Schizophrenia Research 137 (2012) 118–123

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Longitudinal changes in semantic categorization performance after symptomatic remission from first-episode psychosis: A 3-year follow-up study

Christy Lai-Ming Hui [a,*], Julia Longenecker [a], Gloria Hoi-Yan Wong [a], Jennifer Yee-Man Tang [a], Wing-Chung Chang [a], Sherry Kit-Wah Chan [a], Edwin Ho-Ming Lee [a], Eva Lai-Wah Dunn [b], May Yin-King Miao [b], Wai-Song Yeung [b], Chi-Keung Wong [b], Wah-Fat Chan [b], Wai-Nang Tang [b], Eric Yu-Hai Chen [a]

[a] Department of Psychiatry, University of Hong Kong, Hong Kong
[b] Department of Psychiatry, Pamela Youde Nethersole Eastern Hospital, Hong Kong

ARTICLE INFO

Article history:
Received 23 August 2011
Received in revised form 9 February 2012
Accepted 9 February 2012
Available online 25 March 2012

Keywords:
First episode
Schizophrenia
Semantic
Categorization

ABSTRACT

Semantic categorization abnormalities have been observed in schizophrenia, but studies have rarely focused on the longitudinal trajectory. In this study, we consider semantic performance and the relationship with symptomatic changes during recovery from a first-episode of schizophrenia over a period of 3 years. Thirty-seven first-episode patients with schizophrenia were compared to thirty-seven matched controls in a categorization task. Patients were assessed at first episode, after clinical stabilization, and annually for the subsequent 3 years. In the task, participants indicated whether a word belonged to a given category. Each category contained words of varying degrees of semantic relatedness: typical, atypical, borderline, related-but-outside, and unrelated. Reaction times and proportion of 'yes' responses were analyzed. At first assessment, semantic categorization abnormalities were observed in first-episode patients. Patients assigned more semantically-dissimilar words to the categories than controls. As patients stabilized from acute states, their semantic categorization performance improved and then remained stable throughout the entire follow up period of 3 years. Interestingly, semantic performance deficits, particularly a diminished typicality effect, correlated with negative symptoms in the initial episode, but not at stabilization when symptoms subsided. No significant associations between positive and negative symptoms, or pre-defined categorization measures were identified. The data demonstrated semantic memory abnormalities in first-episode schizophrenia. However, an improvement of semantic categorization performance was observed in stabilized schizophrenia patients. Overall, the data are suggestive of a state effect in semantic abnormalities rather than a trait effect. The correlation between degree of impairment and symptoms may explain previous inconsistent findings.

1. Introduction

Semantic memory, a domain frequently cited as the source of language deficits in patients with schizophrenia (Aloia et al., 1996; Goldberg et al., 1998), is conceptualized as more than a linguistic information store (Tulving, 1972). Rather, it includes knowledge necessary for perceptual identification of objects and deriving the meaning of words (Elvevåg et al., 2005). Semantic knowledge, as it is understood, is organized as a network in which the features of elements create categorical boundaries with a hierarchical structure (e.g., the words chair and furniture share properties, but are represented at different taxonomic levels of the same category). A number of studies, employing a variety of paradigms, have found that patients with schizophrenia consistently show poorer performance than healthy persons in tasks involving semantic memory (Spitzer et al., 1993; Chen et al., 1994; McKay et al., 1996). A recent meta-analysis demonstrates that semantic impairments are specifically linked to and especially consistent in the presence of the symptom Formal Thought Disorder (Doughty and Done, 2009).

Two fundamental neurocognitive theories have been postulated to explain these semantic abnormalities: deficits in accessing to, or the storage of, semantic knowledge; or both. Some studies concluded that schizophrenia patients had difficulties retrieving from an intact semantic store (Allen et al., 1993; Doughty et al., 2008), whereas others indicated the semantic store was degraded (McKay et al., 1996; Chen et al., 2000; Rossell and David, 2006). Additional theories, such as abnormal automatic spreading of activation within semantic networks (Goldberg et al., 1998) and reduced inhibition of irrelevant information (Spitzer et al., 1993), have been proposed. Semantic priming using the lexical decision task has been a popular cognitive paradigm for probing the

* Corresponding author at: Department of Psychiatry, University of Hong Kong, Queen Mary Hospital, 102, Pokfulam Road, Hong Kong. Tel.: +852 2255 3064; fax: +852 2855 1345.
E-mail address: christy@lmhui.com (C.L.-M. Hui).

