A neuropsychological analysis of schizophrenic thought disorder

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Abstract

We examined the relationship of schizophrenic thought disorder, as measured by the Thought Disorder Index (TDI), with (1) neuropsychological measures of verbal memory, abstraction, executive function, visual memory, and working memory; and (2) quantitative MRI measures of prefrontal and basal ganglia structures. TDI scores correlated strongly with tests of verbal memory, abstraction and executive functions, modestly with tests of working memory, but did not correlate with scores on tests of visual memory. Neither TDI scores nor their neuropsychological correlates were associated with frontal or basal ganglia magnetic resonance imaging (MRI) measures, with the exception of the measures of working memory that demonstrated a modest relationship with frontal and basal ganglia structures. These findings suggest that schizophrenic thought disorder may be strongly related to neuropsychological impairments in verbal memory, abstraction and executive functions, and modestly related to problems with working memory in this sample of patients. © 1998 Elsevier Science B.V.

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1. Introduction

A hallmark of schizophrenia is a profound disturbance in thinking whereby discourse is often contaminated by idiosyncratic, peculiar, or nonsensical words or phrases. Schizophrenic thought disorder is generally viewed as a breakdown in the form of thinking, which refers to the mechanisms, rules, or laws governing the orderly and logical sequence of thinking. It is distinct from, although often accompanied by, delusional beliefs, which are generally classified as evidence of impaired thought content. Schizophrenic thought disturbance has been carefully and objectively measured by Holzman and colleagues (1979), who developed the well-known Thought Disorder Index (TDI). Studies using the TDI have described schizophrenic thought disorder as "disorganized, confused and ideationally fluid, with many peculiar words and phrases", features which may distinguish schizophrenic thought disorder from the type of thought disorder that accompanies bipolar disorders with psychotic features (Solovay et al., 1987).
Notwithstanding these careful, descriptive, and objective analyses of schizophrenic thought disorder, little is known about the neuropsychological and cognitive mechanisms that presumably contribute to thought disorder. For example, Goldman-Rakic (1991, 1992) speculated that many schizophrenic symptoms, including those presumably related to thought disturbance, reflect a prefrontally based dysfunction in so-called ‘working memory’ operations. Phenomenologically akin to antedated notions of short-term memory (Just and Carpenter, 1992), and more recently described by some (Goldman-Rakic, 1992; Just and Carpenter, 1992) as ‘the blackboard of the mind’, working memory comprises of a set of mental processes, such as temporary storage, rehearsal, or rapid switching of attention (Baddeley, 1992; Cantor and Engle, 1993). It is measured by such cognitive activities as mental arithmetic and memory span exercises (Baddeley, 1992; Cantor and Engle, 1993). Goldman-Rakic (1992) suggested that due to a prefrontally based working memory impairment, schizophrenic patients may lose their train of thought, may fail to perceive causal relationships, and may be unable to regulate their behavior by ‘internalized schemata, symbolic representations, and ideas’.

Other studies have suggested that schizophrenic thought disorder may also be related to a left temporal lobe abnormality in semantic processing (Shenton et al., 1992). In particular, Shenton et al. (1992) demonstrated in a sample of 15, chronic, primarily positive symptom schizophrenic patients a highly significant correlation between thought disorder, as assessed by the TDI, and MRI volumetric reduction in the left temporal lobe, specifically in the left posterior superior temporal gyrus. In addition, Nestor et al. (1993) demonstrated that neuropsychological tests of verbal associative memory, categorical thinking, and basic verbal abstraction correlated with bilateral volumetric reductions in the temporal lobe, including left posterior superior temporal gyrus, in this same group of 15 patients with schizophrenia. Nestor et al. (1993) suggested that these neuropsychological deficits reflect a fundamental disturbance in a hypothetical semantic system, the principal function of which is to organize mental representations of concepts or words by category, level of abstraction, and hierarchy. Nestor et al. (1993) further suggested that a dysfunctional semantic system may underlie schizophrenic thought disturbance, and both of these impairments may originate, in part, from disease-related temporal lobe pathology.

