The continuing story of schizophrenia and schizoaffective disorder: One condition or two?

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ARTICLE INFO

Keywords:
- Schizophrenia
- Psychotic disorders
- Cognition
- Cognitive impairment
- Cerebral cortex

ABSTRACT

Although schizophrenia and schizoaffective disorder remain separable in diagnostic systems, the validity of the distinction is uncertain. This study asked whether schizophrenia and schizoaffective disorder are distinguishable on selected cognitive, social cognitive and structural social brain measures. Outpatients with a diagnosis of schizophrenia (n = 44) or schizoaffective disorder (n = 29) and non-psychiatric control participants (n = 62) were studied. Patients were assessed clinically (Positive and Negative Syndrome Scale) and all participants were administered a battery of cognitive (MATRICS Consensus Cognitive Battery; Wechsler Abbreviated Scale of Intelligence, Wide Range Achievement Reading) and social cognitive (Reading the Mind in the Eyes, Mayer-Salovey-Caruso Emotional Intelligence Test; MSCEIT) tasks. In addition, participants underwent structural magnetic resonance imaging (MRI) to yield cortical thickness data for 42 regions associated with the social brain network. Results showed no significant differences between patient groups on 17/18 cognitive/social cognitive and social brain cortical thickness measures. In contrast, schizophrenia and schizoaffective disorder patients differed from controls on 16/18 and 11/18 measures respectively. Schizoaffective disorder patients outperformed schizophrenia patients on an emotion regulation task (MSCEIT). Schizophrenia and schizoaffective disorder are largely indistinguishable on key cognitive, social cognitive and neural measures. The continuing separation of these syndromes in diagnostic systems and disease models requires further attention.

1. Introduction

It has been long debated whether schizophrenia and schizoaffective disorder represent a single disorder or two distinct conditions (Cheniaux et al., 2008; Malhi et al., 2008). These syndromes share psychotic symptoms, but schizoaffective disorder involves a concurrent mood disorder and does not require evidence of a decline in role functioning. Schizoaffective disorder was retained as a separate diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) and in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (World Health Organization, 1992). However, its validity as a distinct form of psychotic illness remains in question (Kempf et al., 2005; Lake and Hurwitz, 2007). Cognitive performance may provide a way of “carving nature at its joints” within the schizophrenia spectrum and is of key importance in relation to functional outcome (Lepage et al., 2014) and the search for candidate endophenotypes of psychosis (Gur et al., 2007). A series of studies have found significantly more cognitive impairment in schizophrenia than in schizoaffective disorder (Bornstein et al., 1990; Goldstein et al., 2005; Gruber et al., 2006; Heinrichs et al., 2008; Hill et al., 2013; Lindenmayer et al., 1989; Maj, 1986; Stip et al., 2005; Torniainen et al., 2012), but many others report minimal or no differences between these groups (Amann et al., 2012; Beatty et al., 1993; Evans et al., 1999; Fiszdon et al., 2007; Gilvarry et al., 2001; Glahn et al., 2006; Gooding and Tallent, 2002; Hooper et al., 2010; Manschreck et al., 1997; Miller et al., 1996; Moses, 1984; Ovosuo et al., 2013; Pinna et al., 2014; Reichenberg et al., 2009; Roofeh et al., 2006; Savage et al., 2003; Silverstein et al., 1988; Szoke et al., 2008; Townsend et al., 2001). Patients with schizoaffective disorder exhibit a pattern of cognitive impairment that is similar to the findings obtained in patients with schizophrenia, but distinct from those with major depression and bipolar disorder (Abrams et al., 2008; Buchanan et al., 2005; Madre et al., 2016). A meta-analysis concluded that cognitive data failed to support performance differences between patients with schizophrenia and schizoaffective disorder (Bora et al., 2009). Social cognition and its correlated neural circuits have emerged recently as a biobehavioural domain that is distinct from emotionally...
“cold” standard cognitive performance (Mehta et al., 2013). This domain may provide new insights and incremental validity in predicting functional outcome (Couture et al., 2006) and inform the search for more refined behavioural endophenotypes of psychosis (Gur et al., 2007). Components of social cognition include emotion perception and regulation and “theory of mind,” or the ability to imagine the psychological states and experiences of others (Green et al., 2015). The small relevant literature is inconsistent, with some reports that schizoaffective disorder patients outperform those with schizophrenia on theory of mind tasks (Chen et al., 2012; Fiszdon et al., 2007; Tadmor et al., 2016). In contrast, other studies indicate no significant differences between groups in terms of theory of mind (Greig et al., 2004; Hooper et al., 2010) or emotion perception (Fiszdon et al., 2007). It is noteworthy that most studies assessed single rather than multiple domains of social cognition, excluded non-psychiatric control participants and failed to consider both social and non-social aspects of cognition.