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doi:10.1016/j.schres.2012.02.010

structure of the semantic system. However, the findings have been inconsistent and difficult to interpret (Doughty and Done, 2009).

While semantic priming addresses meaning proximity between items (Doughty and Done, 2009), the categorization task specifically addresses a particular form of semantic relationship, that of hierarchical membership within semantic concepts (Chen et al., 1994). This task requires participants to indicate whether or not each word belongs to the specified category according to how semantically-related (typical, atypical, borderline, related or unrelated) it is to the category. Chen et al. (1994) found that patients with schizophrenia, as compared to controls, categorized slower and shifted their response patterns across all conditions. Whilst the borderline condition produced the longest reaction time (RT) for controls, the related-but-outside condition took longest for patients.

However, a later administration of the semantic categorization task in another chronic sample did not replicate these findings (Elvevåg et al., 2002). The authors noted that some patients spent an incommensurate time in the borderline condition, which may have attenuated the difference between conditions by requiring an even longer RT to produce a significant RT shift between the borderline and related-but-outside conditions. This highlights the complexity of the categorization task, where results depend on the relationship between conditions as well as raw RTs. The suggested association between the disorganization of the semantic systems and the severity of particular symptoms is another possible explanation for the varying results. The presence of moderate to severe thought disorder (Goldberg, et al., 1998; Titone et al., 2007; Doughty and Done, 2009) and negative symptoms (Allen, et al., 1993) have been found to further degrade performance among patients in multiple semantic paradigms. Given the differences in patients' characteristics between Chen et al. (1994), who looked at chronic out- and in-patients, and Elvevåg et al. (2002), whose participant group consisted of comparatively younger in-patients, a reevaluation of the task with consideration for symptom profiles was deemed appropriate and necessary.

To date, limited evidence has been gathered regarding the longitudinal changes of the semantic categorization performance in schizophrenia. Rossell and David (2006) studied 16 chronic patients and 16 normal controls at three successive time points, with each separated by 6 to 8 weeks. Using the same categorization task as Chen et al. (1994), the accuracy scores of the 'typical' and 'atypical' conditions were explored. Chronic schizophrenia patients were less accurate than controls in both semantic conditions at all three time points, suggesting a consistently poor performance in schizophrenia over time. Importantly, participants in this study had been ill for an average of 13.6 years. Whether deficits in this semantic categorization task are present from the early stages of illness has not been established and is further complicated by the possibility that they are related to pharmacological treatment. Shedding light on semantic abilities in early stages of illness and across changes in symptoms is vital to identify the impairment as a trait or a state phenomenon in patients.

Therefore, the present study examines semantic categorization performance in patients with first-episode schizophrenia in a three-year longitudinal period. In particular, we aim to (i) investigate whether semantic categorization abnormalities are detectable in first-episode patients with schizophrenia, including a subset of medication naïve patients, as compared to healthy participants; (ii) ascertain whether semantic categorization performance in schizophrenia patients changes over time; and (iii) identify longitudinal patterns of clinical correlates of semantic categorization abnormalities.

2. Methods and materials

2.1. Participants

The patient group consisted of 37 patients with first-episode schizophrenia spectrum disorders. Diagnoses were based on clinical interview, information from informants and case notes using DSM-IV criteria (APA, 1994) and the SCID schedule (First et al., 1995). Patients between ages 18 and 55 were recruited from out- and in-patient psychiatric units in a defined catchment area.

Thirty-seven healthy participants were recruited and matched to the patients in age, gender and education level. Those with personal history of psychiatric or significant medical illness (defined as conditions with a clear impact on health, often requiring long term medication treatment, or conditions with potential impact on brain function, such as epilepsy or diabetes), history of substance abuse, intellectual disability, non-corrected visual or hearing impairment, or illiteracy were excluded from the study. Participants were Cantonese-speaking and all assessments conducted in Chinese (Cantonese). The study was approved by the local institutional review board and was carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent.