To our knowledge, no study has yet to examine how schizophrenic thought disturbance may be related to both working memory and semantic memory processes (and their respective prefrontal and temporal lobe structures). While we have previously reported correlations between magnetic resonance imaging (MRI) temporal lobe abnormalities and both thought disorder and neuropsychological deficits in putative semantic-related functions (Shenton et al., 1992; Nestor et al., 1993), we have yet to examine the relationship of thought disorder with these and other neuropsychological functions in this same group of patients with schizophrenia. Similarly, we (Hokama et al., 1995; Wible et al., 1995) have previously reported MRI abnormalities in basal ganglia (increased volumes) but not prefrontal structures in the same patients who also had previously shown MRI temporal lobe abnormalities. However, we have yet to examine the relationship of MRI basal ganglia and prefrontal lobe volumes with both thought disorder and neuropsychological measures. Thus, in the present study, we now examine correlations between (1) thought disorder, as measured by the TDI, and neuropsychological measures including those of working memory and semantic organization; (2) thought disorder and quantitative MRI measures of prefrontal and basal ganglia structures, both of which are often implicated in schizophrenic pathology (e.g., Buchsbaum, 1990), and neither of which has yet to be empirically related to schizophrenic thought disturbance; and (3) neuropsychological measures, including those of working memory and semantic memory, and quantitative MRI measures of prefrontal and basal ganglia structures.

2. Methods

2.1. Subjects

Fifteen right-handed, neuroleptically medicated, male schizophrenic patients recruited from in-
patient wards at the Brockton Veterans Administration Medical Center and from hospital-affiliated foster care programs participated in the study. At the time of the study, two patients were outpatients, living with family members in the community. The patients were between the ages of 20 and 55 years (mean = 37.6 years), with 10–16 years of education (mean = 11.7 years). All patients met the criteria for schizophrenia according to DSM-III-R. Diagnoses were made on the basis of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (Spitzer and Endicott, 1978), videotaped interviews, and chart reviews. The mean duration of illness was 15.7 years (SD = 8.8). The mean neuroleptic dose was 881 mg (SD = 683) (chlorpromazine equivalents). No schizophrenic patient had a history of ECT, neurological illness, significant alcohol or drug abuse in the preceding 5 years (DSM-III-R diagnosis), or medications with known effects on brain MRI, such as steroids. Comparison of scores on the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) and on the Scale for the Assessment of Negative Symptoms (Andreasen, 1981) indicated that the patients had predominantly positive symptoms (e.g., hallucinations, delusions, and formal thought disorder). All patients had previously participated in MRI studies.

2.2. Thought disorder index

The Holzman-Johnston Thought Disorder Index (Johnston and Holzman, 1979) includes 23 categories of thought disorder rated at four different levels of severity. It is thought to represent most of the deviant verbalizations encountered in clinical practice with psychotic patients. Patients were administered the 10 card Rorschach, with responses audio-recorded, transcribed verbatim, and all peculiar, deviant, and idiosyncratic verbalizations were scored for thought disorder by a team of two judges expert in scoring the TDI.

2.3. Neuropsychological measures

All subjects underwent a comprehensive neuro-psychological evaluation, which included tests of intelligence, memory, attention, and executive functions. These tests were classified into four conceptual groups: (1) working memory; (2) verbal associative memory, including measures of semantic memory and related processes of verbal categorization; (3) visual memory; and (4) executive functions.

2.3.1. Working memory

We administered three neuropsychological tests of working memory, Hebb’s recurring digits (Hebb, 1961), Trails making test (Trails B) (Lezak, 1983), and Alternating semantic categories (Downes et al., 1993; Gotham et al., 1988). For the Hebb’s recurring digits, immediate memory span was determined by the number of digits correctly repeated for one trial on the Digit span forward test of the WAIS-R. Subjects were then asked to repeat sets of aurally presented digits, each set one digit longer than their immediate memory span. Unbeknownst to the subjects, every third set repeated the first set, with a total of 24 sets with 8 repeating or recurring sets. The dependent measure was percentage of numbers recalled for the recurring sets. For the Alternating semantic categories test, subjects were given 60 s to name alternately exemplars from two distinct categories (i.e., boys’ names and fruits; e.g., ‘Mike–Orange, Bob–Apple’). Number of word pairs generated was the dependent measure. For Trails B, a timed pencil-and-paper test, subjects connected alternating numbered and lettered circles (e.g., l-A, 2-B, etc). Performance time was used as the dependent measure. The Hebb’s recurring digits was viewed as a relatively pure measure of temporary storage and both the Alternating semantic categories and Trails B were viewed as measures of attention switching. Both temporary storage and attention switching are thought to represent critical working memory processes (Baddeley, 1992; Cantor and Engle, 1993).