Behavioural studies have been complemented by advances in social and affective neuroscience including the description and analysis of an intrinsic social brain network (SBN) (Dziura and Thompson, 2014). This network links a series of pre- and medial frontal and temporal - parietal lobe regions that appear to mediate social and emotional processing (Dziura and Thompson, 2014). Structural and functional magnetic resonance neuroimaging studies have shown that schizophrenia and schizoaffective disorder share cerebral gray and white matter reductions and altered activation patterns relative to control values (Madre et al., 2016). Regions most affected include several frontal, cingulate and temporal lobe structures implicated in the SBN (Isobe et al., 2016). However, it is not known whether SBN abnormalities occur preferentially or more severely in people with schizophrenia relative to schizoaffective disorder or whether they are common neurobiological features in patients with psychosis. If SBN abnormalities are shared, this would further undermine the validity of psychosis variants like schizophrenia and schizoaffective disorder.

We asked whether patients with diagnoses of schizophrenia and schizoaffective disorder differ significantly, and to what degree, on standard cognitive performance measures, and whether social cognition and cortical thickness in regions associated with the SBN show sensitivity to the diagnostic distinction. More specifically, a multivariate approach was adopted whereby the ability of these measures to recapitulate the diagnostic classification was examined. Differences between the two diagnostic groups were of primary interest, but comparison to demographically similar non-psychiatric control participants was also carried out. This was done to determine whether the two patient groups were cognitively impaired and demonstrated cortical thinning. The results should help clarify whether these two psychosis syndromes are behaviourally and neurobiologically separable and thereby help resolve the underlying issue of disease heterogeneity in the schizophrenia spectrum.

2. Materials and methods

2.1. Participants

The clinical sample comprised 73 male and female patients who met the following criteria: 1) diagnosis of schizophrenia (n = 44) or schizoaffective disorder (n = 29) confirmed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002); 2) outpatient status; 3) history free of developmental or learning disability; 4) age 18–65; 5) history free of neurological or endocrine disorder; and 6) no concurrent DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of substance use disorder. Participants in the non-psychiatric control group (n = 62) were screened for medical and psychiatric illness and history of substance abuse.

All participants were drawn from an earlier study of normal-range and impaired cognitive performance in schizophrenia. Accordingly, clinical participants were recruited from a variety of outpatient programs, but especially those with active and relatively demanding rehabilitation services focused on high-functioning patients (Heinrichs et al., 2015). Settings comprised three outpatient clinics in Hamilton, Ontario, Canada: the Cleghorn Early Intervention in Psychosis Program, the Hamilton Program for Schizophrenia, and the Community Schizophrenia Service affiliated with St. Joseph’s Healthcare. At the same time, a broad range of cognitive ability in the control sample was maximized by recruiting community participants through local newspaper and online classified advertisements, employment centers, and neighborhood organizations and agencies. Written informed consent was obtained from all participants and each received financial compensation for their time. This study was approved by the relevant institutional review boards in Hamilton and by York University in Toronto, Ontario, Canada.