2.2. Assessments

Patients were assessed on all measures prospectively at initial contact (A1), after stabilization from the psychotic symptoms at first episode (A2), and then annually (from initial contact) for the subsequent 3 years (A3, A4, A5). The means of PANSS positive subscore, negative subscore and total score from A1 to A2 were 19.5➔9.14 ($t=11.46$, $p<0.001$), 17.2➔12.5 ($t=4.13$, $p<0.001$) and 72.8➔47.4 ($t=8.08$, $p<0.001$), respectively. The control group was assessed once only with the categorization task at recruitment.

Data on age, gender and years of education were also collected from all participants.

2.2.1. Clinical assessments

The Positive and Negative Syndrome Scale (PANSS) assessed psychotic symptoms in patients (Kay et al., 1987) at each time point.

2.2.2. Categorization task

The semantic categorization task was a variant used by Wilkins (1971) adapted for presentation on a computer screen. The task consisted of 40 pairs of Chinese words, assembled from previously established English norms (Battig and Montague, 1969). The validity of exemplars was examined and confirmed through ratings by local healthy volunteers to ensure consistency between English and Cantonese (unpublished data available upon request). Stimuli constituted four categories (fruit, furniture, drinks and clothing), each subdivided into five degrees of semantic relatedness as follows: (1) typical (members with a higher frequency of characteristic properties of the category, e.g., table within the category furniture), (2) atypical (members with a lower frequency of characteristic properties but still within the category, e.g., bookcase), (3) borderline (examples that are ambiguous and can be classified as either inside or outside the boundary of the category, e.g., clock), (4) related (clearly outside the category but sharing some major features with the category members, e.g., mailbox), and (5) unrelated (examples that clearly do not belong to the category, e.g., word).

Participants were presented with a category title followed by a stimulus word. Participants indicated whether the word was an exemplar of the category by pressing one of two hand-held buttons labeled 'yes' (left) or 'no' (right). RTs – calculated from presentation of word to button press – and number of 'yes' responses were recorded by the computer. Six practice trials were demonstrated to ensure all participants understood the task. Trials were randomized in each presentation to avoid practice effects.

2.3. Data analysis

Using the Statistical Package for the Social Sciences (SPSS for Windows, version 17), basic demographics between patient and control groups were compared using independent *t*-tests and Chi-square tests. Mean reaction times (RT) in milliseconds (ms) and standard

deviations (SD), as well as the proportion of 'yes' responses, were calculated in each semantic-relatedness condition (typical, atypical, borderline, related and unrelated) of the categorization task.

To ascertain whether semantic categorization abnormalities are detectable in first-episode psychosis, comparisons were first made between controls and patients at A1 using analysis of variance (ANOVA: semantic relatedness × group [patients, control]). A further analysis comparing patients at A1 who were medication naïve with those who had started medication at A1 was then made (ANOVA: semantic relatedness × group [medication naïve, medicated]).

Changes in categorization performance of schizophrenia patients over the first 3 years were then explored by repeated measure ANOVA (semantic relatedness × time points [A1, A2, A3, A4, A5]). When there were significant main or interaction effects, post-hoc pairwise least significant difference (LSD) *t*-tests were carried out.

Correlation analyses with Bonferroni correction were performed between symptoms scores (positive and negative symptom subscores of the PANSS) and three pre-defined categorization measures (typicality effect, borderline shift and false relatedness effect) in patients at first episode (A1) and stabilization (A2). Typicality effect occurs when the time to respond to a typical exemplar is shorter than that of an atypical exemplar (atypical condition RT minus typical RT). Borderline shift effect occurs when the RT for a borderline exemplar is shorter than that for a related non-exemplar (related RT minus borderline RT). False relatedness effect occurs when a related non-exemplar is rejected slower than an unrelated non-exemplar (unrelated RT minus related RT).

3. Results

3.1. Basic demographics between patient and control groups

There were no significant differences between the two groups with regard to gender, age at presentation, or years of education. At baseline, 51.4% (19 out of 37) of the first-episode patients were medication-naïve (see Table 1).

