [72]; no history of attention deficit disorder, learning disability or developmental disorder, and no history of birth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy controls (n = 17)</th>
<th>Individuals with schizophrenia (n = 16)</th>
<th>t (df = 31)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.65 ± 11.32</td>
<td>48.69 ± 8.38</td>
<td>−1.446</td>
<td>.158</td>
</tr>
<tr>
<td>Gender</td>
<td>3 females; 14 males</td>
<td>4 females; 12 males</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.47 ± 1.81</td>
<td>13.00 ± 2.25</td>
<td>3.487</td>
<td>.001</td>
</tr>
<tr>
<td>Subject’s SES</td>
<td>2.23 ± 1.01</td>
<td>3.63 ± 1.41</td>
<td>−2.992</td>
<td>.006</td>
</tr>
<tr>
<td>Parental SES</td>
<td>2.54 ± 0.88</td>
<td>3.13 ± 1.45</td>
<td>−1.275</td>
<td>.213</td>
</tr>
<tr>
<td>Onset age (years)</td>
<td>NA</td>
<td>30.23 ± 11.95</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>NA</td>
<td>17.15 ± 11.32</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chlorpromazine equivalent (mg)</td>
<td>NA</td>
<td>381.13 ± 247.18</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Medication type</td>
<td>NA</td>
<td>First generation = 3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second generation = 9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Positive scale PANSS</td>
<td>NA</td>
<td>23.87 ± 9.41</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Negative scale PANSS</td>
<td>NA</td>
<td>22.33 ± 9.56</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>General psychopathology PANSS</td>
<td>NA</td>
<td>43.00 ± 14.64</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total psychopathology PANSS</td>
<td>NA</td>
<td>89.20 ± 30.17</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

SES: socioeconomic status; NA: not applicable; *Independent sample t-test was used for group comparisons.

---

Table 1: Demographic and clinical characteristics of participants (mean ± SD).
complications with resulting consequences for central nervous system as determined by neurodevelopmental interview [73].

The experiment was explained to each participant and all participants gave a written informed consent following HMS and VABHC guidelines. All were paid for their participation in the study.

2.2. Stimuli. Stimuli were 184 adjectives (see Table 3) differing in emotional valence. First, a list of neutral and emotional (pleasant or positive; unpleasant or negative) adjectives was created. Given that the desired number of adjectives for each valence type could not be found in the ANEW dataset [40], we turned to published studies that have used emotional adjectives as stimuli. Thus, we have combined words taken from the ANEW with words from those original studies that published the lists of words as supplementary material [40, 74, 75] to arrive at the final set of stimuli. Five judges (mean age = 31.4 ± 12.10 years, 3 females), all with college degree (mean years of formal education = 16), involved in research and who did not participate in the experimental task, categorized each word as “neutral,” “positive,” and “negative”: 60 words were categorized as neutral, 60 words were categorized as positive, and 64 words were categorized as negative. Neutral adjectives described less arousing and less salient traits and states (e.g., “neutral,” “blue,” and “narrow”), while positive (e.g., “brilliant,” “famous,” “elegant”) and negative (e.g., “dead,” “fearful,” “sad”) adjectives described more arousing and salient affective traits and states (see also [53]).

Psycholinguistic properties were taken from the University of Western Australia database (http://www.psych.rl.ac.uk/MRC_Psych_Db.html). Words in three valence categories (neutral, positive, and negative) were matched for number of letters (four to seven letters), and number of syllables (one to three syllables). No difference was observed between the three valence types (P > 0.05). Word frequency (Kucera-Francis frequency [76]) was in the range of 1–300 per million words. However, it was somewhat lower for negative adjectives relative to both positive (P = 0.020) and neutral (P = 0.002) ones (see Table 2). Familiarity, concreteness, and imageability were also lower for negative relative to both positive (P < 0.001) and neutral (P < 0.001) adjectives.

2.3. Procedure. Adjectives were pseudorandomized and presented to each participant. Pseudorandomization was used in order to avoid sequential presentation of more than 5 stimuli with similar emotional valence. Words were presented in lowercase in 6 blocks in the center of a CRT computer screen, in black Arial 40-point font against white background. Each block consisted of 30 words. A short pause (self-paced) followed each block to minimize participants’ fatigue or distraction. Before the presentation of a word, the fixation cross (5000 ms duration) appeared. A word was then presented for 3000 ms. Following the word presentation, participants had 15000 ms to respond. They were instructed to read each word silently and to rate its emotional valence by using a computerized version of the Self-Assessment Manikin [13]. In this system, each affective dimension is assessed on a 1–9 Likert scale: higher numbers in the valence dimension indicate evaluation as more pleasant. Mean item ratings less than 4 were classified as unpleasant, between 4 and 6 were classified as neutral, and greater than 6 were classified as pleasant. Participants were also given a chance of correcting their response, in case they felt they made a mistake when pressing a button. After the response, a slide appeared (with no time limit) asking participants to confirm (by pressing button 1) or to correct their response (by pressing button 0). If subjects wanted to correct it, the trial would restart. After the confirmation of the response, an interstimulus interval (ISI) of 1000 ms preceded the onset of the next trial.

The rating session was preceded by a practice session. Subjects were given detailed instructions and presented with a block of 9 selected words that were not shown during the actual experiment. All stimuli were presented and synchronized through SuperLab 4.2 (Cedrus Corporation, San Pedro, CA, USA). The same software was used for recording subjects’ responses. Data were analyzed with IBM SPSS Statistics 19 (IBM Corporation, Armonk, NY, USA).

3. Results and Discussion

Words from different categories were rated differently, as suggested by the significant effect of valence (F(2,30) = 182.06, P < 0.001). No group effect or interaction involving group factor were observed. Positive words were rated as

| Table 2: Psycholinguistic properties of adjectives used in the experiment. |
|-----------------------------|-------------|-------------|-------------|
| Psycholinguistic measure    | Neutral (M ± SD) | Positive (M ± SD) | Negative (M ± SD) |
| Kucera-Francis written frequency | 114.93 ± 141.98 | 96.92 ± 163.10 | 41.39 ± 51.42 |
| Familiarity                 | 561.24 ± 44.44 | 568.88 ± 41.99 | 548.17 ± 41.24 |
| Concreteness                | 402.93 ± 51.94 | 342.05 ± 48.65 | 356.32 ± 49.45 |
| Imageability                | 426.40 ± 95.41 | 427.97 ± 53.26 | 427.14 ± 51.88 |
| Word length (number of letters) | 4.92 ± 1.03 | 5.36 ± 1.16 | 5.32 ± 1.36 |
| Word length (number of syllables) | 1.43 ± 0.50 | 1.51 ± 0.51 | 1.60 ± 0.49 |

The range and direction of valence is 1 (extremely unpleasant) to 9 (extremely pleasant).
<table>
<thead>
<tr>
<th>Neutral adjectives</th>
<th>Healthy controls ( (n = 17) )</th>
<th>Individuals with schizophrenia ( (n = 16) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ample</td>
<td>6.12 ± 1.11</td>
<td>6.87 ± 1.64</td>
</tr>
<tr>
<td>Aloof</td>
<td>4.18 ± 0.81</td>
<td>4.20 ± 1.42</td>
</tr>
<tr>
<td>Blue*</td>
<td>5.18 ± 1.88</td>
<td>6.75 ± 1.53</td>
</tr>
<tr>
<td>Aware</td>
<td>6.47 ± 1.42</td>
<td>6.69 ± 1.62</td>
</tr>
<tr>
<td>Blank</td>
<td>4.71 ± 1.10</td>
<td>4.50 ± 1.63</td>
</tr>
<tr>
<td>Airy</td>
<td>5.59 ± 1.37</td>
<td>4.94 ± 1.69</td>
</tr>
<tr>
<td>Annual</td>
<td>5.29 ± 0.59</td>
<td>5.75 ± 1.24</td>
</tr>
<tr>
<td>Basic</td>
<td>5.29 ± 0.69</td>
<td>6.25 ± 1.65</td>
</tr>
<tr>
<td>Blond</td>
<td>6.12 ± 1.32</td>
<td>6.38 ± 1.67</td>
</tr>
<tr>
<td>Actual</td>
<td>5.29 ± 0.59</td>
<td>5.81 ± 1.52</td>
</tr>
<tr>
<td>Broad</td>
<td>5.41 ± 1.18</td>
<td>5.44 ± 1.21</td>
</tr>
<tr>
<td>Casual</td>
<td>6.35 ± 1.58</td>
<td>6.69 ± 1.49</td>
</tr>
<tr>
<td>Brief</td>
<td>5.59 ± 1.12</td>
<td>5.50 ± 1.59</td>
</tr>
<tr>
<td>Brown</td>
<td>5.18 ± 0.88</td>
<td>5.75 ± 1.84</td>
</tr>
<tr>
<td>Classic</td>
<td>6.59 ± 1.23</td>
<td>6.94 ± 2.14</td>
</tr>
<tr>
<td>Bold</td>
<td>6.13 ± 1.09</td>
<td>6.20 ± 1.61</td>
</tr>
<tr>
<td>Common*</td>
<td>5.29 ± 0.85</td>
<td>6.20 ± 1.32</td>
</tr>
<tr>
<td>Close</td>
<td>5.76 ± 1.52</td>
<td>5.25 ± 1.48</td>
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<tr>
<td>Civil</td>
<td>6.44 ± 1.31</td>
<td>6.75 ± 1.48</td>
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<tr>
<td>Central*</td>
<td>5.24 ± 0.56</td>
<td>6.13 ± 1.46</td>
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<tr>
<td>Dense</td>
<td>4.65 ± 1.22</td>
<td>4.06 ± 2.11</td>
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<tr>
<td>Constant</td>
<td>5.71 ± 1.05</td>
<td>6.19 ± 1.64</td>
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<tr>
<td>Compact</td>
<td>5.53 ± 1.46</td>
<td>5.63 ± 1.41</td>
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<tr>
<td>Daily*</td>
<td>5.53 ± 1.12</td>
<td>6.75 ± 1.69</td>
</tr>
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<td>Cubic</td>
<td>5.06 ± 0.24</td>
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<td>Curly</td>
<td>5.47 ± 1.12</td>
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<td>Equal</td>
<td>6.18 ± 1.70</td>
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<td>Deep</td>
<td>5.06 ± 1.03</td>
<td>5.33 ± 2.02</td>
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<td>Dry</td>
<td>4.71 ± 1.49</td>
<td>4.94 ± 2.32</td>
</tr>
<tr>
<td>Direct</td>
<td>6.65 ± 1.54</td>
<td>7.13 ± 1.50</td>
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<td>Green</td>
<td>5.94 ± 1.25</td>
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<td>Long</td>
<td>4.76 ± 1.75</td>
<td>5.75 ± 2.35</td>
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</tr>
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</tr>
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Table 3: Continued.

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Negative adjectives

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higher in valence, followed by neutral, and finally by negative words (*P* < 0.001 for all comparisons).

However, independent *t*-tests examining group differences for particular items showed differences in ratings for a subset of words. In general, some of the words that were previously categorized as “neutral” by a group of volunteers were rated more positively by individuals with schizophrenia when compared with HC, such as “blue” (*P* = 0.013; 

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*P* < .05.
experience (that include ratings of stimuli with affective properties) are more variable than findings on emotional expression, possibly due to differences in the stimuli used (e.g., face expressions, pictures, odors) and to differences in patients’ samples (e.g., schizophrenia subtype, gender, clinical symptoms), replication of these findings is needed with different schizophrenia subtypes and clinical symptoms (e.g., positive versus negative symptomatology) (see [7] for a review of emotional response deficits in schizophrenia).

Future studies could extend the current findings by exploring how schizophrenic individuals assess the arousal of affective verbal material. This could be done by incorporating a 1–9 scale for arousal ratings (from not arousing to extremely arousing) as suggested by Bradley and Lang [13], allowing for the study of group differences in the intensity of stimuli.

Additionally, since deficits in emotion processing are already observed in the prodromal stage of the disorder [5], it would be interesting to explore the representation of affective knowledge and its effects on processing of verbal affect-related stimuli in prodromal and first-episode schizophrenic individuals in comparison with HC and chronic schizophrenia. This would allow a better understanding of possible changes in emotional processing before the frank onset of psychosis and in the first stages of the disease, particularly in terms of ratings of stimuli’s affective properties. Future studies should address these issues and questions.

4. Conclusions

This study aimed to investigate how schizophrenic individuals rate the valence of adjectives, when compared with healthy controls. Results indicated similar ratings of emotional valence of words, providing support for a similar representation of affective knowledge related to words in schizophrenia, at least in terms of the valence dimension. Therefore, these findings further suggest that the process of extracting emotional information from semantically emotional words is similar in individuals with schizophrenia and healthy controls, increasing the confidence in self-reports of affect in this clinical group.

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References


Evidence is reviewed for the existence of a core system for moment-to-moment social communication that is based on the perception of dynamic gestures and other social perceptual processes in the temporal-parietal occipital junction (TPJ), including the posterior superior temporal sulcus (PSTS) and surrounding regions. Overactivation of these regions may produce the schizophrenic syndrome. The TPJ plays a key role in the perception and production of dynamic social, emotional, and attentional gestures for the self and others. These include dynamic gestures of the body, face, and eyes as well as audiovisual speech and prosody. Many negative symptoms are characterized by deficits in responding within these domains. Several properties of this system have been discovered through single neuron recording, brain stimulation, neuroimaging, and the study of neurological impairment. These properties map onto the schizophrenic syndrome. The representation of dynamic gestures is multimodal (auditory, visual, and tactile), matching the predominant hallucinatory categories in schizophrenia. Inherent in the perceptual signal of gesture representation is a computation of intention, agency, and anticipation or expectancy (for the self and others). The neurons are also tuned or biased to rapidly detect threat-related emotions. I review preliminary evidence that overactivation of this system can result in schizophrenia.

1. Introduction

Is there a system for dynamic moment to moment social communication in the brain? Social perception has now been extensively studied in humans and nonhuman primates and is defined as follows: “…the initial states of evaluating the social communicative intentions of others by analysis of eye-gaze direction, facial expressions, body movements, and other types of biological motion.” [1]. Recent evidence suggests that such a system does exist and that abnormal activity in this system may produce the symptoms and cognitive deficits that comprise the syndrome of schizophrenia. A posterior system will be described whose activity may correspond to or underlie the perceptual experience of conversing and interacting with others. Until recently, communication has primarily been studied through language research. This line of research has focused mainly on the structure of the representation and the neural basis of language input (graphemes, phonemes), the internal lexical/semantic representation, and language output (writing and speech production) and has made significant progress in understanding language.