2.2. Procedure and measures

2.2.1. Clinical and cognitive measures

Patients were administered the Structured Clinical Interview for DSM-IV-TR (SCID-I/II) (First et al., 2002) to confirm diagnosis. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 2000). Two indicators of functionality were used for patients based on information obtained from the Social and Psychiatric History Schedule (Psychiatric Rehabilitation Consultants (PRC), n.d.): employment status (full-time, part-time, volunteer or unemployed) and living status (independent or assisted).

All participants’ premorbid intelligence was estimated using the standardized score from the Word Reading subtest of the Wide Range Achievement Test - Fourth Edition (WRAT-4) (Wilkinson and Robertson, 2006). A prorated estimate of current intellectual ability was obtained from the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Cognitive function was also assessed among all participants using the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). The MCCB includes domain measures titled Working Memory, Attention, Verbal Learning, Processing Speed, Reasoning and Problem-Solving, Visual Learning and Social Cognition and yields a composite index of overall performance. However, 86% of the composite score variance is accounted for by three domain measures: Working Memory, Visual Learning, and Processing Speed (Georgiades et al., 2017). An abbreviated composite score index comprising an average of T scores obtained for these domains demonstrates excellent test-retest reliability (intraclass correlation = 0.86). This composite was used as an index of general, non-social cognition in the present study.

The Reading the Mind in the Eyes test (Baron-Cohen et al., 2001) (“Eyes test”) is a widely used theory of mind task that measures the ability to infer and discriminate emotions expressed in the eye region of the face. Participants scored one point for each correct response and total possible scores range from 0 to 36. Emotion perception and regulation was assessed with the Managing Emotions subtest from the Mayer–Salovey–Caruso Emotional Intelligence Test, Version 2.0 (MSCEIT) (Mayer et al., 2002). The ability to manage emotions is assessed by presenting a series of scenarios and asking the test-taker to identify the most adaptive ways to regulate or manage their own feelings (Emotion Management Task) and the feelings of others in these situations (Emotional Relationship Task). The MSCEIT also comprised the Social Cognition domain score in the MCCB but was analyzed separately as a social cognition index. All tests described were administered by trained graduate-level clinical psychology students and a research assistant.

2.2.2. MRI cortical thickness measurement

Participants underwent scanning with a 3.0 Tesla whole body short bore General Electric System MRI scanner with an 8-channel parallel receiver head coil at the Imaging Research Centre, St. Joseph’s Healthcare Hamilton. A T1-weighted axial anatomical scan was
acquired using a three-dimensional fast spoiled gradient recalled echo sequence with inversion recovery preparation. The anatomical image had 152 slices (2 mm thick with 1 mm overlap) with the following imaging parameters: time to repetition (TR)/echo time (TE) = 7.5/2.1 ms, TI = 450 ms, field of view (FOV) = 24 cm, matrix = 512 × 512, flip angle = 12°, receiver bandwidth (rBW) = ± 62.5 kHz, and number of excitations (NEX) = 1.

The T1-weighted images collected for each participant were pre-processed in order to segment the brain and to align cortical structures across the subjects using FreeSurfer automated image analysis (version 5.1.0; http://surfer.nmr.mgh.harvard.edu/). Each image was inspected to correct for motion and underwent spatial and intensity normalization and skull stripping. Cortical thickness was defined as the distance between pial surface to the gray/white matter border across 160,000 vertices in both cerebral hemispheres. Subsequently each image was visually inspected by trained inspectors blind to group assignment to correct inaccuracies. Once images passed inspection, high dimensional registration was used to map them onto a spherical atlas for increased inter-subject alignment accuracy. Surface maps were smoothed with a 15 mm full-width-half-maximum Gaussian kernel.