Most patients were taking conventional antipsychotics during the study period (with haloperidol and trifluoperazine being the most commonly used). The mean dosages in daily chlorpromazine equivalence were 212.9 at A1, 399.3 at A2, 265.7 at A3, 230.9 at A4, and 179.0 at A5. The number of patients on atypical antipsychotics was 1 at A1, 0 at A2, 1 at A3, 6 at A4, and 6 at A5. Atypical antipsychotics included risperidone, olanzapine and quetiapine. Two patients were on clozapine. Fourteen patients received benzhexol, 4 patients received concurrent antidepressant treatment, and 5 patients received concurrent benzodiazepines.

3.2. Are semantic categorization abnormalities detectable in first-episode psychosis?

To address the first research question of whether semantic categorization abnormalities can be observed in first-episode schizophrenia, an ANOVA was performed with group (patients at first-episode vs. controls) as the between-subject variable and semantic relatedness conditions (typical, atypical, borderline, related and unrelated) as the within-subject variable. Overall, RTs in all conditions (see Fig. 1) were higher in patients than in healthy participants ($F(1,72) = 7.831$, $p<0.01$). In addition, a significant main effect of semantic relatedness condition ($F(4,288) = 12.299$, $p<0.001$) and a significant interaction effect between group and condition were found ($F(4,288) = 4.877$, $p<0.005$).

Semantic abnormalities within each group were further studied. Healthy subjects, as expected, showed an inverted, V-shaped function of RT which was highest in the borderline condition (see Fig. 1). A one-way ANOVA revealed a significant main effect of semantic relatedness ($F(4,36) = 19.21$, $p<0.001$). Multiple pairwise *t*-test comparisons found that all semantic relatedness conditions differed significantly from one another, except atypical and unrelated ($p = 0.444$) and borderline and related ($p = 0.143$). Similarly, a one-way ANOVA of the conditions within patients (at A1) found a significant main effect of semantic relatedness ($F(4,36) = 5.25$, $p = 0.001$). Multiple pair-wise comparisons revealed significant relationships between all semantic conditions except typical and atypical ($p = 0.979$), borderline and related ($p = 0.640$), borderline and unrelated ($p = 0.571$), and unrelated and related ($p = 0.789$).

Table 1
Baseline characteristics of first-episode patients with schizophrenia and controls. Mean and standard deviation (SD) or, when appropriate, number and percentage are indicated.

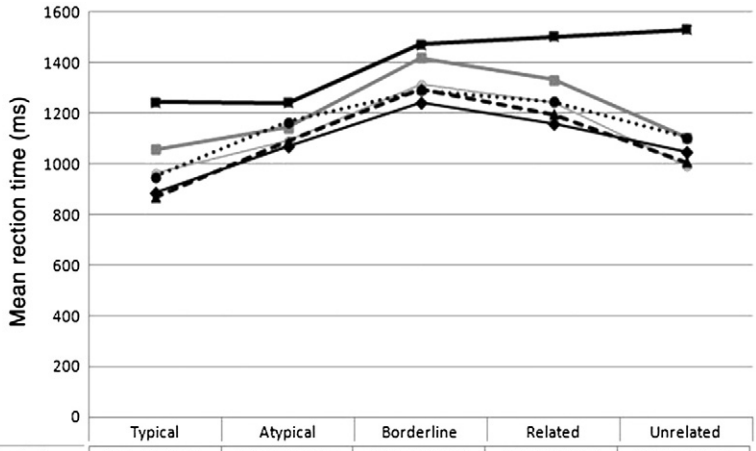
	Patients ($n = 37$)	Normal ($n = 37$)	Comparisons
Males (no.; %)	19; 51	19; 51	Chi-sq = 0.000, $p = 1.0$
Age at presentation (years) (mean ± SD)	32.1 ± 10.35	32.1 ± 10.47	$t = -0.011$, $p = 0.991$
Education (years) (mean ± SD)	11.1 ± 3.61	10.9 ± 2.68	$t = -0.330$, $p = 0.742$
Positive and negative syndrome scale (PANSS) at baseline			
Positive symptoms score (mean ± SD)	19.5 ± 5.12	–	–
Negative symptom score (mean ± SD)	17.2 ± 7.53	–	–
Total score (mean ± SD)	72.8 ± 19.43	–	–
Antipsychotic medications when first approached for assessment			
On medication (no.; %)	18; 48.6	–	–
Not on medication (no.; %)	19; 51.4	–	–