2. Communication Involves Not Only Language Processing but Also Social Cognitive Functions

Communication with another individual involves a set of representations or processes that are outside the scope of traditional language research. Many of these representational systems are studied under the rubric of social cognition. Social communication (in humans) necessitates the dynamic perception of speech, social-emotional cues, and the production of the communicative message (narrative, intonation, and gestures).

The speech signal that is used to communicate is (primarily) both auditory and visual in nature. In naturalistic settings, the perception of speech occurs simultaneously with the dynamic visual perception of gestures, especially
of the face. The audiovisual speech signal not only conveys meaning through words but also contains information about emotion (facial expressions and prosody). Perception during conversation also necessitates a host of other functions that are crucial for communication. During the rapid interplay of conversation, the ability to anticipate other’s thoughts and actions is also essential. Theory of mind is used; this is the ability to “think about thoughts” and to represent other’s point of view. The representation of agency (who is doing what) and intention, both in other’s and in one’s self, are important. The correct deployment of attention and working memory are needed as well as the ability to follow or track other’s behavior and speech. A narrative of the conversation must be built up and maintained; this is an understanding of the context and the story or message that is being conveyed by the individual words and sentences. During conversation, meaning is built up not only from words but also from body and facial gestures as well as intonation (prosody). Recent evidence suggests that there may be a set of brain areas whose functionality matches the representations and processes needed during moment to moment social communication [2–6]. The temporal parietal occipital junction or TPJ (especially in the right hemisphere) is referred to as the “social brain area” [7] because it has been implicated in numerous neuroimaging studies of social cognitive functions such as theory of mind, empathy, social attention, and other functions [2, 3]. Figures 1 and 2 show the functional architecture of the TPJ. It has been hypothesized that the TPJ is involved in lower-level processes associated with empathy, theory of mind, agency, and attentional orienting to salient stimuli and that these processes are crucial to higher-level social function [2] (see Figure 2). The TPJ includes the inferior parietal region as well as the posterior superior temporal sulcus (PSTS) and gyrus (note that only the right hemisphere is shown, but the left TPJ region is also involved in these functions). The functional territory for the PSTS is often thought to extend inferiorly to at least the posterior middle temporal gyrus. The notion that the TPJ is crucial for social interaction/communication has now been tested directly in human subjects. A recent naturalistic functional magnetic resonance imaging (fMRI) study of live face-to-face interaction within an MRI scanner showed strong evidence that the TPJ is a core region for moment to moment social interaction [4]. Medial prefrontal regions have also been hypothesized to play a role in social functioning and data on this point will be reviewed (predominately in the later section of the paper).

3. General Characteristics and Anatomical Connections of the TPJ

The PSTS has a major role in the perception of dynamic gestures. A basic function of the inferior parietal region is in the formation of intentions for action and this region (as well as the intraparietal sulcus) contains mirror representations that are active during either the perception or production of an action [8]. The intraparietal sulcus separates the inferior and superior parietal lobe. Portions of the intraparietal sulcus such as the lateral intraparietal region or LIP are thought to contain a dynamically constructed saliency map that is used to guide gestures such as saccades [8–10]. The TPJ and surrounding regions project to the inferior frontal region and are closely anatomically associated with hippocampal and insular regions [5, 6, 11]. Interoceptive and homeostatic body signals activate the insula (including thirst, sensual touch, sexual arousal, warmth, heartbeat, and bladder distension) [12]. Subjective ratings of these body signals correlate most strongly with activation in the anterior insula and this region has been hypothesized to underlie emotional awareness [12]. Craig describes the anterior insula for “feeling emotion and homeostatic and body feelings”
relative to the anterior cingulate’s limbic motor function or role in initiating or motivating behavior.

4. Social Cognition Is Abnormal in Schizophrenia

It is well known that social cognitive deficits form a major part of the schizophrenic syndrome. Social cognitive deficits are considered to be a major determinant of functional outcome for schizophrenic individuals [13]. Social responsiveness is affected in schizophrenia; the negative symptoms include asociality as well as a lack of facial movement, facial expression, eye contact, and vocal inflection (prosody). In fact the four most prevalent so-called negative symptoms of schizophrenia are a lack of expressive gestures, a lack of vocal inflection and social inattention, as well as a general impairment in attention. Schizophrenic individuals also present with theory of mind deficits and these deficits are related to a lack of expressiveness [14, 15]. It is also important to note that internal experiences of emotion and related sensations (perhaps related to insular function) do not seem to be as abnormal in schizophrenia as emotional responsiveness [16, 17].

5. Building Links between the Syndrome of Schizophrenia and Brain Dysfunction: a Parsimonious Account of Positive and Negative Symptoms as Stemming from the Same, Similar, and/or Adjacent Social Cognitive Modules within the TPJ

These negative symptoms and social cognitive deficits could clearly be described as problems with social communicative representations or systems. However, I will argue that most, if not all, of the schizophrenic syndrome can be understood under the rubric of social communication. Recent advances in understanding this system will be described and used to reframe the symptoms of schizophrenia and to then link them to brain function. It is proposed that the overactivation of the functional modules in the TPJ that subserve social communication produces the syndrome of schizophrenia. Direct evidence for TPJ involvement in schizophrenia will be presented near the end of the paper. The formulation presented here is new and remains to be systematically tested. However there are many lines of evidence that will be described below here in after. For example, schizophrenic symptoms are evoked by stimulation to the TPJ [18–21], electrical brain activity within the TPJ coincides with the presence and absence of symptoms [22], and the disruption of TPJ activity alleviates symptoms [23–28].

6. Reframing the Schizophrenic Syndrome and Evaluating the Evidence for the Involvement of the TPJ in Social Processing

Understanding aspects of this system at the neural (single cell) and systems neuroscience levels may provide a basis for the understanding the disparate symptoms and cognitive deficits found in the schizophrenic syndrome. Several principles were used to guide the construction of the current framework. Neuroimaging alone cannot provide evidence for a region’s involvement in a particular function and taken alone constitutes relatively weak evidence for a link between a function and a brain region. Lesion studies must also show that the function is impaired when the region is damaged. In evaluating human lesion data it is important to analyze each case individually [29]. The extent of involvement of other damaged regions should be taken into account. Data from patients with brain trauma from head injury or with epilepsy should be viewed with caution as these patients often have diffuse damage that may be missed in a radiologic examination. Converging evidence from several sources provides the strongest basis for positing a relationship between brain and function. For example, in interpreting functional imaging data, it is also important that other sources show convergence with the theory, including brain stimulation, transcranial magnetic stimulation (TMS), and data from neuronal recordings in humans or animals. Data from single case studies with circumscribed brain lesions that contradict a specific theoretical position must be accounted for and are a serious indictment of the theoretical position [29]. For each functional domain discussed here in after, I will cite neuroimaging and lesion data to show that the TPJ is a core substrate for the function (as well as data from the other techniques as discussed previously). When single neuron data are described, I will cite evidence showing similar findings from human studies in order to provide explicit links between cellular properties and systems level function (a detailed description of all the studies cited here can be found in [5, 6]).

7. The Phenomenology of the Schizophrenic Syndrome Reframed

For brevity, this paper will describe the most prominent symptoms and their relationship to brain function; a detailed account for the other symptoms can be found in [6]. Auditory hallucinations of voices are the most prevalent symptom [30]. Patients have the feeling that someone is actually there and speaking. Auditory hallucinations can also take the form of hearing conversations between voices. Patients will sometimes report that it seems like there is actually another person or persons in their head. Some types of auditory hallucinations may be due to a misattribution of the patient’s thoughts to an outside source (abnormal agency attribution for the voice). Visual hallucinations of people in action are the next most prominent category of hallucination [31]. The most common delusions, delusions of persecution and delusions of reference, are characterized by the feeling of being followed, watched, or that people are secretly communicating using gestures or clothes [32]. The prominent positive symptoms of schizophrenia revolve around the perception or feeling of an entity that is speaking, communicating, watching, following, observing, or spying. Schizophrenia is also characterized by abnormal agency
judgments; patients can feel as though their actions and thoughts are controlled by an outside force or entity (e.g., delusions of control, thought insertion, thought broadcasting). Therefore, the prominent hallucinations and delusions may be reframed as the misperception of a social entity or entities or overactivation of representations in the TPJ that subserve many aspects of dynamic social processing. Throughout the paper I will review properties of dynamic social perception and interaction that may be important for understanding the schizophrenic syndrome. For example, recent advances in cognitive neuroscience show that the perception of a social entity is accompanied by an intrinsic and automatic perception of agency, intention, and social prediction [33–36]. These functions are intrinsic to the representation of dynamic action at the single neuron level [33, 34, 36]. It has also been shown that self and other processing overlap and the feeling of a presence can also stem from abnormal activation of the self-representation [19–21, 37]. The prominent negative symptoms are related to abnormal social responding and a lack of social expression or response primarily in the face and voice. The regions that are used to perceive dynamic social interaction are also used in the formation of intentions for the production of social, emotional, and attentional gestures as well as for theory of mind [2, 7, 38–42]. This reframing of the syndrome is parsimonious in that it postulates that the symptoms can be understood as the integrated action of one region (as opposed to widespread abnormalities or complex interactions between anterior and posterior regions).

In the following sections, I will describe the functional architecture (the arrangement or juxtaposition of functional regions) as well as properties of the neuronal representation of dynamic social action that can be used to understand the schizophrenic syndrome. The functional contributions of the TPJ have been described in several disparate subfields of neuroscience and cognitive neuroscience that are conceptually overlapping but motivated by the investigation of different psychological functions [2, 5, 6]. In describing these findings, I will also show how individual schizophrenic symptoms can be reframed and organized under the rubric of TPJ function.


The neural code used by the TPJ reflects the fact that communication occurs not only through auditory language comprehension but also through gestures that can occur simultaneously with the speech signal. A basic and prominent function of the TPJ is to represent dynamic gestures, especially in lateral temporal and inferior parietal regions centered on the PSTS in humans [42]. Lesions and repetitive transcranial magnetic stimulation (rTMS) to these regions impair biological motion perception [43, 44]. The homologous regions in the monkey have neurons that are multimodal and respond to the sight, sound, and somatosensory aspects of biological motion [41, 45]. Single-cell recordings in monkeys show that audiovisual representation is the most predominant type of representation followed by visual-tactile representation [45]. The PSTS combines information about biological motion, social/biographical information and speech [41, 46]. In humans, the representation of audiovisual speech occupies a large portion of the TPJ territory (see Figure 1 [47]). These relative proportions match the fact that hallucinations of voices and the feeling that someone is speaking predominate in schizophrenia followed by visual hallucinations of people and then by tactile hallucinations. Hearing voices also activates the TPJ [48].

Multimodal gesture representations have properties that allow the neurons to participate in more conceptual functions such as the computation of agency, the ability to keep track of other’s behavior, and the ability to predict the actions of others (social prediction) [33, 34, 49–51]. For example, repetition suppression in the monkey STS creates a situation in which neurons that are tuned to sequences of dynamic gestures are maximally responsive to gestures that are about to occur [33]. Single-cell recordings in monkeys have shown that these functions are automatically computed and are an inherent part of the gesture representation at the single neuron level. Neuroimaging has confirmed that activity in the PSTS in humans is also modulated by the perceived intentionality of the gesture or movement [35]. In addition, the human STS was found to be a region in which interactions occur between observed action and the reafferent motor-related copy of that action [52].

Hence, overactivation of this dynamic gesture system could produce the erroneous perception of speech, visual human action (visual hallucinations of people), or tactile hallucinations. Direct evidence for this supposition comes from the fact that cortical stimulation of the TPJ (in nonpsychotic individuals) and lateral posterior temporal lobe can result in visual hallucinations of action scenes involving people [18]. Cortical stimulation of the TPJ can also cause feelings of limbs or body parts changing shape in nonpsychotic individuals (e.g., somatosensory hallucinations and delusions [19]). The overactivation of gesture representations could be graded so that some patients might experience frank hallucinations and others might experience a feeling that there are persons acting, watching, or communicating with them. In addition, this overactivation would be predicted to produce a feeling of agency or of an agent with intentions and would be expected to interfere with social prediction and social interaction.

Activity in these PSTS/TPJ multimodal neurons that encode gestures (especially audiovisual gestures) has been shown in monkeys and humans to provide rapid feedback excitation (within 30 msec) to unimodal regions and to result in gamma synchronization [53]. This phenomenon has been documented in several studies (reviewed in [5, 6]). Hence, erroneously activated audiovisual speech representations may cause the aberrant activation of auditory cortex and the gamma synchronization of TPJ and primary auditory regions. This would result in increased attention and activity in auditory channels.
9. The TPJ Is a Core Substrate for Theory of Mind

The TPJ is a core neural substrate for theory of mind or the ability to understand and represent another’s point of view or thoughts [39, 54, 55]. Neuroimaging studies of theory of mind have shown several foci including the TPJ, the orbital frontal cortex, amygdala, anterior insula, and medial frontal regions [56]. The medial prefrontal cortex or the anterior paracingulate cortex—approximately corresponding to Brodmann area (BA) 9/32—had been thought to be a key region for theory of mind function [56]. However, previous reports of an association between theory of mind, social processing, and the medial prefrontal cortex have relied on patients with traumatic brain injury or epilepsy. These types of patients often have diffuse brain damage that is difficult to detect in radiologic exams (see Bird et al. (2004) [57] for a critical discussion of these studies). There have now been several reports of circumscribed lesions to the medial prefrontal cortex where the patients do not show theory of mind impairments [57–60]. Bird et al. (2004) [57] present a carefully documented case of a patient whose injury is circumscribed and coincides with the region identified in several fMRI studies to be involved in theory of mind (see Figure 3). This individual did show impairments in planning and memory as well as a tendency to confabulate but did not show theory of mind deficits on any of a battery of tasks [57]. In another study, three patients with anterior cingulate damage were tested on theory of mind, social situation processing, and motivational decision making. Two of the patients had selective anterior cingulate damage (one also had temporal lobe damage). These two patients were not impaired in theory of mind, motivational decision making, or social situation processing [58].