2.3.2. Verbal associative memory and related semantic processes

We administered tests of verbal memory taken from the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987). These included logical memory subtests, which involve immediate and
delayed recall of orally presented stories, and the verbal paired associates test, which involves immediate and delayed recall of a list of eight word pairs, half of which were highly associated (e.g., baby–cries) and the other half of which were of low association (e.g., school–grocery). The similarities subtest of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) was used as a measure of verbal categorization and abstraction. In this test, subjects determine how various pairs of words (e.g., dog–lion, fly–tree) are alike.

2.3.3. Visual memory
We administered immediate and delayed recall versions of the visual reproduction subtest of the WMS-R. For immediate recall, subjects are shown four designs, one at a time, for 10 s, and are then asked to draw the design from memory. For delayed recall, subjects are asked to draw these designs following a 30 min interval.

2.3.4. Executive functions
The Wisconsin Card Sorting Test (WCST) (Heaton, 1981) was used as a measure of executive functions which include planning, self-monitoring and response regulation, all of which presuppose intact working memory processes. The WCST involves sorting 128 response cards, each of which has a geometric figure that may vary along three dimensions (color, form, number). The task is to sort these cards according to a specific principle (color, form, or number), which the subject must deduce on the basis of performance feedback.

2.4. MRI scanning
As described elsewhere in detail (Shenton et al., 1992; Hokama et al., 1995; Wible et al., 1995), MRI of the whole brain, in two different planes (axial and coronal), was done on a 1.5 tesla General Electric SIGNA MRI system (GE Medical Systems, Milwaukee) with a standard 30-cm head coil. The MRI procedure began with localizer scans, and then a three-dimensional Fourier-transform spoiled gradient-recalled acquisition pulse sequence was used to obtain coronal slices with voxels (pixel volumes) measuring $1.5 \times 0.975 \times 0.975$ mm. This procedure gave excellent gray–white matter contrast, with CSF appearing dark. Regions of interest were manually outlined on a workstation display screen for each slice containing the regions of interest. The voxels included in each of these spaces were summed to calculate region-of-interest volumes. For the purpose of this study, we examined relative measures of gray matter volume for prefrontal and basal ganglia structures, the latter of which was subdivided into putamen, caudate nucleus, and globus pallidus (see Shenton et al., 1992; Hokama et al., 1995; Wible et al., 1995; for illustrations of these regions and inter-rater reliability data).

3. Results
Mean TDI for these 15 schizophrenic patients, as reported by Shenton et al. (1992) was 60.4 (SD = 60.8). This indicated a markedly severe thought disorder, particularly when normal controls typically have TDI scores of less than 5. Table 1 presents the scores on neuropsychological tests of working memory, executive functions, and associative memory for the schizophrenic patients. Table 2 shows the mean relative gray matter MRI volumes of basal ganglia and prefrontal structures, as reported by Hokama et al. (1995) and Wible et al. (1995), for schizophrenic patients.

Spearman rank correlations were computed between TDI and neuropsychological test scores. As shown in Table 3, TDI scores correlated significantly with scores on neuropsychological tests of logical memory for both immediate (rho = −0.71, p < 0.01) and delayed (rho = −0.89, p < 0.001) recall, for immediate recall of verbal paired associates (rho = −0.62, p < 0.05), and for verbal categorization, as measured by the similarities subtest (rho = −0.68, p < 0.01). Likewise, TDI scores correlated significantly with categories achieved on the WCST (rho = −0.76, p < 0.01) and with slower performance on Trails B (rho = 0.63, p < 0.05). These correlations indicated that increased, or more severe thought disorder was associated with poorer scores on these neuropsychological tests. TDI scores did not correlate with scores on Hebb’s recurring digits or Alternating semantic categories.
Table 1