With respect to mean percentage of 'yes' responses in the five semantic-relatedness conditions (see Fig. 2), healthy controls gave 'yes' responses to nearly 100% of the typical stimuli and virtually never responded 'no' to exemplars which were totally unrelated to the category. Interestingly, patients behaved similarly in the atypical, typical and borderline conditions. However, the percentage of 'yes' responses in related-but-outside (mean = 45.22, SD = 18.842) and unrelated (mean = 46.90, SD = 22.302) conditions approximately matched borderline condition (mean = 50.23, SD = 22.469). An ANOVA of 'yes' responses was carried out with the five conditions as the within-subject variable and patient vs. control groups as the between subject variable. Significant main effects of condition ($F(4,288) = 167.688$, $p<0.001$) and group ($F(1,72) = 7.104$, $p = 0.009$), and an interaction effect ($F(4,288) = 50.559$, $p<0.001$) were identified. Post hoc comparison showed that controls differed significantly from patients in all conditions (typical, atypical, related and unrelated; all with $p<0.001$) except borderline (ns).

To further study the role of medication on semantic performance in schizophrenia patients, comparisons were made between medication naïve ($n = 19$) and medicated patients ($n = 18$) at A1. No significant group differences were identified with respect to RT ($F(1,35) = 2.403$, $p = 0.13$) or 'yes' response in the categorization task ($F(1,35) = 0.083$, $p = 0.775$).

3.3. Longitudinal changes in categorization performance—does performance by patients change over time?

The changes in speed of the categorization performance in schizophrenia patients ($n = 37$) were assessed with repeated measure ANOVA. Significant main effects of time point ($F(4,144) = 12.711$, $p<0.001$) and semantic relatedness ($F(4,144) = 26.021$, $P<0.001$), and a significant interaction effect between time points and semantic relatedness ($F(16,576) = 2.508$, $p = 0.001$) were identified. Post hoc comparisons using paired *t*-tests between time points (A1 vs. A2, A2 vs. A3, A3 vs. A4 and A4 vs. A5) and semantic relatedness performance were further explored. It was shown that significant differences between A1 and A2 were identified in typical ($t = 2.78$, $p = 0.008$),



	Typical	Atypical	Borderline	Related	Unrelated
Control	964.1 (331.0)	1094.5 (401.9)	1314.5 (580.0)	1244.7 (493.6)	991.1 (324.1)
Patients (A1)	1243.6 (494.9)	1241.6 (559.1)	1472.0 (513.4)	1503.2 (544.1)	1531.4 (706.3)
Patients (A2)	1057.3 (513.6)	1143.5 (394.7)	1418.8 (522.3)	1333.1 (322.1)	1105.8 (314.1)
Patients (A3)	950.0 (224.9)	1165.6 (393.4)	1290.9 (446.7)	1246.6 (462.9)	1105.8 (330.1)
Patients (A4)	867.3 (294.6)	1087.4 (382.0)	1298.1 (568.8)	1195.6 (393.0)	1008.5 (351.8)
Patients (A5)	883.6 (296.7)	1067.6 (369.0)	1241.7 (525.1)	1159.1 (386.6)	1050.1 (530.8)

Fig. 1. Longitudinal changes of the mean reaction times across the five time points for first-episode patients with schizophrenia as compared to healthy controls when categorizing words in the five semantic relatedness conditions. Measurements are mean reaction time in milliseconds with standard deviations.

related ($t=2.25$, $p=0.031$) and unrelated conditions ($t=3.58$, $p=0.001$). However, no significant differences in any of the semantic relatedness conditions were found between A2 and A3, A3 and A4, and A4 and A5, respectively (all ns) (see Fig. 1).