TPJ lesions do impair theory of mind [60]. In addition, recent neuroimaging studies have shown that the (right) TPJ has a response profile that is more selective for theory of mind than other regions such as the posterior cingulate and the medial prefrontal cortex. The right TPJ was selectively involved in the attribution of mental states rather than reasoning about general socially relevant facts about a person [54]. The ability to make inferences about mental states or beliefs and intentions during moral judgments was also impaired when TMS was applied to the right TPJ [61]. Neurons in the monkey STS that respond to dynamic action or biological motion are tuned to respond to physical or vocal actions that are about to occur or to anticipate action [33, 49]. Aberrant activity in the TPJ would interfere with theory of mind computations resulting in abnormal or slowed social behavior. This abnormal activity would also interfere with dynamic social response and the tracking and hence understanding of other’s social behavior. These impairments are core components of the schizophrenic syndrome which includes symptoms such as asociality and social inattention as well as theory of mind deficits as described previously [13–15, 62, 63].

10. Emotional Perception and Reaction

Emotional gesture perception and reaction for the face and body as well as prosody perception are dependent on the TPJ, presumably because of its role in voice and gesture representation (e.g., eyes and face). Emotional perception and reaction are linked; the perception of facial expressions produces a subtle version of the expression on the viewer’s face [64]. The perceptual circuits that are used to perceive other’s actions are also used to represent and plan our own actions, and several regions are active during both observation and imitation of dynamic gestures [7, 64, 65]. Single neurons in the monkey PSTS respond to emotional gestures [49]. Human neuroimaging studies also show that the TPJ is involved in emotional gesture and prosody perception [66, 67]. Lesions within the primary/secondary somatosensory cortex, supramarginal gyrus (part of inferior parietal cortex/TPJ), and insula (adjacent and medial to the TPJ) result in a deficit in the ability to perceive facial emotion and prosody [40]. The supramarginal gyrus may be especially important for the creation of the intentions or plans for emotional and prosodic reaction. Hence, the overexcitation of emotional gesture perceptual circuits could interfere with reaction or with the formation of intentions for facial emotional reaction. This would result in social unreactivity or asociality as well as a lack of facial movement, eye contact, vocal inflection, and facial expression; these are all prominent negative symptoms of schizophrenia.

11. Eye Gestures, Social Attention, and Agency

Movements of the eyes are especially important in social cognition and communication; they not only convey emotion but also convey the focus of attention. Dynamic representations of emotional gesture and attention are used in the perception of more conceptual aspects of social
cognition [35, 68]. The TPJ and especially the posterior STS and superior temporal regions are core components of a system for the representation and perception of eye gaze [38, 69, 70]. The TPJ was shown to be selectively involved in representing joint or social attention in a neuroimaging investigation of live social interaction [39]. The perception of gaze direction and the control of attention via gaze are impaired with TPJ damage [70, 71]. Aberrant activity in this system could produce a deficit in the tracking of others' eye gestures resulting in abnormal social attention and hence social reaction and understanding.

As discussed previously, the perception of intentionality and agency are an inherent component of the perception of dynamic gestures, including eye gaze [35, 72–74]. For example, in the monkey, neurons in the STS combine information about gestures of the arm (e.g., reaching) with information about the direction of gaze (the focus of attention) to compute agency or intentionality [34]. Overactivation of gaze and other gesture representations would produce the qualia not only of a presence (of being watched) but also of a presence with intentions. This assumption is corroborated with data; direct cortical stimulation of the TPJ can cause the feeling of a "shadowy presence" [20].

12. Gesture Neurons Are Tuned to Rapidly Detect Threat

Another property of gesture representation in the TPJ is that the neurons in this neural circuit are tuned to rapidly detect emotionally negative or socially threatening gestures. The amygdala is most often cited with regard to this function. However, amygdala damage does not cause a deficit in the detection of dynamic body expressions of fear [75, 76]. This means that there is another brain region that is the core substrate for this function. Single neuron recording in the monkey STS showed that the neurons are tuned or biased to detect potentially threatening biological motion [41]. Event-related potential (ERP) and neuroimaging studies in humans have confirmed that the TPJ is used to perceive threatening or emotionally negative gestures [41, 77]. Hence, although this region is generally used to perceive dynamic gestures, there is a neural tuning for the detection of social threat. Hence, overactivation of these gesture representations might produce the feeling of being in a socially threatening situation. This feeling could be a component of delusions of persecution and other symptoms.

13. Self-Representation, Embodiment, and Agency

The perception of self-made gestures from our own visuospatial perspective and the corresponding auditory, visual, tactile, and vestibular information resulting from actions may provide the concrete scaffolding that is used to create and sustain the self-representation or the feeling of being an embodied, thinking, and acting person [37]. There are also more fixed body schemas that are presumably constructed through experience and that are used in the dynamic representation of the self (these are also located in the vicinity of the TPJ—in the intraparietal sulcus and the secondary somatosensory cortex; see [6] for a summary). Our sense of self is so evident and constant that it may be surprising to learn that it is actually a perceptual construct. However, this construct can break down and be demonstrably associated with certain neural circuits in the same way as other psychological functions such as memory and language. Changes in the feeling of embodiment can be affected by manipulating visual-somatosensory percepts that are represented within the TPJ, by stimulation of the TPJ, or by lesions in the TPJ [37, 78]. For example, the experimental manipulation of visuospatial perspective and simultaneous tactile stimulation can cause the feeling of inhabiting a different body or body swapping [79]. Stimulation or lesion in the TPJ region can cause out-of-body experiences and other changes in the feeling of embodiment [19]. For example, a patient (Susan) with right temporoparietal damage was reported who had a “Capgras syndrome for her mirror image” [80] (see pages 73–75). This patient used sign language and was observed communicating with the person in the mirror (her own reflection). She believed that there was this other “Susan” in the mirror who had the same background, appearance, and age and went to the same school as she did (but she did not know her in school). The other Susan was judged to be a bit slower and not as good at sign language as the real Susan.

The regions and representations that are used to represent the self overlap with those that are used to represent others (see detailed discussion in [6, 37, 81]). The regions that are thought to compute the self-representation are also activated by the perception of dynamic visual (gesture), auditory, or somatosensory stimulation from others, including the TPJ, somatosensory cortex, secondary somatosensory cortex, the extrastriate body area, the intraparietal sulcus, and ventral premotor regions [42, 82]. For example, the secondary somatosensory area responds to touch regardless of whether it was felt on one's own skin or seen on another [83]. Most of the functional components that have been identified with self-representation in the TPJ are modulated by auditory, visual, and tactile inputs and hence overactivation of these channels would be expected to disturb the self-representation [6].

Abnormal feelings of agency and of a presence could also occur as a result of a disturbance of the TPJ self-representation (reviewed in [5, 6]). The bulk of the experimental evidence shows that abnormal activity in TPJ regions and vestibular cortex (insula/inferior parietal lobe) can produce these phenomena [21]. Heautoscopy, the experience of an alternate self or Doppelganger, is associated with either abnormal activity or damage in the TPJ [21]. Visual hallucinations of people are the second most prominent type of hallucination in schizophrenia and may arise from abnormal activation of the self-representation. When the body double is seen (visual hallucination), the visual appearance may or may not mirror the person's own image, but the imitation of body gestures by the double can produce the feeling that the double contains the real mind. The experience of the self can be perceived to arise from the body double or can alternate between the physical body and the body double. This type
of hallucination can also be experienced as a feeling of a presence or multiple presences of closely projected doubles that are not visible [21]. This feeling of a presence has been induced by electrical stimulation of the PSTS region [20]. Aberrant activation of the self-representation would be expected to interfere with feelings of embodiment and agency for one's thoughts and actions as is seen in symptoms such as delusions of control and could also produce the qualia (feeling of a presence) associated with delusions of persecution, delusions of jealousy, and delusions of reference or visual hallucinations.

Several neuroimaging studies of schizophrenia have shown that abnormal agency processing in patients is related to overactivation in (especially the right) IP or TPJ (reviewed in [5, 84]). For example, one study of agency processing found abnormal activity in the right inferior parietal region in schizophrenic subjects and this overactivation was also positively correlated with the Schneiderian score [85].

### 14. The Medial and Orbital Frontal Regions, Social Cognition, and Self-Representation

Impairments in self-awareness related to abnormal activity in midline structures have been hypothesized to play a role in the social processing problems that have been identified in schizophrenia [86]. Several central and medial regions of the brain, including those in the frontal lobe (medial orbital, the ventromedial prefrontal cortex, the anterior cingulate cortex, dorsomedial prefrontal cortex), have been theorized to be involved in self-referential processing and self-reflection [87, 88]. The evidence for this supposition comes mainly from neuroimaging studies where central midline regions have been found to show activity in tasks such as the recall of personal information, the assessment of self-personality traits, appearance, attitudes, or feelings [87, 88]. Gillihan and Farah (2005) [89], in a critical review of this literature, noted that confounding factors were not adequately controlled in many of these studies. A recent study used TMS to disrupt processing and to probe the brain response to self-related stimuli with non-self-related stimuli. Superior performance on self-related items (the self-reference effect) was found. TMS to left and right parietal cortex suppressed the self reference effect, but no effects on the self-reference effect were found with TMS to the medial prefrontal lobe [90]. It was discussed previously how patients with circumscribed and well-documented medial frontal lesions do not present with a deficit in social situation processing nor have deficits in self-related processing been reported [57, 58, 91]. Confabulation is known to occur with frontal lobe damage [80]. The current framework assumes that delusions are not confabulations but rather explanations of bizarre sensory phenomena as suggested by Brendan Maher (2006) [92].

The dorsal anterior cingulate has previously been associated with action monitoring or the monitoring of response conflict and in cognitive control (see review in [93]). This function is thought to be used in social situations [87, 93, 94]. However, there are now several reports of individuals with circumscribed lesions of this area. These individuals have not been found to have deficits in tasks used to measure response conflict such as the Stroop nor in behavioral measures of cognitive control; see for example, [91]. In fact, recent evidence suggests that the dorsal anterior cingulate response to errors may be more related to levels of negative affect during task performance than to response conflict [95]. These results are consistent with the view that the dorsal anterior cingulate plays a role in the control of autonomic responses that accompany cognitive effort (see review in [91]). The dorsal anterior cingulate may be involved in response selection based on reward contingencies; data from single unit studies in monkeys and in humans and further lesion data from humans undergoing cingulotomy support this hypothesis (see review in [91]). The dorsomedial aspect of the prefrontal cortex may have a role in empathy, in representing emotional pain in others, and/or in the ability to use emotional pain or negative consequences to constrain behavior [96]. Although empathy and theory of mind scores are correlated, the precise relationship between them is unclear [57]. A recent FMRI study found that the anterior middle cingulate cortex responded to both emotionally and physically painful events, while the dorsomedial prefrontal cortex responded selectively to emotional pain [96]. A lack of empathy does not seem to be central to schizophrenia, although it is a symptom of the manic phase of bipolar disorder.

Orbital and ventral medial frontal lesions also do not cause theory of mind deficits [97] but rather result in an acquired sociopathy [98]. Orbital and ventral medial frontal lobe damage has generally been reported to result in a lack of empathy, euphoria, irresponsibility, a lack of concern for the future, and a lack of concern for social rules [97–99]. When tested explicitly on measures of social judgment and responding, individuals with orbital and inferior medial frontal lesions present with an intact knowledge of social rules and the ability to judge the outcomes [98]. However, their autonomic responses to socially meaningful stimuli may be abnormal and it is has been hypothesized that these patients fail to activate somatic (body emotional) states in response to social stimuli [99]. Another report surmised that orbital damage results in a reduced ability to use the expectation of negative emotional reactions (anger) to constrain behavior [97]. Recently it has been reported that orbitofrontal lesions cause a diminished sensitivity to varying reward magnitudes [100]. These data are consistent with single unit recordings in monkeys showing neuronal responses that were associated with various aspects of reward computed from experience with behavioral choices [101]. It is claimed that damage to the orbital and ventral medial prefrontal cortex leads to an inability to “develop a coherent model of one’s own self” and hence emotional liability and aberrant social functioning [87]. However, the function of orbital and ventral medial frontal cortices has been repeatedly shown to be related to an inability to use negative emotions to constrain behavior or to competently compute and use reward or punishment outcomes. This syndrome seems more closely aligned with mania where decision making is impaired and individuals often do risky
things without regard to the emotions of others (manic symptoms include euphoria, lack of empathy, impulsiveness, lack of concern for consequences of behavior and for social rules) and manic patients sometimes confabulate as is seen in patients with frontal lobe lesions [80].

In summary, medial prefrontal regions have been shown to be activated during tasks assessing theory of mind and self-related processing; this presupposes a role for these regions in social processing. Anterior cingulate regions show coactivation with the TPJ in many neuroimaging studies and hence abnormal activity in the TPJ could be expected to affect activity in this region. However, as yet there are many competing theories concerning the role of this part of the system and hence it is unclear what the functional consequences of abnormal activity would be and what form they would take (overactivation, lack of activation).

15. Direct Evidence for TPJ Involvement in Schizophrenia

It is hypothesized that the TPJ (and primary efferent areas) should show slightly elevated baseline activity interposed with epochs of hyperactivation that correspond to the abnormal qualia (hallucinations and delusions) and responsive deficiencies (negative symptoms) seen in schizophrenia [5, 6, 102]. Although it is not often acknowledged (perhaps because of the almost axiomatic belief in frontal lobe abnormalities), there is strong evidence for TPJ involvement in psychosis and schizophrenia. Activity has been recorded in the TPJ that corresponds to the experience of symptoms, activity has been found that is correlated with symptoms, and recent large-scale morphometric studies show volume reductions in the TPJ in schizophrenia. Torrey [103] wrote an extensive review of the evidence for inferior parietal involvement in schizophrenia that includes an account of the relationship between prodromal symptoms and parietal function (we will not reiterate that evidence here). The TPJ region is a relatively anatomically variable region and hence volume abnormalities could be relatively difficult to detect; the inferior parietal region is one of the last regions in the brain to be myelinated and develops into late adolescence [104]. However, recently two large-scale morphometric studies of schizophrenic volume reductions have been published. Both of these studies show core reductions in TPJ volumes [105, 106]. Direct evidence for abnormal activity in the TPJ during psychosis comes from brain recordings; right inferior parietal activity was related a delusional state in a magnetoencephalography (MEG) study [22]. When the abnormal activity subsided, the delusions subsided. Correspondingly, interference with TPJ activity alleviates schizophrenic symptoms. At first rTMS was applied to the TPJ to treat auditory hallucinations; at least 6 published studies have now shown that TMS applied to the TPJ alleviates auditory hallucinations and some reports show reductions in other symptoms as well [23–28]. For example, in one study schizophrenic subjects with treatment-resistant auditory hallucinations were given daily rTMS treatments for 10 days and showed a reduction in the frequency of auditory hallucinations and an improvement in many other symptoms [23].