Cortical parcellations were obtained for regions of interest (ROIs) using the methods described by Destrieux and colleagues in Freesurfer (Destrieux et al., 2010). The Destrieux atlas involves bilateral hemispheric parcellation of both gyral and sulcal structures. A total of 21 ROIs in each cerebral hemisphere were chosen for analysis based on their inclusion in the SBN as described in recent research (Dziura and Thompson, 2014; Grossmann, 2013; Lavin et al., 2013; Lewis et al., 2011). A visual representation of these brain regions is provided in Fig. 1.

### 2.2.3. Statistical analysis

One-way analysis of variance (ANOVA) and frequency/cross-tabulation analyses were used to compare groups on continuous and categorical demographic and clinical variables respectively. Multivariate analysis of variance (MANOVA) was carried out on the cognitive/social cognitive and cortical thickness data depending on satisfaction of required assumptions. These included non-significant covariance matrix (Box’s test) and error variance (Levene tests) inequality across groups. Overall group comparisons were followed by Bonferroni-corrected pairwise group comparisons on individual variables. If MANOVA assumptions were not met, transformations were considered along with non-parametric ANOVA and independent groups tests (Kruskal-Wallis, Mann-Whitney). Discriminant function analysis was applied to the data to test the ability of cognitive/social cognitive performance and social brain-related cortical thickness to recapitulate and hence validate the diagnostic groups. This technique builds linear functions of continuous variables that discriminate maximally the categorical grouping variable. Given the relatively large number of variables relative to sample size and to ensure statistical economy, decision rules were applied to limit redundancy and unnecessary testing.

### 3. Results

#### 3.1. Demographic and clinical characteristics

Table 1 provides demographic information for the three study groups and clinical statistics for patients. One-way analysis of variance (ANOVA) and frequency analysis (chi-squared) showed that the three groups did not differ significantly in terms of age, gender distribution, years of education or first language. The two patient groups did not differ significantly in the proportion taking first versus second generation anti-psychotic medication, benzodiazepines or mood stabilizers. The differing frequencies of anti-Parkinsonian medication approached (P = .1) but did not reach significance. Mean daily doses of the three most commonly prescribed anti-psychotic medications did not differ between patient groups (risperidone: t(61) = 1.32, P = .19; olanzapine: t(60) = −0.50, P = .62; clozapine: t(62) = 1.12, P = .27). The patient groups also did not differ significantly in the severity and duration of illness as indexed by the number of years since psychotic symptom onset or hospitalizations. Similarly, there were no differences in the severity of positive or negative symptoms and general psychopathology. However, schizoaffective disorder patients showed elevated depression scores relative to schizophrenia patients. The PANSS data suggest low-average symptom severity relative to the original normative validation study (Dziura and Thompson, 2014). In addition, a lower proportion of schizophrenia patients were living independently, although there were no significant differences in frequency of employment.

### 3.2. Cognition and social cognition

Assumptions of MANOVA were examined and upheld. The findings with respect to 11 cognitive/social cognitive performance indicators are presented in Table 2. The omnibus MANOVA showed a significant main effect of group (Λ = 0.59, F(20, 246) = 3.77, P < .001). Follow-up ANOVA indicated that the groups differed significantly on 9 measures including the MCCB composite, Processing Speed, Attention/Vigilance, Verbal Learning, Visual Learning and Reasoning/Problem

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**Fig. 1.** Social brain regions. Left: lateral and medial cortical regions associated with social network; middle and right: significant social network sub-region thinning in patient groups relative to controls after correction.
Solving domains. In addition, main effects of group were found for the MSCEIT (managing emotions), Reading the Mind in the Eyes test (theory of mind) and the WRAT-4 reading task, but not for WASI IQ.

Post-hoc multiple comparisons adjusted with Bonferroni correction were carried out for each significant overall univariate F ratio. Findings revealed lower scores in schizophrenia patients relative to schizoaffective patients on one task: MSCEIT Managing Emotions ($t(71) = 2.60, P < .01$), Processing Speed ($t(89) = −4.89, P < .01$), Verbal Learning ($t(89) = −3.26, P < .05$), Visual Learning ($t(89) = −3.02, P < .05$) and Reasoning/Problem-Solving ($t(89) = 4.03, P < .01$) domains.