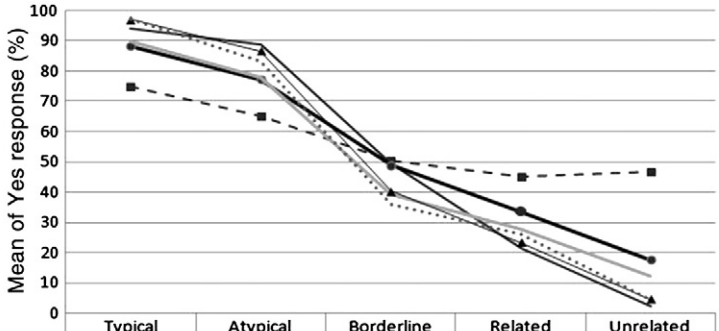
Likewise, with respect to 'yes' response data, there were significant main effects of time point ($F(4,144)=5.327$, $p<0.001$), semantic relatedness ($F(4,144)=320.813$, $p<0.001$) and interaction effect between time points and semantic relatedness ($F(16,576)=16.387$, $p<0.001$). Post hoc paired sample *t*-tests between semantic relatedness performance at A1 vs. A2, A2 vs. A3, A3 vs. A4 and A4 vs. A5 were carried out. Significant differences were identified between A1 and A2 in terms of the typical ($t=-2.56$, $p=0.015$), atypical ($t=-2.61$, $p=0.013$), related ($t=2.34$, $p=0.025$) and unrelated conditions ($t=6.67$, $p<0.001$). However, subsequent paired *t*-tests comparisons were insignificant between semantic relatedness at A2 vs. A3, and A4 vs. A5. Significant differences in the typical ($t=-2.66$, $p=0.012$), atypical ($t=-2.43$, $p=0.02$) and unrelated conditions ($t=2.84$, $p=0.007$) were also identified between A3 vs. A4 (see Fig. 2).

3.4. Correlation between categorization measures and clinical variables

At initial assessment (A1), negative symptoms as measured by the PANSS were significantly negatively correlated with typicality effect ($r(37)=-0.472$, $p=0.003$), meaning that more negative symptoms were related to a diminished typicality effect. However, both positive and negative symptoms were unrelated to borderline shift and false-relatedness effects at presentation. Likewise, at stabilization (A2), none of the pre-defined categorization measures, namely typicality, borderline shift and false-relatedness effects were associated with positive or negative symptoms.

4. Discussion

In this study, as compared to controls, semantic categorization abnormalities were found in first-episode psychosis patients. The initial pattern observed was similar to those found in previous studies on chronic patients (Chen et al., 1994; Rossell and David, 2006). After



	Typical	Atypical	Borderline	Related	Unrelated
Control	94.1 (8.7)	88.6 (11.1)	49.8 (22.3)	21.4 (16.1)	2.3 (5.2)
Patients (A1)	75.0 (20.6)	65.1 (20.0)	50.2 (22.5)	45.2 (18.8)	46.9 (22.3)
Patients (A2)	88.3 (20.8)	77.2 (22.8)	48.9 (24.0)	33.7 (20.6)	17.8 (22.5)
Patients (A3)	89.8 (14.4)	78.1 (18.6)	39.4 (23.3)	27.7 (19.9)	12.5 (15.8)
Patients (A4)	96.9 (5.5)	86.6 (14.0)	40.2 (27.3)	23.3 (18.7)	4.7 (8.5)
Patients (A5)	97.0 (5.4)	83.3 (17.3)	36.0 (27.5)	26.4 (23.0)	4.4 (7.3)

Fig. 2. Longitudinal changes of 'yes' responses of patients with first-episode schizophrenia and healthy volunteers. Measurements are mean percentage of 'yes' responses with standard deviations.

initial episode, semantic categorization performance was found to be improved at stabilization period, and then remained stable for up to the conclusion of our research, 3 years later. One possible interpretation of this finding is that the observed semantic categorization abnormality represents a reversible feature associated with the 'state' of the psychotic episode. In agreement with those findings of Rossell and David (2006) for chronic patients, in which the intra-category performance is stable over time (typical, atypical). We further reported in this study that extra-category responses (related-but-outside, unrelated) appear to be related to psychotic state and then become stable over time.

Similar to previous study of chronic patients (Chen, et al., 1994), first-episode patients appeared to find the related non-exemplar condition most difficult (they were slower and made more errors in this condition). This suggests that patients may have difficulty in handling items that shared some features with the category but otherwise lay outside the category. For acutely psychotic patients, more errors were made in the unrelated as well as the typical conditions which may reflect non-specific disruption of performance due to the acute psychotic state. Interestingly, we found that negative symptoms during first-episode psychosis were associated with a diminished typicality effect (i.e., the speed advantage of a responding to a typical vs. atypical exemplar is reduced).