Data from our previously published studies have consistently supported TPJ involvement; schizophrenic symptoms such as auditory hallucinations and thought disorder were correlated with levels of FMRI activity in the inferior parietal and superior temporal sulcus in several studies [107–109]. One of the most systematic FMRI symptom capture studies of schizophrenia was one of a single schizophrenic subject who heard voices for approximately 26 seconds and then no voices for approximately 26 seconds; this periodicity is relatively optimal for an FMRI design [110]. FMRI activation was detected surrounding the PSTS approximately 3 seconds prior to the conscious detection of the auditory hallucination. Activation of the inferior parietal and inferior frontal regions followed. The PSTS activation (which extended into the superior and middle temporal regions) was persistent through the entire experience. This coincides with the unusual extended neural responses (e.g., 7 seconds) recorded in monkey STS neurons that are activated by dynamic multimodal gestures [49].

TPJ over-activation could stem from a number of causes, but it is hypothesized that in schizophrenia the source is most often from over-activation of the hippocampal system [111]. The activity of the hippocampus shows a high association or correlation with activity in the TPJ (so-called default mode or cortical hub activity) and evidence from epileptic individuals shows that abnormal hippocampal activity underlies active psychosis and that the TPJ region is also involved [6]. Note that resting state abnormalities have been repeatedly found in schizophrenia and that a seed placed within the hippocampus will produce activity in most of the “default mode” regions [112–115] (see [6] for a detailed discussion of hippocampal involvement).

16. Summary

In summary, the regions that make up the TPJ form a core system for the perception and production of emotional face and body gestures as well as prosody. This region shows functional activity that indicates that it is preferentially involved in the perception of narrative (versus words or sentences) [3]. This area is a core component for the perception of social attention or of the process of joint attention (the deployment of attention according to social and communicative cues). This area is also the core region in the brain for theory of mind or understanding other’s intentions and thoughts. The neural activity in this system is biased to detect or anticipate future multimodal social acts, or in other words to anticipate speech and actions. Inherent in the representation of multimodal gestures is a coding of intention and agency. Even though this system is used for the perception and production of biological motion or gestures, there is a neural bias or tuning for the rapid identification of social threat and parts of the TPJ are core components of fear perception (reviewed in [5, 6]). The TPJ not only represents other’s actions but may also be a core area for representing the self. This is the only region of the brain that
produces verbal memory deficits when damaged and hence is the neural substrate for verbal working memory (reviewed in [5, 6]). Since neural activity in this region corresponds to social perception and joint attention, over-activation of this region could result in the erroneous perception of being within a dynamic social situation. Over-activation of this region would have widespread consequences for many domains including social perception, social reactivity, and attention.

When the consistency and weight of the evidence is considered, the characteristics of TPJ function more closely match the symptoms of schizophrenia. Hippocampal activity has been consistently shown to be abnormal in schizophrenia which is highly correlated with both TPJ and anterior cingulate/paracingulate activity [113–115]. The characteristics of which is highly correlated with both TPJ and anterior cingulate/paracingulate activity [113–115]. The characteristics of TPJ function more closely match the symptoms of schizophrenia. Hippocampal activity is considered, the characteristics of TPJ function more closely match the symptoms of schizophrenia. Hippocampal activity has been consistently shown to be abnormal in schizophrenia which is highly correlated with both TPJ and anterior cingulate/paracingulate activity [113–115]. The characteristics of medial prefrontal function (especially from the lesion data) may match those of bipolar disorder more closely than those of schizophrenia.

Conflict of Interests

The authors declare that this paper was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests (6, 2950-2967).

Acknowledgments

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References


Research Article

Faulty Suppression of Irrelevant Material in Patients with Thought Disorder Linked to Attenuated Frontotemporal Activation

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Formal thought disorder is a feature schizophrenia that manifests as disorganized, incoherent speech, and is associated with a poor clinical outcome. The neurocognitive basis of this symptom is unclear but it is thought to involve an impairment in semantic processing classically described as a loosening of meaningful associations. Using a paradigm derived from the n400 event-related potential, we examined the extent to which regional activation during semantic processing is altered in schizophrenic patients with formal thought disorder. Ten healthy control and 18 schizophrenic participants (9 with and 9 without formal thought disorder) performed a semantic decision sentence task during an event-related functional magnetic resonance imaging experiment. We employed analysis of variance to estimate the main effects of semantic congruency and groups on activation and specific effects of formal thought disorder were addressed using post-hoc comparisons. We found that the frontotemporal network, normally engaged by a semantic decision task, was underactivated in schizophrenia, particularly in patients with FTD. This network is implicated in the inhibition of automatically primed stimuli and impairment of its function interferes with language processing and contributes to the production of incoherent speech.

1. Introduction

Bleuler’s work in psychosis continues to be highly influential in furthering understanding of the signs and symptoms of schizophrenia [1]. Nevertheless, one of his primary conceptual contributions in understanding schizophrenia, “disturbance of associations” [2, 3], remains to be explained in terms of underlying neural basis. In turn, Bleuler’s ideas were influenced by Jung’s word association task [4]. Regardless of the psychological or affective mechanisms that may influence the production of speech, Jungian word association is by nature a semantic association test. Interpretations of the broader meanings of “split mind” and “association”, arising from the psychoanalytical field, are not incompatible with an inbuilt characteristic of this test, which taps into the concept of semantic priming [5], extensively investigated in schizophrenia (see Minzenberg et al. [6] for a review in single-word semantic priming in schizophrenia). However, some studies do not take into account specific symptoms proposed by Bleuler, such as formal thought disorder, as an underlying factor that would interfere with task performance (e.g., [7]), mixing up performance of patients with a range of distinct symptoms. Of note, there is a line of investigation suggesting that formal thought disorder (FTD) is associated with hyperactivation of the semantic network [8–14]. These studies mainly employ semantic tasks based on word-pair
semantic priming paradigms. It is important to note that such kind of studies, although provided evidence for altered semantic processing associated with FTD, may fail to tap into the type of communication impairment clinically seen in FTD patients. The latter manifests itself in linguistic units that range from large thoughts, such as whole periods with several sentences embedded, to small utterances, such as words within the same sentence [15], or even a single word (e.g., neologism).

Bleuler also suggested that, within its symptoms, FTD is possibly the closest to the neural substrate of schizophrenia [2]. Biological evidence for a neural basis of FTD has been provided by methods employing functional measures of brain activity. EEG studies employing the n400, an event-related potential (ERP) that is a neural marker of semantic processing [16–18], demonstrated a reduction in n400 amplitudes and increased latency in schizophrenia during a sentence processing task [19–21], consistent with impairment in semantic integration, particularly associated with FTD [22–26].

Functional neuroimaging of schizophrenia suggested that FTD is associated with altered resting activity in the medial temporal cortex [27] and with altered activity (brain metabolism or Blood Oxygen Level Dependent-BOLD-activity) during tasks that engage language processing in the dorsolateral prefrontal, bilateral anterior cingulate, and lateral temporal cortices [28–32]). FTD has also been linked to reductions in grey matter volume in the inferior frontal [33, 34] and the temporo-parietal cortex [35]. Collectively, the studies particularly implicate the prefrontal, middle frontal, temporal, and anterior cingulate cortices in the pathophysiology of FTD in schizophrenia.

In summary, FTD is a symptom of schizophrenia that manifests itself as disorganized, incoherent speech. Andreasen [36] has operationalized studying this symptom by creating a scale that decomposes the concept of “loosening of meaningful associations” into measurable items. Thus, this clinical manifestation of schizophrenia, which can be objectively measured, is thought to involve impairment in semantic processing, deficits in executive functioning, and altered brain activity in the left frontal, temporal, and anterior cingulate cortices.

The objective of the present study was to use event-related fMRI to examine the extent to which regional activation during semantic processing is altered in schizophrenic patients with FTD. Methodological issues which were not tackled by some of the functional imaging studies mentioned above (small sample sizes, block design fMRI task and an overt production of speech) were carefully addressed. Particularly, we devised a task likely to engage areas associated with linguistic processes with heavier demands [37] using a paradigm derived from semantic decision procedures used in the ERP studies that originally correlated FTD with n400 abnormalities in schizophrenia. We sought to engage the top down modulation of semantic processing by requiring suppression or inhibitory mechanisms to take place, necessary to process semantic incongruent information. Activation of the left inferior frontal and left middle temporal [38, 39], right anterior cingulate [38], and bilateral precuneus [39] was found in studies that required the generation of semantically incongruent endings to complete a previously primed incomplete sentence stem. Therefore, these areas are activated in tasks requiring suppression of endings (meanings) automatically activated by sentences.

We hypothesized the following:

(1) Incongruent sentences would engage left inferior frontal, left middle temporal, right anterior cingulate, and bilateral precuneus more than congruent sentences.

(2) FTD patients with schizophrenia would show diminished activation relative to controls and patients without FTD in:

(a) areas previously demonstrated to show aberrant activity in this group: left prefrontal (middle and inferior), left temporal, and bilateral anterior cingulate cortex and
(b) areas associated with manipulation of incongruent material (i.e., the above and also the precuneus).

2. Methods

2.1. Subjects. Ten healthy adult volunteers and 18 patients meeting DSM-IV criteria for schizophrenia [40] took part in the study. Acutely psychotic patients with either high or low levels of positive FTD were recruited from the South London and Maudsley NHS Trust. Controls were recruited from the same geographical area through local advertisement.

All subjects were dextral [41], males with National Adult Reading Test Revised [42] IQ ≥ 80, and native speakers of British English. Exclusion criteria for controls were a previous history of a neurological or psychiatric disorder, substance dependence, or a medical disorder that could affect the brain. Exclusion criteria for patient were another DSM-IV axis I diagnosis and age of onset of schizophrenia prior to 18 years of age. Subjects received oral and written information about the procedures and gave written consent to participate, with £30 in return for participating. The project was approved by the Research Ethical Committee of the Institute of Psychiatry.

Psychopathology was assessed using the Scale for the Assessment of Positive Symptoms (SAPS) [36] and the Scale for the Assessment of Negative Symptoms (SANS) [43]. Positive FTD was assessed on the basis of the corresponding 8 items in the SAPS (derrailment; incoherence; illogicality; circumstancelessness; pressure of speech; dextrable speech; tangentiality; clanging).

In each patient, the score on each FTD SAPS item (range 0–5) was summed to yield a total FTD score (range 0–40). The FTD score was then used both as a classifier to split the patients sample in two subgroups (as described below) and as a continuous measure (see Figure 2(b)), without
distinctions within the patients. Thus, patients who had a FTD score 0–4 were classified as non-FTD and those with scores ranging from 5–40 were classified as FTD. The patients sample was split into two groups on this basis producing a subgroup with (FTD, n = 9) and a subgroup without FTD (Non-FTD, n = 9). There were no significant differences between these subgroup in SAPS total score, SANS total score, scale for the Assessment of Global Functioning (GAF) [40] score, antipsychotic medication dose (in chlorpromazine equivalent), duration of illness, number of psychiatric admissions, or age at first admission (Table 1).

There were also no differences in the score for negative FTD, as defined by the SANS items (poverty of speech, poverty of content of speech, thought blocking, and increased latency of response).

The two patient subgroups and the healthy controls had similar demographic characteristics (Table 2).

2.2. Task

2.2.1. Sentence Stems. Eighty sentence stems (i.e., last word missing) were used with the degree of constraint previously defined in a large sample drawn from the same population as the control subjects in the present study [44]. Forty stems had a high semantic constraint (HCT) (cloze probability > 0.94) and 40 low semantic constraint (LCT) (cloze probability < 0.34). For example, “He posted the letter without a...”, is a HCT stem (completed by the word “stamp” by 96% of subjects), while “She couldn’t imagine anyone less...” is a LCT stem.

2.2.2. Target Words. Two types of words were presented as target stimuli, taken from completions that had originally been produced for the stems [44]. These words were either congruous with the sentence stem (i.e., semantically related) or incongruous (semantically unrelated). To avoid phonological priming [45], words with the same initial phoneme as the most frequent congruent completion (best completion) for that stem were excluded.

2.3. Experimental Paradigm

2.3.1. fMRI Stimuli. Sentence stems were presented onto a screen subtending a visual angle of approximately 1° (text height) by 7°, (stem length). Stems were presented for 2.5 sec. After an interval of 0.7 sec during which the screen was blank, the target word appeared (Figure 1). During the inter stimulus interval, subjects were instructed to fixate on an asterisk for at least 13.7 sec. Eighty trials of 20.4 seconds duration were presented, divided into 5 runs of 16 trials each. Trial type per run was pseudorandomized to control for order effects between subjects. Subjects were instructed to read the sentence stem, then decide if the target completed the stem in a sensible way or not making their choice using one of two buttons on a button box (for accuracy and response time recordings). Prior to scanning, all subjects underwent a training session to make sure they were able to understand and perform the task.

2.3.2. fMRI Data Acquisition. Gradient-echo planar MR images were acquired using a quadrature head coil in a 1.5 Tesla GE Signa System (General Electric, Milwaukee, WS, USA). Head movement was minimised by foam padding and a supporting band across the forehead. A gradient echo EPI axial acquisition (TR 1700 milliseconds-ms, TE 40 ms, FA 90°, matrix 64 × 64, FOV 24 cm, thickness 7 mm, gap 0.7 mm, 192 volumes) was used to collect 12 slices parallel to the intercommissural (AC-PC) plane. The total number of images acquired (in 5 runs) was 960 with just under five minutes between them. Structural images were acquired using gradient echo IR EPI sequence (TR 1600 ms, TE 40 ms, TI 180 ms, matrix 128 × 128, FOV 20 cm, thickness 3 mm, gap 0.3 mm, NEX 8, 43 slices). This latter image was used for normalisation to a standard template.