A discriminant function analysis including the 9 cognitive/social cognitive variables with significant univariate F ratios yielded two functions. The first explained 79.2% of the variance in group means, while the second explained 20.8%. In combination these functions significantly differentiated the groups ($Λ = 0.62, χ^2(18) = 60.57, P < .001$). However, on removal of the first function the second was only marginally significant on its own ($Λ = 0.90, χ^2(8) = 13.96, P = .08$). The tasks that differentiated the control group from the two diagnostic groups and correlated highly with the first function were the MCCB composite ($r = 0.60$), Reasoning/Problem-Solving ($r = 0.75$),

| Table 1 | Demographic, clinical and functional characteristics of diagnostic and comparison groups. |
|---------|--------------------------------------------------------------------------------------------------|
| Age (years) (SD) | Schizophrenia (n = 44) | Schizoaffective (n = 29) | Comparison (n = 62) | Statistic |
| 41.07 (11.75) | 41.97 (8.36) | 38.89 (11.55) | 0.95* |
| Education (years) (SD) | 12.81 (1.97) | 13.03 (2.54) | 12.53 (2.22) | 0.55* |
| Sex (% male) | 64 | 55 | 62 | 0.56* |
| First language (% English) | 89 | 96 | 94 | 1.78 |
| Antipsychotic medication | 2nd generation (%) | 66 | 76 |  |
| 1st generation (%) | 16 | 14 |  |
| Gogebits (%) | 8 | 23 |  | 2.79* |
| Benzodiazepines (%) | 89 | 46 |  |
| Mood stabilizers (%) | 10 | 19 |  | 0.97 |
| Length of illness (years) (SD) | 18.22 (11.67) | 16.19 (8.29) |  | 0.80 |
| Hospitalizations, mean (SD) | 4.90 (7.04) | 5.07 (7.72) |  | −0.10 |
| PANSS T scores | M(CORB) | 35.43 (10.37) | 35.14 (9.87) | 43.35 (10.38) | 10.9 | .001 |
| MCCB composite (T score) | M(CORB) | 35.14 (8.87) | 35.14 (9.87) | 43.35 (10.38) | 10.9 | .001 |
| MCCB processing speed (T score) | M(CORB) | 35.14 (11.85) | 33.86 (9.11) | 45.48 (12.77) | 14.34 | .001 |
| MCCB attention/vigilance (T score) | M(CORB) | 34.57 (13.42) | 35.76 (12.32) | 42.52 (1.71) | 4.93 | .001 |
| MCCB working memory (T score) | M(CORB) | 38.25 (12.20) | 37.93 (12.88) | 43.81 (12.35) | 3.52 | >.05 |
| MCCB verbal learning (T score) | M(CORB) | 36.52 (9.88) | 37.76 (9.40) | 45.14 (10.31) | 11.20 | <.05 |
| MCCB visual learning (T score) | M(CORB) | 32.91 (12.79) | 33.62 (12.27) | 40.77 (10.64) | 7.61 | <.05 |
| MCCB reasoning (T score) | M(CORB) | 41.43 (9.42) | 41.00 (9.14) | 50.52 (9.42) | 16.40 | <.001 |
| MCCB reasoning (T score) | M(CORB) | 41.43 (9.42) | 41.00 (9.14) | 50.52 (9.42) | 16.40 | <.001 |
| MSCEIT managing emotions (correct/36) | M(CORB) | 36.66 (10.86) | 44.31 (12.96) | 45.76 (12.90) | 7.47 | .001 |
| Reading the mind in the eyes (correct/36) | M(CORB) | 36.66 (10.86) | 44.31 (12.96) | 45.76 (12.90) | 7.47 | .001 |
| WASI IQ | M(CORB) | 93.59 (21.18) | 100.72 (20.77) | 101.56 (20.33) | 2.07 | .130 |
| WRAT-4 reading (standard score) | M(CORB) | 88.55 (11.34) | 94.69 (10.55) | 95.27 (11.99) | 4.85 | .001 |

Note. PANSS, Positive and Negative Syndrome Scale; SPHS, Social and Psychiatric History Schedule.