Neuropsychological test scores of 15 patients with schizophrenia

<table>
<thead>
<tr>
<th>Measure</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
</tr>
<tr>
<td>Hebb's recurring digits^a</td>
<td>0.776</td>
</tr>
<tr>
<td>Alternating semantic categories^b</td>
<td>11.3</td>
</tr>
<tr>
<td>Trails B^c</td>
<td>120.2</td>
</tr>
<tr>
<td>Verbal memory and semantic processes</td>
<td></td>
</tr>
<tr>
<td>Immediate recall^d</td>
<td>20.5</td>
</tr>
<tr>
<td>Delayed recall^d</td>
<td>16.3</td>
</tr>
<tr>
<td>Verbal paired associates</td>
<td></td>
</tr>
<tr>
<td>Immediate recall^e</td>
<td>15.5</td>
</tr>
<tr>
<td>Delayed recall^f</td>
<td>6.9</td>
</tr>
<tr>
<td>Similarities subtest^g</td>
<td>7.9</td>
</tr>
<tr>
<td>Visual memory</td>
<td></td>
</tr>
<tr>
<td>Immediate recall^h</td>
<td>31.5</td>
</tr>
<tr>
<td>Delayed recall^i</td>
<td>26.7</td>
</tr>
<tr>
<td>Executive functions</td>
<td></td>
</tr>
<tr>
<td>Wisconsin card sorting test^j</td>
<td>2.3</td>
</tr>
</tbody>
</table>

^aPercentage of numbers recalled for recurring set.
^bNumber of word pairs generated.
^cPerformance time in seconds.
^dRaw score (maximum score = 50).
^eRaw score (maximum score = 24).
^fRaw score (maximum score = 8).
^gScaled score (mean = 10, S.D. = 3).
^hRaw score (maximum score = 41).
^iRaw score (maximum score = 41).
^jNumber of categories achieved (maximum score = 6).

Table 2

Relative gray matter volumes of frontal and basal ganglia structures of 15 patients with schizophrenia

<table>
<thead>
<tr>
<th>Structure</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-frontal lobe</td>
<td>4.033</td>
<td>3.809</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.30</td>
<td>0.30</td>
</tr>
</tbody>
</table>

To examine the relative contributions of age and neuropsychological tests scores to TDI scores, we performed two stepwise multiple regressions. In the first stepwise regression, we entered age and scores on neuropsychological tests of similarities, WCST, logical memory, and verbal associative memory. The stepwise regression revealed that the similarities subtest accounted for a significant proportion of the variance of TDI scores with adjusted $R^2=0.60$ (adjusted for the number of variables and subjects) ($F=15.78$, $p<0.01$). Age and the other neuropsychological test scores did not significantly add to the magnitude of this $R^2$. For the relationship of working memory and thought disorder, we regressed age and scores on Hebb's recurring digits, Alternating semantic categories, and Trails B on TDI scores. The stepwise regression revealed that Trails B accounted for a significant proportion of the variance of TDI scores, with the adjusted $R^2=0.26$ ($F=4.96$, $p=0.05$). Again age and the other neuropsychological test scores did not significantly add to the magnitude of this $R^2$. Likewise, stepwise regressions also indicated that neither patient SES nor parental SES significantly added to the magnitude of $R^2$. Spearman rank correlations were also computed.
between TDI scores and relative gray matter volume measures of prefrontal and basal ganglia structures. TDI scores did not correlate with either left prefrontal gray matter (\( \rho = -0.11, p = 0.75 \)) or right prefrontal gray matter (\( \rho = -0.19, p = 0.55 \)). Similarly, TDI scores did not correlate with either left (\( \rho = -0.36, p = 0.11 \)) or right caudate nucleus (\( \rho = 0.10, p = 0.38 \)) or right globus pallidus (\( \rho = 0.17, p = 0.28 \)), and left (\( \rho = 0.10, p = 0.375 \)) or right putamen (\( \rho = 0.05, p = 0.44 \)). These non-significant correlations indicated that relative gray matter volume of basal ganglia and prefrontal structures did not influence level of thought disorder severity in this group of schizophrenic patients.