2.4. Analysis. This experiment is part of a larger study [46] in which a series of experiments were designed to test the semantic network and executive functions in FTD patients. The present experiment manipulated semantic constraints and congruencies. In this paper, we only addressed effects of semantic congruency.

2.5. Online Behavioral Data. Repeated Measures (SPSS, General Linear Model) analyses were performed for accuracy scores and reaction times (RT) using semantic congruency as within-subject factors. A “yes” response for a semantically incongruent word or “no” response to a congruent word was considered inaccurate. The percentage of correct responses across trials of the same condition was used as within-subject factor.

2.6. Neuroimaging Data. Imaging data were analysed with xbam v3.4, Department of Biostatistics and Computing, Institute of Psychiatry, King's College London [47]. More details about the software can be obtained at http://www.brainmap.it/.

2.6.1. Movement Estimation and Correction. The mean signal intensity over all time points (960) was averaged to create a target image (average image intensity at every voxel across all time points) and the sum of absolute differences in grey scale values between the voxels of each observed image (at each time point) and its corresponding base image was computed. A rigid body registration search algorithm was used to estimate the extent of translation and rotation (3 rotations + 3 translations), minimising the total difference between match and base images. The match images were realigned relative to the base image by tricubic spline interpolation and the realigned T2*-weighted time series were regressed on the concomitant and lagged time series of estimated movement at each voxel [48]. Residual time series resulting from the last stage of this procedure were thus uncorrelated with estimated rigid motion in 3D.

2.6.2. Data Analysis. A nonparametric procedure [49] was adopted that avoids assumptions about the distribution of statistics under the null hypothesis. First, the experimental
Table 1: Clinical characteristics of the Patient Groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-FTD</th>
<th>FTD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive FTD</td>
<td>0 (1)</td>
<td>17 (11)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Negative FTD</td>
<td>5 (7)</td>
<td>6 (6)</td>
<td>0.546b</td>
</tr>
<tr>
<td>SAPS (sum)</td>
<td>23 (16)</td>
<td>14 (10)</td>
<td>0.471b</td>
</tr>
<tr>
<td>SANS (sum)</td>
<td>19 (9)</td>
<td>27 (13)</td>
<td>0.588b</td>
</tr>
<tr>
<td>GAF</td>
<td>31 (13)</td>
<td>30 (14)</td>
<td>0.546b</td>
</tr>
<tr>
<td>Chlorpromazine equivalent in (mg/day)</td>
<td>700 (967)</td>
<td>517 (350)</td>
<td>0.772a</td>
</tr>
<tr>
<td>Duration of illness (in years)</td>
<td>6 (12)</td>
<td>11 (14)</td>
<td>0.190a</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>2 (4)</td>
<td>6 (9)</td>
<td>0.142a</td>
</tr>
</tbody>
</table>

aMann-Whitney [median (interquartile range) min and max], bANOVA [Mean (SD) and range], cFischer Exact.

Table 2: Demographic Description of the Sample.

<table>
<thead>
<tr>
<th>Groups</th>
<th>AGE Median (interquartile range); min and max</th>
<th>Nart IQ Mean (SD); range</th>
<th>Years of full-time education median (interquartile range); min and max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>35 (10); 24–54</td>
<td>108.3 (13.5); 89–126</td>
<td>14.3–(5.3); 9–24</td>
</tr>
<tr>
<td>NON-TD</td>
<td>38 (21); 24–63</td>
<td>101.4 (12.7); 86–122</td>
<td>11.0 (1.5)*; 9–15</td>
</tr>
<tr>
<td>TD</td>
<td>33 (16); 23–55</td>
<td>99.2 (10.7); 82–115</td>
<td>11.0 (3)*; 9–12</td>
</tr>
<tr>
<td>Analysis results</td>
<td>$P = 0.222^a$</td>
<td>$P = 0.267^b$</td>
<td>$P = 0.029^a$</td>
</tr>
</tbody>
</table>

*Kruskal Wallis, ^b one-way ANOVA, ^ no difference between TD and non-TD patients for years of education.

design was convolved with two poisson functions chosen to model the haemodynamic delays of 4 and 8 seconds (see Figure 1). The best fit (weighted sum) of these two convolutions to the observed time series at each voxel was then computed by least squares analysis. The use of the two convolutions within the experimental design allows the time delay between stimulus onset and peak bold response to vary between these limits, which encompass the normal range of haemodynamic delays. Using the parameters of the least squares model fit, the sums of squares of deviations from the mean image intensity over the whole time series due to the model and the residuals were calculated. The ratio of these sums of squares of residuals (model/residuals) was then calculated (called SSQ ratio). The appropriate null distribution of this statistic was obtained by reconvoluting the model fitting procedure after wavelet-based permutation of the time series [47] twenty times at each voxel and combining the data over all voxels. For any desired type I error rate, the appropriate critical threshold value of SSQ ratio could be obtained from this distribution. Any value of SSQ ratio that exceeded this threshold was deemed to indicate the presence of a voxel responding to the experimental paradigm.

In order to construct group images, the observed and “null” SSQ ratio maps for each experimental condition were then transformed into Talairach space [50]. Median activation maps for each condition were computed after smoothing with a Gaussian filter (FWHM 7.2 mm). Three maps were produced: (1) condition “b” versus “a”, (2) condition “c” versus “a”, and (3) condition “b” versus “c”, where “a” means baseline and “b” and “c” the experimental conditions tested.

The main effect of semantic congruency was assessed by contrasting the 40 congruent trials (20 low congruent + 20 high congruent) and 40 incongruent trials (20 low incongruent + 20 high congruent) [conditions “b” and “c” maps]. In order to probe the analysis to the main cognitive process under investigation, we chose the 3rd TR in an event-related design, in which the presentation both of the sentence stem and the final word has already taken place, as shown in Figure 1.

Differences in the responses between conditions were obtained at each voxel by regression of the linear model $F = a_0 + a_1P + e$, where the vector of responses in all subjects at a voxel, $P$ is a dummy coding vector expressing the particular contrast between experimental conditions of interest, and $e$ is the vector of random errors. Values of $a_1^*$ were tested for statistical significance by randomly reallocating the data of each voxel between conditions, thus realising the null distribution under the hypothesis of no difference between responses to different experimental conditions. The analyses reported in this study were carried out using cluster-level statistics to avoid harsh multiple comparison corrections required if each voxel is tested individually [51]. Initially, maps of $a_1^*$ were thresholded retaining only clusters with a probability of type I error = 0.0001, for main effects of the task in healthy controls. However, the patients group showed a diminished overall strength of activation relative to healthy controls. We thus decided to report results from maps thresholded at a voxel/cluster probability of type I error =
0.05/0.01, adjusted to get less than 1 false positive per map, to facilitate interpretation of the results, particularly the differences found between controls and patients and between patients themselves (FTD and Non-FTD). The integral of the SSQ ratio values for each of the resulting three-dimensional clusters was then tested against the distribution of cluster SSQ ratio integrals generated after random reallocation of data between conditions at each voxel (see above). Maps reflecting the contrast between conditions (i.e., congruent versus incongruent) in each group were analysed with ANOVAs, producing 2 maps, one showing regions more activated in the first condition and the other showing the reverse.

To minimize the potentially confounding effect of differences in task performance on brain activation, all incorrect trials were excluded from the image analysis. Thus the neuroimaging data were derived from trials in which subjects correctly decided whether the final word was or not semantically congruent with the previous sentence stem.

2.6.3. Data Analyses to Compare Groups. To investigate between group differences due to effects of semantic congruency, the images resulting from the contrast between semantic congruent versus incongruent trials were directly compared between groups, first contrasting all groups in a 3-Group ANOVA with cluster probability of type I error set at 0.01. This analysis produced a range of maps in which one group showed greater activation than the other groups and vice versa. These maps are presented in the results section below (Figure 2 and Table 3).

Further analyses were conducted to investigate the nature of the results arising from the semantic congruency analysis: we wanted to determine whether differences in activation maps observed between controls and patients could be due to a specific pattern of activation associated with FTD or not. Therefore, separate post-hoc ANOVAs contrasting FTD with controls and FTD with Non-FTD were performed.

3. Results

3.1. Online Behavioral Responses

3.1.1. Accuracy. We did not observe an effect of semantic congruency in performance accuracy ($F = 0.65, P = 0.43, df = 1$). Equally, there was no significant interaction between congruency and group ($F = 0.46, P = 0.64, df = 1$). Post-hoc tests (Tukey) demonstrated that there was a significant contrast between FTD and controls [mean Difference $= -0.128$; Std error $= 0.397$; $P = 0.009$; CI: $-0.227$ to $-0.029$], reflecting impairment seen in incongruent trials (Figure 4) with FTD showing the worse performance (more mistakes than both other groups). Non-FTD showed an intermediate level of performance, making more mistakes than FTD and fewer relative to controls, without significant differences in both contrasts.

3.1.2. Reaction Times. In all groups, responses to congruent trials were faster than incongruent ones (see Figure 5), with an observed significant effect of semantic congruency on reaction times ($F = 14.17, P = 0.001, df = 1$) and no significant interactions between semantic congruency and group ($F = 0.84, P = 0.442, df = 2$). A robust main effect of group on RT was found ($F = 34.10, P < 0.001, df = 2$). Non-FTD patients were slower than FTD and controls in both conditions (congruent and incongruent trials). Controls were faster than FTD in both conditions. Post-hoc contrasts demonstrated significant differences in RT between all pairs contrasted, that is, controls versus FTD [mean difference $= -0.442$; std error $= 0.800$; $P < 0.001$; CI: $-0.639$ to $-0.244$], controls versus NON-FTD [mean difference $= -0.672$; std
4. Neuroimaging Results

4.1. Control Subjects

4.1.1. Congruent and Incongruent Sentences (Table 3). Congruent trials were associated with increased activation relative to incongruent trials in the dorsal portion of the left inferior frontal gyrus, the orbital portion of the right inferior frontal gyrus, the anterior cingulate bilaterally, the right caudate nucleus, the left posterior middle temporal gyrus, the left parahippocampal gyrus, the right precuneus, and the right inferior frontal gyrus. Conversely, incongruent trials were associated with more activation than congruent trials in the left middle frontal gyrus, the right medial frontal gyrus, and the left superior frontal gyrus.

4.1.2. Between Group Differences: Controls versus Non-FTD versus FTD (Table 3). The contrast between congruent and incongruent sentences was associated with greater activation in the dorsal portion of the left inferior frontal cortex in controls than Non-FTD patients, which in turn had increased activation relative to FTD patients in the same region (Figure 2(a)). In this analysis, we did not find regions in which the patients groups showed more activation than controls.

4.1.3. Activation Associated with FTD. POST-HOC contrasts of FTD patients versus controls and FTD versus Non-FTD patients confirmed attenuated activation in the left inferior frontal cortex in the FTD group. Relative to controls, FTD patients showed less activation in the dorsal portion...
Table 3: The semantic decision match fMRI task: neuroimaging results: 3D cluster sizes, Talairach coordinates (of peak voxels) and cluster P values for main effects of the semantic congruency.

(a) Within group analysis: congruent versus incongruent trials in healthy controls (n = 10). Displayed only clusters > or = 6 in size

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Size</th>
<th>Tal(x)</th>
<th>Tal(y)</th>
<th>Tal(z)</th>
<th>Probability</th>
<th>Cerebral Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congruent &gt; Incongruent</td>
<td>2189</td>
<td>43.33</td>
<td>14.81</td>
<td>14.85</td>
<td>0.000656</td>
<td>Left inferior frontal gyrus, dorsal portion</td>
</tr>
<tr>
<td></td>
<td>312</td>
<td>46.94</td>
<td>29.63</td>
<td>-7.15</td>
<td>0.000656</td>
<td>Right inferior frontal gyrus, orbital portion</td>
</tr>
<tr>
<td></td>
<td>181</td>
<td>0.00</td>
<td>11.11</td>
<td>31.35</td>
<td>0.000656</td>
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</tr>
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<td>3</td>
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<td>11.11</td>
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<td>Incongruent &gt; Congruent</td>
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<td>37.04</td>
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<td>0.000678</td>
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<td>55.56</td>
<td>9.35</td>
<td>0.000678</td>
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(b) Between Groups Analyses: 3-Group ANOVA: Semantic Congruency (congruent versus incongruent) trials. Comparison of healthy controls (n = 10) versus schizophrenic patients with Formal Thought Disorder (FTD, n = 9) versus schizophrenic patients without formal thought disorder (Non-FTD, n = 9)

<table>
<thead>
<tr>
<th>Results</th>
<th>Size</th>
<th>Tal(x)</th>
<th>Tal(y)</th>
<th>Tal(z)</th>
<th>Probability</th>
<th>Cerebral Region</th>
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</thead>
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<tr>
<td>Controls &gt; NTD &gt; TD</td>
<td>79</td>
<td>-43.33</td>
<td>14.81</td>
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<td>0.007784</td>
<td>Left inferior frontal gyrus, dorsal portion</td>
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<tr>
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<td>95</td>
<td>28.89</td>
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<td></td>
<td>92</td>
<td>50.56</td>
<td>25.93</td>
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<td>0.002553</td>
<td>Right inferior frontal gyrus, dorsal portion</td>
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<td>67</td>
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<td>25</td>
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<td>NON-FTD &lt; TD</td>
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<td>-55.56</td>
<td>20.35</td>
<td>0.003912</td>
<td>Right posterior cingulate</td>
</tr>
</tbody>
</table>

of the inferior frontal cortex bilaterally, the left middle temporal gyrus, precuneus, and lingual gyrus and in the cerebellum bilaterally (Figure 3(a)). No areas were relatively more activated in the FTD than the control group.

Relative to Non-FTD patients, FTD patients showed less activation in the left middle frontal gyrus and bilaterally in the anterior cingulate gyrus (Figure 3(b) and Table 3). Conversely, the FTD subgroup showed more activation than the Non-FTD subgroup in the right posterior cingulate gyrus and the left cerebellum (Figure 3(c)).