* F test from one-way ANOVA (non-significant).
* Chi-squared test (non-significant).
* t Test (non-significant).
* t Test (P < .05).
* Chi-squared test (P < .05).
* Medication data based on 37 schizophrenia and 26 schizoaffective disorder patients.
* Medication data based on 37 schizophrenia and 26 schizoaffective disorder patients.

| Table 2 | Cognitive/social cognitive and neural comparisons of diagnostic and comparison groups. |
|---------|--------------------------------------------------------------------------------------------------|
| Measures | Schizophrenia (n = 44) | Schizoaffective (n = 29) | Comparison (n = 62) | P (2,132) | P-value |
| MCCB composite (T score) | 35.43 (10.37) | 35.14 (8.87) | 43.35 (10.38) | 10.9 | <.001 |
| MCCB processing speed (T score) | 35.14 (11.85) | 33.86 (9.11) | 45.48 (12.77) | 14.34 | <.001 |
| MCCB attention/vigilance (T score) | 34.57 (13.42) | 36.48 (12.32) | 42.52 (1.71) | 4.93 | <.01 |
| MCCB working memory (T score) | 38.25 (12.20) | 37.93 (12.88) | 43.81 (12.35) | 3.52 | >.05 |
| MCCB verbal learning (T score) | 36.52 (9.88) | 37.76 (9.40) | 45.14 (10.31) | 11.20 | <.001 |
| MCCB visual learning (T score) | 32.91 (12.79) | 33.62 (12.27) | 40.77 (10.64) | 7.61 | <.05 |
| MCCB reasoning (T score) | 41.43 (9.42) | 41.00 (9.14) | 50.52 (9.42) | 16.40 | <.001 |
| MSCEIT managing emotions | 36.66 (10.86) | 44.31 (12.96) | 45.76 (12.90) | 7.47 | .001 |
| Reading the mind in the eyes (correct/36) | 21.20 (5.41) | 22.93 (4.57) | 25.23 (5.35) | 7.81 | <.05 |
| WASI IQ | 93.59 (21.18) | 100.72 (20.77) | 101.56 (20.33) | 2.07 | .130 |
| WRAT-4 reading (standard score) | 88.55 (11.34) | 94.69 (10.55) | 95.27 (11.99) | 4.85 | .001 |

Note. MCCB, MATRICS Consensus Cognitive Battery; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; WASI, Wechsler Abbreviated Scale of Intelligence; WRAT-4, Wide Range Achievement Test - Fourth Edition.

* Significantly different from schizophrenia patients.
* Significantly different from schizoaffective patients.
Processing Speed ($r = 0.70$), Verbal Learning ($r = 0.62$), Visual Learning ($r = 0.51$) and Attention/Vigilance ($r = 0.41$) domain scores as well as the Reading the Mind in the Eyes task ($r = 0.50$). The MSCET Managing Emotions ($r = 0.61$) and WRAT-4 Reading ($r = 0.53$) scores contributed to the smaller second function. Classification results revealed that these measures achieved jointly an overall accuracy of 57.0%. The cognitive/social cognitive variables correctly classified 50.0% of the schizophrenia patients, but 29.5% were incorrectly classified as having schizoaffective disorder and 20.5% as control participants. The accuracy for the schizoaffective disorder group was 55.3%, with 20.7% misclassified as schizophrenia patients and 24.1% as control group participants. Finally, 62.9% of participants in the control group were correctly classified, with 24.2% misclassified as having schizophrenia and 12.9% as having schizoaffective disorder.