For neuropsychological test scores and MRI relative volume measures, significant Spearman rank-order correlations were obtained between right frontal gray matter volume and performance time on Trails B (\( \rho = -0.59, p < 0.05 \)) and on scores on Alternating semantic categories (\( \rho = 0.58, p < 0.05 \)). There was a statistical trend (\( p's < 0.10 \) two-tail, or \( p's < 0.05 \) one-tail) for reduced left prefrontal gray matter to be correlated with poorer scores on Hebb's recurring digits (\( \rho = 0.50, p < 0.10 \)), Trails B (\( \rho = -0.52, p < 0.07 \)), and Alternating semantic categories (\( \rho = 0.56, p < 0.06 \)). For basal ganglia measures, right caudate volume correlated significantly with Hebb's recurring digits (\( \rho = -0.62, p < 0.05 \)). This indicated increased basal ganglia volume correlated with reduced temporary storage capacity, as assessed by Hebb's recurring digits. Scores on tests of memory, verbal categorization, and executive functions did not correlate with MRI relative volume measures of either prefrontal or basal ganglia structures.

Finally, Spearman rank correlations were computed among the various neuropsychological measures. Tests of verbal memory and executive functions were highly intercorrelated. For example, WCST categories achieved correlated, with scores on tests of verbal paired associates for both immediate (\( \rho = 0.58, p < 0.05 \)) and delayed (\( \rho = 0.53, p < 0.05 \)) recall. Similarly, WCST categories achieved correlated with scores on immediate (\( \rho = 0.76, p < 0.01 \)) and delayed (\( \rho = 0.58, p < 0.05 \)) recall of logical stories. By contrast, tests of working memory did not correlate with WCST categories achieved or with tests of verbal memory. Among the tests of working memory, only Trails B correlated with scores on the similarities subtest (\( \rho = -0.63, p < 0.05 \)), a measure of basic verbal categorization. Immediate but not delayed visual memory correlated with working memory tests, namely Hebb's recurring digits (\( \rho = 0.67, p < 0.05 \)) and performance time on Trails B (\( \rho = -0.63, p < 0.05 \)).

4. Discussion

The principal aim of this study was to examine neuropsychological correlates of schizophrenic thought disorder, as assessed by the TDI. Severity of thought disorder strongly correlated with poor performance on neuropsychological tests of verbal memory, verbal categorization, and executive functions. Severity of thought disorder also appeared to be influenced by working memory, albeit to a lesser extent, with only one of the three tests of working memory correlating with TDI scores in this sample of schizophrenic patients. By contrast, tests of visual memory did not correlate with severity of thought disorder. With respect to the MRI data, neither TDI scores nor their neuropsychological correlates were associated with frontal or basal ganglia MRI volume measures, with the exception of the measures of working memory that demonstrated a modest relationship with frontal gray matter, and to a lesser extent, with basal ganglia volume measures in this group of schizophrenic patients.

We (Shenton et al., 1992; Nestor et al., 1993) have previously reported significant correlations between temporal lobe volume and both thought disorder and neuropsychological deficits in the same group of schizophrenic patients examined in this current study. These current data provided additional and more direct evidence that schizophrenic thought disturbance may be intimately related to a relatively specific configuration of neuropsychological deficits, which, in turn, correlated primarily with MRI abnormalities in temporal but not frontal or basal ganglia structures. That is, poor performance on neuropsychological
tests of verbal memory, verbal categorization, and executive functions, all of which were strongly correlated with TDI, were also highly intercorrelated for schizophrenic patients. While these tests measure a variety of cognitive functions, one common denominator may be related to a fundamental ability to generate and to use verbal categories. Indeed, even our measure of executive functions, the WCST, requires, among others, a basic ability for categorical thinking. In schizophrenic patients, failure to generate or to use categories may also contribute to thought disturbance.