5. Discussion

5.1. Behavioral Results. Semantic congruency influenced RTs, with minimum values in trials with congruous endings, as expected (see Figure 5). Therefore, we observed an effect of inhibition (or interference) associated with processing of incongruent sentences in all groups. The patients made more errors than controls, particularly those with FTD. This was most evident on incongruent trials where patients with FTD performed much worse than both patients with no FTD and controls, showing deficiency in processes where inhibition is expected.

5.2. Neuroimaging Results

5.2.1. Semantic Processing in Healthy Controls. We found that incongruent sentences activated the left middle frontal cortex more than congruent ones, an area associated with suppression when the same type of semantic material was employed
Figure 3: Post-hoc 2 group comparisons: semantic congruency (congruent versus incongruent trials). (a) healthy controls (n = 10) versus schizophrenic patients with formal thought disorder (FTD, n = 9) (b, c) FTD versus schizophrenic patients without formal Thought Disorder (Non-FTD, n = 9). (a) Controls show greater activation relative to FTD in the inferior frontal gyrus bilaterally, dorsal portions, in the left middle temporal gyrus (BA 22), in the left lingual gyrus, in the left precuneus, and in the cerebellum (posterior lobe) bilaterally. (b) Non-FTD patients showed greater activation of bilateral middle frontal gyrus and bilateral anterior cingulate, relative to FTD. (c) FTD patients show greater activation relative to Non-FTD patients in the right posterior cingulate. The left side of the brain images correspond to the right side of the brain. The superior part of the brain images correspond to the anterior brain region.

[39] and with inhibition of stereotyped responses [52]. However, in our study, we observed greater activity for congruent than incongruent trials in healthy controls in the right precuneus, contrary to our hypothesis. Therefore, our first hypothesis was partially confirmed. A possible explanation for these differences observed between ours and Allen et al.’s study may be the fact that their task required overt production of a final completing word for visually presented priming sentence stems, whilst ours only required making a decision upon a visually presented final word.

The general pattern of activation we found was expected because the semantic task used placed high demands on executive control, such as maintaining competing items on hold whilst checking for semantic appropriateness [53] and inhibiting unnecessary items. Thus, in healthy controls, we observed more activation for congruent than incongruent trials in the right inferior (orbital) and left inferior (dorsal) cortices, left posterior temporal cortex, bilateral anterior cingulate, and left precuneus. Our findings are in line with data supporting an important role of the left hemisphere in
the final integration of semantic aspects present in sentences and texts [54] and recent meta-analytical studies showing activity in these regions associated with semantic processing [55–57].

5.2.2. Semantic Processing in FTD Schizophrenic Patients. We also hypothesized that FTD patients would show decreased activation in the prefrontal (middle and inferior), temporal, and cingulate cortices. Relative to controls, FTD patients showed a diminished activation in dorsal inferior frontal cortex (bilaterally) and in the left middle temporal gyrus when processing incongruent relative to congruent sentences. We predicted that these differences would also be evident when contrasting patients with and without FTD. We found that for the incongruent/congruent contrast, the FTD subgroup showed less activation than Non-FTD patients bilaterally in the left inferior/middle frontal gyri and the anterior cingulate gyri. Thus, our second hypothesis was confirmed. The differential brain activity observed in FTD patients while performing a task, without mistakes, seem to be arising from an early point of the semantic processing, since these attenuated activations were observed in areas in which controls showed increased activation for congruent trials relative to incongruent ones and not the other way round (contrary to our initial prediction). Although this may seem a contradictory finding, the current study confirms altered brain activity in these areas specifically associated with FTD in schizophrenia [28–32].

Manipulation of incongruent sentences requires overcoming a prepotent response, that is, suppression of automatically activated word(s) after a primed sentence stem [36]. The latter process needs to be maintained “active” for a longer period. Activity in the DLPFC has been associated with working memory and contextual information in experiments requiring heavier semantic processing demands [31, 58]. These group differences in inferior frontal and left middle temporal responses reflected less activation of these areas in patients with FTD relative to both controls and patients without FTD. This differential pattern of response is similar to that evident in their behaviour, where patients with FTD performed markedly worse than both other groups on trials involving semantically incongruent sentences, making more mistakes and also having a shorter RT than Non-FTD patients. Relative to Non-FTD, FTD also had less activation in the anterior cingulate cortices, which have been suggested by several authors to participate in demanding processes, such as monitoring conflict of response [59], engagement of cognitive control [60], top-down inhibitory modulation [61], detection of mnemonic competition, and retrieval induced forgetting [62].

A final point should be made about the activity in the precuneus. This region has been demonstrated to be involved in semantic processing [39, 57, 63, 64] episodic memory retrieval [65], retrieval-induced facilitation [66], and dopamine regulation of working memory [67]. FTD patients, but not Non-FTD patients, had less activation in the left precuneus than controls. Despite some subtle inconsistencies in hemispheric localization (not rare in fMRI studies of schizophrenia), this finding suggests a problem in episodic memory retrieval that might have contributed to the FTD group worse task performance. Thus, FTD patients showed robust diminished activation in areas implicated in the suppression of irrelevant material as well as detection and resolution of mnemonic conflict [68], selecting context-appropriate meanings in the presence of competing meanings [69], and differences between impaired and facilitated information [66]. Interestingly, Arcuri [46] found that FTD patients produced significantly more expected words than controls, when overtly producing anomalous endings for sentences of a high degree of constraint, in a modified version of the Hayling Task [70]. That study included the scanned FTD patients (n = 9) from the present study but had a larger sample of FTD patients (n = 21). Thus, FTD patients who showed diminished activation in areas implicated in aspects of executive control, when deciding whether a final target word is semantically appropriate for a previously presented sentence, also had difficulties in inhibiting automatically activated words that followed sentences of high semantic constraint, when they were asked to openly generate semantically incongruent completions for those sentences.

The differences between FTD and the Non-FTD patients are not attributable to sociodemographic or other clinical
differences as they are matched in all respects other than the severity of positive FTD. Moreover, although the FTD patients performed the task more poorly than Non-FTD patients and controls, the image analysis was restricted to correct trials, indicating that the differences in activation were not simply secondary to the more impaired task performance in this subgroup. The differences in regional responses may thus be linked to the pathophysiology of incoherent speech. The prominent role of the inferior frontal cortex in language processing and particularly semantic processing is consistent with this suggestion. However, the fact that a qualitatively similar but less severe reduction in activation was evident in patients with no FTD indicates that findings in this area are also associated with the disorder of schizophrenia, independent of the presence of this particular symptom.

Liddle et al. [27] proposed that the disorganisation syndrome (disorders of the form of thought and inappropriate affect) is associated with a differential pattern of brain activity in frontal, temporal, and cingulate cortices relative to the two other syndromes (psychomotor poverty and reality distortion). In our sample, although we focused specifically on the symptom of FTD, it was significantly correlated with inappropriate affect, that is, patients with FTD had higher scores in inappropriate effect as well, pointing to the same direction of a distinct syndrome of disorganisation within schizophrenia.

5.3. Limitations. The sample was small, and larger studies should be done to confirm our results and possibly explain the limitations in the observed data, which might have contributed to a possible lack of power in our analyses.

6. Conclusion

The frontotemporal network normally engaged by a semantic decision task was underactivated in schizophrenia, particularly in patients with FTD. This network is implicated in the inhibition of automatically primed stimuli and impairment of its function interferes with language processing and contributes to the production of incoherent speech.

Acknowledgments

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Cognitive Control and Discourse Comprehension in Schizophrenia

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1. Introduction

Impaired cognition across a wide range of cognitive domains is a pervasive feature of schizophrenia and is connected to poor functional outcome for patients [1, 2]. Of the cognitive deficits that have been observed in schizophrenia patients, language abnormalities are among the most salient and include disorganized speech as well as deficits in comprehension. However, there is no general consensus as to whether the cognitive impairments seen in schizophrenia can be attributed to a single disrupted mechanism, to multiple disrupted systems, or to low-level perceptual deficits.

Accounts of language deficits in schizophrenia might be divided into theories that focus on irregularities in semantic memory structure and functioning, and those that emphasize deficits in the ability to effectively use context [3].
Accounts that posit abnormalities in semantic memory in schizophrenia, such as the exaggerated spread of activation in a semantic network [4], are largely based on studies involving the processing of words in isolation. In contrast, accounts of high-level language processing have focused on impairments in the ability to build and maintain context as the root of language deficits in schizophrenia. Such deficits have been attributed to problems with general cognitive processes of enhancement and suppression in a prominent theory of discourse processing, the structure-building framework [5]. Kuperberg [6] has proposed an imbalance between semantic-memory-based processing systems and combinatorial mechanisms in schizophrenia, such that patients often rely to a greater extent on semantic-memory-based processing at the expense of the structured build-up of context. The interaction between the semantic-memory-processing stream and the combinatorial stream has been proposed to be influenced by cognitive control mechanisms [7]. According to this view, control mechanisms should therefore be recruited when integration demands are high.

In the remainder of this theoretically-oriented review paper we seek to increase understanding and highlight novel hypotheses related to impairments in aspects of language processing in schizophrenia. We will begin with a discussion of language comprehension in the healthy human brain and will highlight the potentially important role of cognitive control processes, especially during discourse comprehension. We will then review the literature on cognitive control deficits in schizophrenia. Finally, we will review evidence suggesting that schizophrenia patients are particularly impaired at processing meaningful discourse as a result of impaired control functions. We conclude that schizophrenia patients are impaired in discourse comprehension when control demands are particularly high, for example, when different aspects of language input conflict with one another.

2. Cognitive Control and High-Level Language Processing in Healthy Participants

Outside of the laboratory, natural language processing almost always involves a rich signal, featuring multiple connected sentences that each generates a meaningful context and also must be linked to the overall meaning provided by discourse context. For example, a sentence such as “Yesterday he went to the bank” may be interpreted as describing a person visiting a financial institution, yet that interpretation would be incorrect if the preceding discourse was about a person going to the side of a river. In short, discourse context is a complex web of information including word-level, sentence-level, and message-level meaning, as well as syntactic structure, previously stored background information, and other context information (e.g., speech-accompanying gestures used by the speaker).

In order to construct a coherent meaning representation, language users must integrate these various sources of information, and some prominent models of language comprehension predict that this involves specific control mechanisms. As briefly discussed earlier in this review, one theory that proposes an important role of control mechanisms during discourse comprehension is the structure-building framework, which emphasizes suppression ability as critical to language comprehension [8–10]. According to this framework, incoming language input is mapped onto mental structures via the enhancement of relevant information and suppression of irrelevant information. When input fits well with the current structure, it will be incorporated into that structure. This process is referred to as mapping, which involves adding on to the developing representation of the text. Integration of new information into an existing representation places fewer demands on cognitive resources than the initial construction of a discourse representation; therefore, incoming input that is coherent with the previous context leads to faster processing. When input is less coherent with the existing structure, the comprehender will construct a new substructure in order to accommodate the new information into the overall representation (shifting). The creation of a new substructure has been labeled “shifting,” and it requires additional processing, which can slow down comprehension. A failure to effectively suppress irrelevant information that is activated by the incoming input (e.g., the financial-institution meaning of the word “bank” in the example above, when context-irrelevant) may result in the construction of excessive substructures [8–10]. The cognitive processes of mapping and shifting are thought to rely on control networks; inefficient mapping, and particularly shifting, has been argued to result in poor discourse comprehension in healthy adults, since this could lead to lingering activation of discourse-irrelevant information [8–10]. Excessive shifting could also result in the disorganized discourse representations that have been observed in schizophrenia patients [5].

Another model of language processing that recognizes a role of cognitive control mechanisms during language processing is the memory, unification, and control (MUC) model [11]. Briefly, according to the MUC model, language processing requires activation and retrieval of semantic and syntactic memory representations stored in left temporal cortex. Unification refers to the construction of a meaning representation involving multiple words (or sentences), using information about the words that were activated and retrieved. Unification processes are proposed to be mediated by the left inferior frontal cortex (Broca's complex). Finally, control processes are assumed to be mediated by the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) and are recruited when attentional control is necessary, for example, during turn-taking in conversation and during the selection of situation-appropriate language in bilinguals [11]. (Other theories also suggest a direct role of cognitive control during processing of other aspects of the language input (for reviews, see [12, 13]).)

In sum, prominent theories of high-level language processing concur that comprehension is supported by control mechanisms. In addition, in the case of incoherent discourse, one or more sources of information may conflict (e.g., activation of the financial-institution meaning of the word bank would conflict with discourse-level context in which the side-of-the-river meaning is promoted), placing even
greater demands on these control mechanisms to support comprehension.

3. Cognitive Control and Schizophrenia

Cognitive control is somewhat of an umbrella term in that it refers to domain-general processes that govern processing in other systems, including the allocation of attentional resources, conflict detection and resolution, the maintenance of task-relevant information, and inhibition. According to the Guided Activation Model, control mechanisms mediating top-down processing are based in the prefrontal cortex [14]. Specifically, the PFC maintains and represents task-relevant context, including goals, which serves to guide processing in relevant neural regions associated with task execution [14]. Deficits in this ability to maintain context in order to guide processing would be expected to result in a wide range of impairments across cognitive domains. Several theories postulate that impaired cognitive control might account for the widespread deficits in cognition seen in schizophrenia [15–18]. As noted above, alternative explanations suggest that deficits in sensory or perceptual systems may account for the cognitive deficits seen in schizophrenia (e.g., [19]). In the current paper, we adopt the approach outlined by Lesh and colleagues [18]; namely, that a single underlying deficit in prefrontally mediated control functions is at the heart of the broad range of cognitive deficits that have been observed in schizophrenia patients.