From the 'yes' response data, patients demonstrated over-inclusive responses, not only in the related and unrelated conditions, but also the typical and atypical conditions. In contrast to previous suggestions of an outward shift in semantic category boundaries in schizophrenia (Chen et al., 1994), we would explain these semantic differences as failures of executive functioning to efficiently manage categories during the task (Doughty and Done, 2009). Over-inclusiveness may reflect a failure to suppress inappropriately distant associations in the semantic network, leading to indiscriminate activation of irrelevant information which interferes with the processing of semantic items.

The potential role of medication on semantic performance is an important issue for consideration. Our study is the first to report categorization abnormalities in medication naïve patients. No difference in categorization performance was found between medication naïve and medicated patients with first episode psychosis, suggesting that the observed abnormality cannot be due to medication alone. Indeed, even with medication, the categorization performance improved as the clinical state stabilized. Nevertheless, conventional antipsychotics may be associated with slowing of responses, particularly when higher dosages were used (Woodward et al., 2007).

In our sample, a high proportion of patients were on low dose conventional antipsychotics (less than 5 mg of haloperidol or equivalent) and, not surprisingly, the patient group had an overall slower response time.

The current study has an important limitation: while patients were assessed with the categorization task at multiple time points, healthy controls were only assessed once. As a result, we cannot directly estimate the contribution of practice effects towards the observed changes. Although we favored an interpretation that the 'normalization' of categorization abnormalities was due to resolution of the psychotic state, we cannot definitely rule out the possibility that repeated performance may also contribute to the effect. As compared with memory tests, where repeated presentation of items is expected to increase rate of recognition, categorization tasks assess grouping of known concepts and do not directly assess recall; thus recognition effect will be less prominent. Importantly, during the categorization task, no feedback was given to the patients regarding their responses. Indeed, responses cannot be said to be correct or incorrect in some of the conditions (e.g., borderline). It is therefore less likely that repeated performance of the categorization task may influence the observed results, apart from a general familiarization with the test procedure. Additionally, the test was repeated at long intervals (several months to 1 year), which also makes significant practice effects less likely. Furthermore, in the study of Rossell and David (2006), the categorization task was repeated in chronic patients and controls within a shorter time frame (only 6–8 weeks apart on the three assessment time points) and categorization performance was found to be stable. Nevertheless, we acknowledge that further studies using alternate forms for the different time points will help to resolve this issue definitively.

Our study is the first study of semantic categorization in first episode psychosis patients. We also included a subgroup of patients tested in a medication naïve state. Importantly, the study provides long term longitudinal data for categorization performance in a well characterized group of patients.

In conclusion, an improvement of semantic performance in patients from first-episode to stabilization suggests that the cognitive demands of the categorization task are highly dependent on the symptom profile of patients. This dependency may explain some inconsistencies in previous findings. Based on the relationship between semantic performance, symptoms, and medication state, this effect certainly deserves more exploration, particularly with respect to tie to the dopaminergic system. Future studies looking at specific symptomatology by separate clinical measures such as formal thought disorder in patients with schizophrenia could further elucidate the relationship between the structure of the semantic network, the application of semantic knowledge by more complex cognition processes, and active psychotic symptoms.

Role of funding source

This work was supported by grant 21500.10202404 from the Research Grants Council of Hong Kong. The Institutional Review Board ethics committees of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster and Hong Kong East Cluster approved the study.

Contributors

CLMH and JL were involved with the statistical analysis and writing of the manuscript. CLMH, JL, GWHY, JMYT, WCC, SKWC, EHML and EYHC interpreted the data. ELWD and WNT coordinated the study and collected data. GWHY, JMYT, MYKM, WSY, CKW, and WFC participated in data collection. EYHC was principal investigator and contributed to all elements of the study. All authors contributed to revision of the paper and have seen and approved the final version.

Conflict of interest

EYHC has participated in paid advisory board for Otsuka, has received educational grant support from Janssen-Cilag, and has received research funding from AstraZeneca, Janssen-Cilag, Pfizer, Eli Lilly, Sanofi-Aventis, and Otsuka. All other authors declare that they do not have any conflicts of interest.

Acknowledgements

The authors would like to thank all the patients for participating in the study.

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