A fundamental disturbance in the ability to think in terms of categories may reflect a dysfunctional semantic system in patients with schizophrenia. Within the semantic system, knowledge may be represented in terms of functional, conceptual, and associative networks (Caplan, 1987). There is considerable neurological evidence that the semantic system is highly dependent upon intact temporal lobe structures (Squire and Zola-Morgan, 1991), and that a loss of semantic knowledge often accompanies left temporal lobe lesions (Kolb and Whishaw, 1990). Yet the semantic impairment of neurological patients with temporal lobe lesions is most likely considerably different from that which characterizes schizophrenia. Principal among these differences is that neurological patients with temporal lobe lesions do not typically demonstrate a schizophrenic-like disturbance in thinking. These patients generally demonstrate a profound decay or loss of semantic knowledge but do not, for example, demonstrate loose associations, neologisms, word salad, and other signs and symptoms of a schizophrenic thought disturbance.

It is therefore likely that schizophrenic thought disturbance may reflect an interaction between disease-related impairments in both semantic and working memory. Each representational element of semantic memory may have an associated activation level with a corresponding threshold value (e.g., Tulving, 1983; Glass and Holyoak, 1986). When activation exceeds a minimum threshold value, an element is thought to be part of working memory. Threshold parameters of various semantic elements may be reduced or somehow compromised by the temporal lobe pathology of schizophrenia. In this sense, schizophrenia may be characterized by dysfunctional semantic structures, as opposed to a loss of semantic structures, as is typically the case in neurological patients with temporal lobe pathology (Kolb and Whishaw, 1990; Parasuraman and Nestor, 1993). Because threshold values may be reduced, working memory may become overloaded. Representational products may then become difficult to purge from working memory, and spurious connections may develop among elements.

In this scenario, a failure to purge or inhibit these elements may reflect a prefrontally based working memory impairment in schizophrenia, whereas aberrant threshold values would be related to temporal lobe pathology. Support for this model is derived from studies (Kwapil et al., 1990; Manschreck et al., 1988; Spitzer et al., 1994) which have demonstrated that schizophrenic patients show an enhanced priming effect on word pair tasks, often interpreted as evidence of abnormal overactivation of semantic networks (see Nestor et al., 1997; Niznikiewicz et al., 1997). Similarly, other behavioral studies using experimental procedures to isolate specific working memory processes have also indicated an attentional inhibition deficit in patients with schizophrenia (Nestor et al., 1992).

This neuropsychological model of schizophrenic thought disorder must, however, be viewed as tentative for a number of reasons. First, in the current study, neither tests of working memory nor MRI measures of frontal volumes correlated strongly with thought disorder scores. However, we did not subdivide frontal gray matter into orbital and dorsolateral regions, the latter of which has been thought to play an important role in neuropsychological abnormalities in patients with schizophrenia. Similarly, extant MRI measures may not be sufficiently sensitive to detect some reported histological abnormalities in prefrontal cortical areas 9 and 46 in patients with schizophrenia (Selemon et al., 1993). Second, the current study examined overall severity of thought disor-
der, as measured by the TDI. There is obviously tremendous heterogeneity in schizophrenic thought disorder. The current investigation did not examine any particular dimensions of schizophrenic thought disturbance that may be related to both neuropsychological and MRI measures. Third, this study examined male patients with chronic, positive-symptom schizophrenia, who, as a group, demonstrated quantifiable MRI abnormalities in both temporal lobe and basal ganglia regions, but not in frontal structures. The extent to which these findings will extend to other schizophrenic patient groups is unknown. Finally, all patients were medicated. Although our previous findings have not demonstrated a significant relationship between MRI findings and neuroleptic medication, the effects of these somatic treatments on our present findings is unclear.

In summary, the current data provided preliminary evidence that severity of schizophrenic thought disorder may reflect, in part, a dysfunctional semantic system, secondary to disease-related temporal lobe pathology. The extent to which a disease-related, prefrontally based working memory impairment also contributes to schizophrenic thought disturbance is difficult to establish on the basis of the current data. However, it is likely that the schizophrenic thought disturbance represents a complex set of neuropsychological impairments, some of which we have shown are strongly related to disease-related temporal pathology, and others which may, in future studies, be linked to disease-related prefrontal pathology.

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