A detailed discussion of cognitive dysfunction in schizophrenia, and the evidence that suggests deficits in control mechanisms are the basis for this dysfunction, is beyond the scope of this review. However, it is important to note that there is substantial evidence suggesting a domain-general control deficit in schizophrenia patients and specifically showing reduced DLPFC activity accompanied by impaired behavioral performance in patients during tasks that are demanding of cognitive control (see [18] for a review), though a recent meta-analysis of executive-function tasks also showed that reduced DLPFC activation is present in schizophrenia whether performance is impaired or matched [20]. One salient example of empirical evidence for a control deficit in schizophrenia comes from a study by MacDonald and colleagues [21]. They presented never-medicated, first-episode schizophrenia patients, as well as never-medicated nonschizophrenia psychosis patients and healthy controls, with the AX-CPT task in an fMRI session [21]. The AX-CPT is a task that is specifically designed to tax cognitive control functions: subjects are instructed to press a button every time they see an “X” that immediately follows an “A” and to otherwise withhold their response. This type of trial (AX trial) is highly frequent, accounting for 70% of total trials; this leads to the tendency to respond to an X and to anticipate making a response after an A. Therefore, false alarms often occur in response to AX trials (where “Y” stands for any letter except “X”) as the context of “A” leads to the expectation of an upcoming response. Finally, BX trials (where “B” stands for any letter except “A”) are least frequent and are most demanding on the controlled maintenance of context, because participants must use the context of having just encountered a “B” in order to correctly inhibit their response to the “X.” Compared to controls and nonschizophrenia psychosis patients, never-medicated schizophrenic patients made more errors on BX trials [21]. fMRI results for BX trials for which controls responded appropriately showed increased activity in the DLPFC and also the posterior parietal areas compared to the less demanding AX trials. For the patient group, this same contrast showed that DLPFC activity was significantly reduced compared to controls and that reduced DLPFC activity was linked to increased disorganization symptoms in the schizophrenic individuals [21]. These results are consistent with several other studies that have also found reduced DLPFC activity corresponding to poor performance on control tasks in schizophrenia patients (e.g., [22–24]) as well as the results of a recent meta-analysis [20]. Importantly, the reduction in DLPFC activity found for schizophrenia patients compared to controls is most pronounced under control-demanding task conditions; when control demands are relatively low, DLPFC activation for patients has been shown to approximate that of controls (e.g., [23]) or even to exceed that of controls (e.g., [25, 26]).


Language dysfunction is a hallmark of schizophrenia, leading to the production of disorganized speech as well as deficits in language comprehension (for reviews, see [6, 27, 28]). However, schizophrenia is far from a homogenous disorder; symptoms vary across individuals and symptoms within an individual can vary over time as well. When present, common language phenomena observed in schizophrenia patients include tangentiality (jumping from topic to topic without providing obvious links in response to a question), derailment (disjointed speech that slips from topic to topic), incoherence (incomprehensible speech), and poverty of speech (reduction in the quantity of speech) [29, 30]. Although many of the features of language dysfunction in schizophrenia are observed in production at the discourse level (e.g., tangentiality and derailment), the bulk of the research on real-time language comprehension in schizophrenia patients has focused on the word- and sentence-levels of processing.

A prominent area of research on language comprehension in schizophrenia has been the influence of word-level meaning associations on the processing of incoming words (i.e., semantic priming paradigms). Results from these studies suggest that the activation and retrieval of stored meaning representations of words is relatively intact, and some studies even show larger-than-normal effects of semantic priming (e.g., [7, 31–33]). Interestingly, under “automatic” priming conditions (e.g., when targets follow closely after primes), schizophrenia patients show normal or exaggerated semantic priming effects but show smaller or absent effects when controlled processing is required, such as evaluation of the relation between prime and target [3, 33]. This pattern of
results has been interpreted as an indication of semantic memory dysfunction in schizophrenia, specifically involving a faster and more extensive propagation of activation in semantic memory [4, 28, 34].

At the sentence level, there is also a great deal of work showing various deficits in schizophrenia compared to healthy adults (e.g., [35–37]). Much of this work can be summarized as suggesting a deficit in the build-up and maintenance of context: compared to healthy controls, schizophrenia patients have been shown to be unable to benefit from linguistic context in a word-monitoring task [35] and to have difficulty using sentence context to select the context-appropriate meaning of an ambiguous word [36]. Sitnikova and colleagues [36] presented schizophrenia patients and healthy controls with sentences that biased towards either the dominant meaning of an ambiguous word (e.g., bridge as an architectural structure) or the subordinate meaning (bridge as a card game). The second clause of the sentences also contained a word that was semantically associated to the dominant meaning of the ambiguous word that had appeared earlier in the sentence (e.g., ... because the river had rocks in it, following either “diving was forbidden from the bridge ...” or “The guests played bridge ...”). Sitnikova and colleagues [36] measured the electrical activity of the brain as healthy controls and patients read the sentences. Event-related potentials (ERPs) were extracted for critical words that were either consistent or not with the preceding sentence contexts. Of particular relevance to this study is an ERP effect that has been labeled the N400. The N400 is a negatively deflecting ERP waveform that is modulated by semantic fit, such as relatedness to previous words and congruence or predictability given prior context (for a review, see [38]). Controls showed a decreased N400 amplitude for target words like river when they were appropriate given the previous sentence context (diving was forbidden from the bridge ...) compared to when they were inappropriate (the guests played bridge ...). However, patients’ N400 effects to context-appropriate and context-inappropriate target words were indistinguishable, suggesting that patients were unable to benefit from context to suppress the irrelevant meaning of the ambiguous word (e.g., river) [36]. In contrast, the patient and control groups did not differ in their response to unambiguous context-congruent compared to incongruent words (e.g., ... the river had rocks/cracks in it ...), such that both groups showed a larger N400 amplitude in response to incongruent words (cracks) than to congruent words (rocks) [36]. This set of results is suggestive of a specific impairment when the controlled use of linguistic context is required, such as to suppress context-inappropriate meanings of words, rather than of an overall lack of sensitivity or attention to language context.

Further evidence supporting deficits in the use of linguistic context in schizophrenia comes from a 2006 study from Kuperberg and colleagues. Patients and controls were presented with syntactically well-formed sentences that contained an imicity violations (e.g., for breakfast the eggs would only eat toast and jam). Previously, a P600 effect was found in healthy adults when comparing these types of sentences to those containing no animacy violation (e.g., for breakfast the boys would only eat toast and jam) [27]. Semantic violations typically elicit N400 effects, whereas P600 effects have traditionally been linked to syntactic manipulations (see [38] for a review). The so-called “semantic P600” found in healthy adults has been interpreted as reflective of conflict between the syntax-dictated sentence meaning (e.g., that the eggs were eating) and the aggregate meaning based on relations among individual words (e.g., that eggs and eat are typically combined such that the eggs are being eaten) [27, 39]. Interestingly, schizophrenia patients show a reduced semantic P600 effect relative to controls [37]. This pattern of results suggests that when strong semantic relations amongst individual words are in conflict with sentence-level meaning as dictated by syntax, schizophrenia patients appear to be overly influenced by the word-level relations.

In contrast, very few studies have looked at online discourse comprehension in schizophrenia. As discussed earlier, several theories of high-level language comprehension predict that demands on cognitive control are high during discourse processing, as discourse is a rich and multilevel signal containing a great deal of information to maintain and integrate, all with the potential to generate conflict. Given a model of cognitive dysfunction in schizophrenia based on control deficits [18], clear difficulties in language processing might be expected at the discourse level.

Indeed, offline studies of memory have shown that patients do not benefit from discourse organization to the same extent as controls, manifesting as a lack of improved text recall with increased text coherence [40–43]. Further, a recent electrophysiological study presented schizophrenia patients and healthy adults with three-sentence passages in which the individual sentences were highly related to one another, intermediate related, or unrelated [44]. For example, a highly related passage might describe two characters as having an argument in the first sentence, as hitting each other in the second sentence, and as having bruises the next day in the third sentence. In order to understand the third sentence of this type of passage, no inference is necessary: the context of the previous two sentences directly states a cause for the bruising. An immediately related passage, however, might only mention in the second sentence that the characters were upset. In this case, an inference is necessary in order to build a coherent representation of the meaning of the passage. Finally, in an unrelated passage, the third sentence would be completely incongruent with the previous two sentences. In response to these types of passages, controls showed context effects on the N400 to critical target words (e.g., bruises) in the final sentences, with the greatest reduction in the N400 waveform for highly related passages (the “easiest” condition, when no inference was needed), followed by immediately related passages, and finally by the unrelated condition. In contrast, ERP results in the patient group did not distinguish among conditions in the N400 time window [44]. However, both the control and patient groups showed a similar pattern of behavioral responses to the stimuli, rating highly related passages as “very related”, followed by the immediately related passages as slightly less related, and the unrelated passages as unrelated. In addition, although
the electrophysiological response for the patient group did not differentiate among relatedness conditions in the N400 time window, patients did show a difference between related passages and unrelated passages in a later time window (700–1000 ms after reading the critical target word); in contrast, the control group did not show a difference amongst conditions in this late time window [44]. This suggests that, although patients did not show differential N400 responses depending on relatedness condition, they were attending to the task and may have attempted to integrate the targets in the unrelated condition at a later processing point compared to controls. The generation of inferences such as in the intermediately related example above is often necessary in order to properly understand discourse context, as language input often does not directly contain all of the information needed to comprehend the message. Therefore, the patient group’s failure to differentiate amongst degrees of causal relatedness in the same time window as the control group suggests that schizophrenia patients have difficulty generating inferences to construct a coherent discourse representation on the same time scale as healthy adults [44].

Consistent with this pattern is another recent ERP study that presented patients and controls with five-sentence passages, each of which contained a noun that could serve as the referent of a noun in the fourth sentence but varied in terms of semantic fit [45]. For example, upon encountering outfit (The night before work, Lisa ironed the outfit) in the fourth sentence, possible referents mentioned in previous sentences would be suit (context appropriate and lexically associated), costume (context inappropriate but lexically associated), or ring (context inappropriate and lexically unassociated). The control group showed a graded ERP response throughout the N400 time window, showing the smallest amplitude for the context-appropriate/associated condition, followed by the context-inappropriate/associated condition, and finally the context-inappropriate/unassociated condition. In contrast, in the early portion of the N400 time window (300–400 ms), the schizophrenia group distinguished between globally appropriate and inappropriate semantic fit (reduced amplitude for the context-appropriate referent in comparison to either context-inappropriate referent, irrespective of lexical association). However, in the later portion of the N400 time window (400–500 ms), the pattern switched so that patients distinguished between locally associated and unassociated semantic fit (reduced amplitude for both associated conditions, regardless of context appropriateness, compared to the inappropriate-unassociated condition) [45]. In other words, the controls seemed able to benefit from the combination of context-level fit and word-level fit, whereas the schizophrenia patients seemed to be toggling between sensitivity to global and local fit [45].

In summary, the literature on high-level language comprehension in schizophrenia patients shows that they are most impaired when control demands are highest, as when the use of context is needed to constrain word meaning [36] or construct a meaning at odds with the associative relations amongst individual words [37]. These results are suggestive of a role for a cognitive control deficit in abnormal language processing in schizophrenia, leading patients to fail to suppress context-irrelevant information as well as maintain linguistic context in order to guide the processing of incoming words. This pattern of results is much in line with the type of context-maintenance deficits seen in patients when performing the AX-CPT task described above, in which patients have difficulty maintaining the context of having just seen a “B” in order to respond correctly by suppressing a response to an ensuing “A” (e.g., [21]). Further, studies of discourse comprehension, a level of language processing that places relatively high demands on control mechanisms, have shown that schizophrenia patients are impaired at building coherent discourse representations [44] and are unable to effectively integrate global discourse-level context with local word-level context [45]. These studies of online discourse comprehension are supported by several offline studies showing that schizophrenia patients are unable to make use of discourse coherence when recalling discourse content [40–43].

The evidence reviewed above shows that deficits in discourse comprehension in schizophrenia can be accounted for by a domain-general deficit in cognitive control. As mentioned in the introduction, several theories converge on control mechanisms as related to the range of cognitive deficits seen in schizophrenia patients [5, 6, 39]. Therefore, an important question concerns specifically what aspects of control affect discourse comprehension in schizophrenia. We suggest that the current evidence is consistent with the idea that discourse comprehension deficits in schizophrenia result from (1) deficits in the controlled maintenance of context-relevant information, which may be mediated by dysfunction of the DLPFC and (2) deficits in the ability to resolve conflicting information in the language input, and the inability to monitor the incoming input for conflict, which may be mediated by dysfunction of the ACC. Following from the Guided Activation Model discussed above, in which prefrontal regions engaged in context maintenance guide activation in the neural regions responsible for task execution, prefrontal dysfunction in schizophrenia is expected to result in processing and integration difficulties in the perisylvian-language network. Specifically, we suggest that deficits in the maintenance of context-relevant information will lead to impoverished discourse representations that are heavily reliant on word-level meaning relations. This kind of loosely integrated representation may suffice, provided incoming input does not introduce conflict. Therefore, discourse comprehension in schizophrenia patients should be most successful when the words contained in the context are related in meaning but will be more difficult for these patients when the semantic fit amongst individual words and sentences is poor.

5. Conclusions

In summary, we conclude that prefrontally mediated cognitive control mechanisms are impaired in schizophrenia and that during language comprehension this will most likely impact the integration and maintenance of context,
which involves (especially in the case of high-level language processing) multiple levels of meaning. As context accumulates, demands on control mechanisms governing integration and maintenance are increased, resulting in discourse-level processing as a particularly demanding level of processing in terms of control. Further, as context accumulates, the potential for multiple aspects of the input to conflict increases; conflicting aspects of context maximally tap into control processes. Two main predictions are generated from this hypothesis that may be tested as part of a future research agenda using methods from the cognitive neuroscience of language: (1) schizophrenia patients will be most impaired during processing at discourse level; (2) the construction of coherent discourse representations will be most successful when supported by strong relations amongst individual words, and patients will be most impaired when aspects of the context conflict with each other.

Stemming from these predictions are several implications for future approaches to the study of high-level language comprehension in schizophrenia. First, more research on comprehension at the discourse-level is needed, with a particular emphasis on studies that deliberately manipulate sources of conflict and competition within discourse context. As noted above, sources of conflict, such as word-level ambiguity, are not special challenges to the comprehension system only found in laboratory settings, but instead are rather commonplace during natural language comprehension. Likewise, other challenges to the comprehension system, such as the generation of inferences in order to understand. Likewise, other challenges to the comprehension system only found in laboratory settings, but instead are rather commonplace during natural language comprehension. Likewise, other challenges to the comprehension system, such as the generation of inferences in order to understand.