### 3.3. Cortical thickness

Parametric analysis of variance procedures using all 42 social brain regional thickness values were not feasible due to a significant Box’s M (1993.12, F (903, 26,008) = 1.20, $P < .001$) indicating unequal covariance matrices across groups/variables, and a significant Levene tests for variance inequality. Common transformations (e.g., log, square root, reciprocal) did not alter the variance results. Therefore, a series of non-parametric (Kruskal-Wallis) ANOVAs were carried out. Following Bonferroni correction, 6 regional variables remained significant across patient and control groups (Table 3). Pair-wise comparisons (Mann-Whitney U test) revealed no significant differences between schizophrenia and schizoaffective patients on any of these regions. However, schizophrenia patients and control participants differed on all six regional cortical thickness measures and schizoaffective patients and controls differed on 5/6 comparisons.

A SBN composite value that satisfied multivariate distribution and variance assumptions was created by averaging across the 6 significant regional thickness values identified by non-parametric analysis. This allowed for discriminant function analysis to assess classification accuracy with the SBN variable added to the 9 cognitive/social cognitive performance indicators, reading-based estimates of premorbid ability and aspects of social cognition, including theory of mind (Hooper et al., 2010; Reichenberg et al., 2009) as well as aspects of brain structure and physiology (Madre et al., 2016) all fail to distinguish clearly these syndromes.

Nevertheless, it is noteworthy that schizoaffective disorder patients outperformed those with schizophrenia on an emotion regulation task, scoring in the average range and close to control values. Recent evidence suggests that most patients with mood disorder perform normally on emotional intelligence tasks in contrast with the impairment observed in schizophrenia (Frajo-Apor et al., 2016). Perhaps mood disturbance enhances cognitive aspects of emotion processing and makes affect regulation salient and subject to awareness in a way that is less likely to occur in non-affective psychosis. In partial support of this idea, our data showed elevated symptoms of depression in the schizoaffective disorder group relative to schizophrenia patients, implying mood disturbance as a significant aspect of clinical status at the time of testing. However, mood-related group differences are not surprising in light of the diagnostic criteria for schizoaffective disorder. Hence social cognitive performance in the schizophrenia spectrum requires additional study, especially in terms of affect regulation, because schizoaffective patients’ relative proficiency may not include theory of mind and emotion perception.

Diffuse cortical thinning is characteristic of schizophrenia and here we extend this finding to show that thickness values in several medial (posterior cingulate) and temporal (superior sulcus) regions specifically associated with social processing are reduced significantly relative to those with schizophrenia. Multivariate classification analysis using the study measures demonstrated generally weak discrimination between patient groups, with better, but still modest discrimination relative to control participants. Therefore, in view of our results, the continuing diagnostic and clinical separation of these essentially overlapping syndromes is difficult to justify. The results suggest that the broad cognitive impairment regarded as intrinsic to schizophrenia also occurs in patients with psychosis who have a co-existing mood disturbance. Similarly, structural brain deficiencies in several socially-relevant regions appear to be shared across diagnoses, possibly reflecting a common underlying pathology in psychotic patients. Our data are consistent with and extend a substantial body of literature, including meta-analyses, showing that overall impairment rates, composite performance indicators, reading-based estimates of premorbid ability and aspects of social cognition, including theory of mind (Hooper et al., 2010; Reichenberg et al., 2009) as well as aspects of brain structure and physiology (Madre et al., 2016) all fail to distinguish clearly these syndromes.