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Clinical Study

Stability of Facial Affective Expressions in Schizophrenia

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Thirty-two videorecorded interviews were conducted by two interviewers with eight patients diagnosed with schizophrenia. Each patient was interviewed four times: three weekly interviews by the first interviewer and one additional interview by the second interviewer. 64 selected sequences where the patients were speaking about psychotic experiences were scored for facial affective behaviour with Emotion Facial Action Coding System (EMFACS). In accordance with previous research, the results show that patients diagnosed with schizophrenia express negative facial affectivity. Facial affective behaviour seems not to be dependent on temporality, since within-subjects ANOVA revealed no substantial changes in the amount of affects displayed across the weekly interview occasions. Whereas previous findings found contempt to be the most frequent affect in patients, in the present material disgust was as common, but depended on the interviewer. The results suggest that facial affectivity in these patients is primarily dominated by the negative emotions of disgust and, to a lesser extent, contempt and implies that this seems to be a fairly stable feature.

1. Introduction

Studies of facial behaviour have shown a clear reduction of facial expressiveness and of facial affective expressiveness in patients diagnosed with schizophrenia [1–11]. The reduction of facial expressiveness is especially prominent in the upper face [12] and has also been observed while patients are confronted with emotional stimuli [6, 10, 12, 13] as well as when they are imitating emotional stimuli [14]. Interestingly, most findings point at the conclusion that reduction of facial expressiveness is not correlated with impaired emotional experience [8, 10, 11]. The patients’ capacity for emotional recognition is also reduced [11], a very robust finding according to a recent review [15]. However, facial emotional expressiveness is also reduced in patients with depression [6, 12], but patients with schizophrenia are still distinguished in this respect from patients with depression, Parkinson’s disease, and right hemisphere brain damage [10] since their diminished expressiveness is more prominent. Furthermore, patients with schizophrenia have been found to limit their facial affective repertoire to mainly negative affective expressions [7, 11, 16], an observation that may be present even before the clinical onset of psychosis [17]. Contempt was found to be the most frequent affect shown by these patients [5, 7, 18] and they showed significantly less happiness compared to healthy subjects [5]. Healthy subjects, on the other hand, interacting with each other, usually show a variety of both negative and positive affects, and the most frequent affect shown by them is usually happiness [16]. Overall facial activity has been reported as 2.3 times higher in interactions amongst healthy subjects compared to healthy subjects interacting with inpatients with schizophrenia [5, 7, 19].

1.1. Objectives. The objective was to replicate previous findings regarding negative facial affectivity in schizophrenia and to study the stability of these facial affective expressions. One focus was to examine whether facial affective behavior
is dependent on temporality. The other focus was to test whether the patient's affective behavior is person dependent. The following hypotheses were tested.

1. There are no substantial changes in the type of affects that the patients display across several interview occasions.
2. The patient's affects are not altered by the change of interview partner.

### Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Psychosis diagnosed</th>
<th>Schizophrenia diagnosed</th>
<th>Type of schizophrenia</th>
<th>Medication interv.</th>
<th>Medication interv. A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>27</td>
<td>1992</td>
<td>1997</td>
<td>Paranoid 295.30</td>
<td>Risperidone</td>
<td>Risperidone</td>
</tr>
<tr>
<td>M</td>
<td>40</td>
<td>1987</td>
<td>1989</td>
<td>Paranoid 295.30</td>
<td>Olanzapine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>M</td>
<td>32</td>
<td>1991</td>
<td>2000</td>
<td>Undiff. 295.90</td>
<td>Perphenazine</td>
<td>Perphenazine</td>
</tr>
<tr>
<td>M</td>
<td>52</td>
<td>1967</td>
<td>1971</td>
<td>Paranoid 295.30</td>
<td>Zuclopenthixol</td>
<td>Zuclopenthixol</td>
</tr>
<tr>
<td>M</td>
<td>36</td>
<td>1994</td>
<td>1994</td>
<td>Paranoid 295.30</td>
<td>Olanzapine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>F</td>
<td>48</td>
<td>1985</td>
<td>1985</td>
<td>Paranoid 295.30</td>
<td>Zuclopenthixol</td>
<td>Zuclopenthixol</td>
</tr>
<tr>
<td>F</td>
<td>52</td>
<td>1972</td>
<td>1982</td>
<td>Paranoid 295.30</td>
<td>Ziprasidone</td>
<td>None</td>
</tr>
<tr>
<td>M</td>
<td>27</td>
<td>1998</td>
<td>1998</td>
<td>Catatonic 295.20</td>
<td>Olanzapine</td>
<td>Olanzapine</td>
</tr>
</tbody>
</table>

The interviews included pauses and sighing. When these interviews were finished the patients were interviewed another time by the second interviewer (interview A2). Each interview lasted about 45 minutes. Verbatim transcripts of the interviews included pauses and sighing.

### 2.2. Video Recording

The interviews were recorded by three remote-control cameras. One camera focused on the patient’s face, one on the interviewer’s, and one on the whole scene. The camera overlaps were synchronised and displayed on a single screen provided with time code. These were stored on DVD-discs and replayed including slow motion on a computer using Power-DVD version 3.0 software.

### 2.2.3. Coding

The Emotion Facial Action Coding System (EMFACS) [21], a coding system for video data, was used to evaluate the patient’s and interviewers’ facial affective behaviour. EMFACS is based on the Facial Action Coding System (FACS) [22] a coding system for registering all visible facial mimic movements, called Action Units (AUs). Two sequences, 3 minutes each, where the patients were describing their psychotic experiences were selected from each interview. These narratives seemed emotional and were assumed to trigger facial affectivity. First, the interviews were replayed several times and all visible mimic movements (AU) were coded for the patient and interviewer. In a second step the AUs were interpreted with an emotional dictionary software. This software compares the combinations of AUs with the EMFACS dictionary and registers seven affects: anger, contempt (AU 14, unilateral AU 12 or AU 14), disgust (AU 9 or AU 10), sadness, fear, surprise, and happiness (AU 6 + AU 12). Positive affects were operationalised as happiness and surprise and negative affects as contempt, disgust, anger, sadness and fear. When referring to happiness only Duchenne smiles were coded (AU 6+12) and not just social smiles (just AU 12). Both AUs and affects are brief and last approximately for milliseconds or seconds. A total of 7,834 visible muscular movements (AU) were coded, corresponding to 1.805 facial affective expressions. The retest reliability for EMFACS has been reported to vary from 0.89 to 1.00 and intercoder agreement from 0.87 to 1.00 [5]. The validity has been confirmed in ethnological and ethological studies [23, 24]. In the present study two independent coders at the University of the Saarland in Saarbrücken, Germany,
performed the coding. They did not have command of the language spoken in the interviews since they had a different language background than the patients and the interviewers and were blind to the diagnoses of the patients. All interviews for each patient were coded by the same coder. As a reliability check, a sample of the interviews (6 minutes of interview time) was presented to both coders who scored an excellent intercoder agreement (κ > 0.80) on rating AU.

2.2.4. Statistics. The statistical package SPSS, version 15, was used. Descriptive statistics were used to summarise the frequency and variation of the facial affects displayed. Within-subjects ANOVAs were performed to test whether the amount of affects varied across the interviews. The affects served as dependent variable with interview as the within-factor having three levels (interview A1, interview B1, interview C1). Wilcoxon tests for repeated measures were employed to test whether the patients displayed identical affects for both interviewers. The independent variable was the interviewer and the depended variable the affects shown by the patients. Finally Mann-Whitney U test was used to compare the interviewers’ facial affectivity.

3. Results

Overall, facial affectivity in patients was predominantly negative. Disgust, contempt and anger predominated (see Figures 1 and 2 and Table 2 for descriptive statistics).

As the standard deviation in Table 2 shows, there was considerable variation among patients regarding the frequency of affects. Furthermore a closer examination of the patients’ affects in data from interviews A1, B1, and C1 reveals that there was a considerable range in total affects displayed (see Figure 3) contributing to the high standard deviations. However, all patients displayed mostly negative affects.

The ANOVAs of data from the 24 interviews (interview A1, interview B1, interview C1) with interviewer 1 revealed no significant effect among patients for any affect, (all \( F_{(2,14)} \leq 2.246, P \geq 0.143 \)) indicating that the amount of facial affectivity displayed by the patients did not vary throughout the interview series. Error variance for the patients’ four most frequent affects was, anger \( (F_{(2,14)} = 0.640) \), contempt \( (F_{(2,14)} = 1.103) \), disgust \( (F_{(2,14)} = 0.585) \), and happiness \( (F_{(2,14)} = 2.246) \).

Figure 4 shows the average number of affects for the four affects most frequently observed in the patients. The error bars indicate standard error of the mean. Happiness was infrequent and not observed in 3 patients, which contributed to a lower variance for this affect. Disgust appears to increase, although not significantly.

The patients’ affects in interview A1 and A2 were then compared. Although both disgust and contempt dominated the patients’ facial affects, the relative frequency differed. For interviewer 2, the patients displayed more contempt than disgust; yet when interacting with interviewer 1 the same

<table>
<thead>
<tr>
<th></th>
<th>Anger</th>
<th>Contempt</th>
<th>Disgust</th>
<th>Fear</th>
<th>Sadness</th>
<th>Surprise</th>
<th>Happiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Mean</td>
<td>2.63</td>
<td>5.00</td>
<td>14.25</td>
<td>0.25</td>
<td>0.00</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.04</td>
<td>8.21</td>
<td>15.04</td>
<td>0.71</td>
<td>0.00</td>
<td>0.35</td>
</tr>
<tr>
<td>B1</td>
<td>Mean</td>
<td>2.25</td>
<td>7.75</td>
<td>14.00</td>
<td>0.38</td>
<td>0.13</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>2.96</td>
<td>9.92</td>
<td>10.01</td>
<td>0.74</td>
<td>0.35</td>
<td>0.52</td>
</tr>
<tr>
<td>C1</td>
<td>Mean</td>
<td>3.38</td>
<td>4.50</td>
<td>17.88</td>
<td>0.00</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.40</td>
<td>5.40</td>
<td>14.82</td>
<td>0.00</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>A2</td>
<td>Mean</td>
<td>3.63</td>
<td>14.13</td>
<td>11.38</td>
<td>0.00</td>
<td>0.50</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.02</td>
<td>19.42</td>
<td>14.32</td>
<td>0.00</td>
<td>1.07</td>
<td>0.35</td>
</tr>
</tbody>
</table>

![Figure 1: Percentage of patients’ facial affective expressions in 24 interviews (interview A1, interview B1, interview C1) with interviewer 1.](image1)

![Figure 2: Percentage of patients’ facial affective expressions in 8 interviews (interview A2) with interviewer 2.](image2)
patients displayed more disgust than contempt. However, the other affects displayed towards both interviewers did not differ significantly (all $P > 0.18$), except for the higher amount of contempt ($z = 2.207, N$-Ties = 6, $P = 0.027$, two-tailed) shown to interviewer 2. Thus, with the exception of contempt, the second hypothesis was retained.

Both interviewers’ facial affective expressions were also compared with each other in the A interviews. With the exception of sadness, which bordered on significance ($U = 14.5, N_1 = 8, N_2 = 8, P = 0.06$, two-tailed), there was no significant difference (all $P > 0.10$) between the facial affective expressions of the two interviewers.

4. Discussion

The patients showed elevated amounts of negative facial affectivity. Patients most frequently displayed either disgust or contempt, followed by anger. These findings are in accordance with previous research which found that negative facial affectivity is to be expected in the facial activity of patients with schizophrenia [5, 7, 18]. However, contrary to previous findings [5] the most frequent affect in the present study was disgust as well as contempt. Due to the smallness of the sample this should be interpreted with cautiousness. Previous research found disgust to be the second most frequent affect after contempt [5].

Regarding the stability of facial affective expressions we found no substantial and systematic changes in the amount of affects the patients displayed at the various interviews, which suggests that affects appear stable and seem fairly independent of interview occasion. The patients’ affects were not altered by the change of interview partner, with the exception that contempt was more frequently displayed with the first interviewer. No conclusions can be drawn about the reason for this finding, since we cannot relate the results to changes in the pathological state of the patients due to lack of corresponding data. Though, we do not believe that this finding is due to differences in the interviewers’ facial affective expressiveness, since we also analyzed their facial affectivity and found no significant differences. We then know that their facial affective behaviour is similar to each other.

Most of the patients in the present study remained on the same antipsychotic medication at both data collections. To our knowledge there are no studies examining the impact of antipsychotic medication on facial affective behaviour in schizophrenia. Studies examining the effects of antipsychotic medication on facial expressiveness in general show contradicting results [3, 4, 6, 25, 26]. However, a newly published review claims that diminished expression in schizophrenia is observed independently of medication [10]. Nonetheless, if there is an impact on facial expressiveness, it is improbable that the type of facial affective expression should be selectively affected. While it is possible that the medicated patients may show reduced amounts of facial affective behaviour in comparison with unmedicated patients, it seems unlikely that the quality of affects shown, whether it was disgust or happiness, was affected.

As the sample was nonrandom and small, caution is advised in generalising the results to the total population of patients diagnosed with schizophrenia. This type of in-depth investigations does not allow big samples thereby limiting the power. On the other hand, the results are strengthened by the repeated measurement procedure with the same patients participating at several occasions. However, a limitation was that interviewer 2 only performed one interview (A2) that was compared with interview A1. However, since the analysis of interviews A1, B1, and C1 was performed first and showed that facial affectivity in the patients seemed stable over time, it was therefore assumed that interview A2 would be representative of a hypothetical series A2, B2 and C2 and could be used alone without jeopardizing validity. Naturally transcription and use of full series would have permitted more robust comparisons.

Another limitation is the use of only two interviewers both female. Facial affectivity may vary across genders. Also the uneven gender distribution among the patients may raise questions with regard to results generalizability since facial expressivity has been found to be lower in healthy males than in females. However, findings in patients with schizophrenia have been contradicting regarding this matter.
focus on psychotic experiences may partly explain the relationship to the person's disgusting experiences connected to the patients' sickness and suffering. As low self-esteem frequently can be observed in schizophrenia [33–35], facial affective expressions of disgust and contempt may also be seen as an expression of self-disgust or self-contempt. Low self-esteem, feelings of shame and guilt are frequently found in first-episode psychosis [36]. The connection between low self-esteem and the facial affective expressions of disgust and contempt in schizophrenia could therefore be a possible next step for future research.

To summarise, negative facial expressivity, mainly disgust and contempt, seems to dominate the facial expressions of patients with schizophrenia in clinical interviews while speaking about psychotic experiences. In the present study this finding seems to be a fairly stable feature independent of time and interviewer. Due to the small sample these findings need to be further replicated.

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