Table 3: Regional cortical thickness (mm) in diagnostic and control groups.

| Region                          | Schizophrenia (n = 44) M(SD) | Schizoaffective (n = 29) M(SD) | Control (n = 62) M(SD) | Kruskal-Wallis/F P |
|---------------------------------|------------------------------|------------------------------|------------------------|-------------------|
| Left posterior cingulate gyrus  | 2.99 (0.22)*                 | 2.96 (0.22)*                 | 3.14 (0.20)           | < .001            |
| Left posterior ventral cingulate gyrus | 2.39 (0.36)*                 | 2.44 (0.34)*                 | 2.64 (0.33)           | < .001            |
| Left lateral fusiform gyrus     | 2.64 (0.23)*                 | 2.70 (0.16)                  | 2.83 (0.24)           | .001              |
| Left superior temporal sulcus   | 2.31 (0.19)*                 | 2.33 (0.14)*                 | 2.46 (0.15)           | < .001            |
| Right posterior cingulate gyrus | 2.97 (0.25)*                 | 2.93 (0.19)                  | 3.14 (0.23)           | < .001            |
| Right superior temporal sulcus  | 2.40 (0.24)*                 | 2.43 (0.14)*                 | 2.52 (0.20)           | < .001            |
| Social brain average            | 2.61 (0.19)                  | 2.63 (0.14)*                 | 2.78 (0.15)           | < .001            |

* Mann-Whitney test significantly different from control group ($P < .05$).
* t-Test significantly different from control group ($P < .001$).
* $F(2, 132) = 18.72$. 

4. Discussion

The findings of this study indicate that patients with schizophrenia and schizoaffective disorder are largely indistinguishable in terms of overall cognitive performance and a specific social cognition measure, as well as in relation to brain network structures relevant to social processing and behaviour. The single exception was a finding of more proficient emotion regulation in schizoaffective disorder patients relative to those with schizophrenia. Multivariate classification analysis using the study measures demonstrated generally weak discrimination between patient groups, with better, but still modest discrimination relative to control participants. Therefore, in view of our results, the continuing diagnostic and clinical separation of these essentially overlapping syndromes is difficult to justify. The results suggest that the broad cognitive impairment regarded as intrinsic to schizophrenia also occurs in patients with psychosis who have a co-existing mood disturbance. Similarly, structural brain deficiencies in several socially-relevant regions appear to be shared across diagnoses, possibly reflecting a common underlying pathology in psychotic patients. Our data are consistent with and extend a substantial body of literature, including meta-analyses, showing that overall impairment rates, composite performance indicators, reading-based estimates of premorbid ability and aspects of social cognition, including theory of mind (Hooper et al., 2010; Reichenberg et al., 2009) as well as aspects of brain structure and physiology (Madre et al., 2016) all fail to distinguish clearly these syndromes.
thinning in social brain regions is a shared neurobiological characteristic within the schizophrenia spectrum (Watsky et al., 2016). However, the present study did not include functional brain imaging measures of regional metabolism, blood flow or connectivity data. Nevertheless, the absence of neurobiological and cognitive validation reported in several studies and across imaging modalities (Madre et al., 2016) makes it difficult to maintain that separable disease processes underpin mood-based distinctions between psychotic disorders. This kind of differential validation continues to be a challenge in terms of many mental illnesses. Nevertheless, it is noteworthy that relatively high accuracy in recapitulating standard psychiatric syndromes has been achieved with some algorithms. Thus, classification rates up to 80% have been reported in relation to schizophrenia and depression using fronto-temporo-limbic MRI volumetric data (Koutoulieris et al., 2015). However, and consistent with our own data, recent biotyping has failed to validate schizoaffective disorder as a syndrome that is separable from schizophrenia within the psychosis spectrum (Clementz et al., 2016).

Additional limitations to the current study should be noted. Patient sample sizes were relatively small and may have restricted our ability to detect group differences by limiting statistical power. The relative modesty of our sample sizes was a further reason for utilizing an efficient cognitive battery sensitive to psychotic illness and for focusing on a subset of cortical regions, as an exhaustive representation would have been under-powered. Moreover, the relatively small patient sample size and inclusion of patients only from outpatient settings limits the generalizability of our findings to other settings (e.g. inpatient) or phases of the illness (e.g. prodromal, residual). Our study did not include a breakdown of depressive versus bipolar types within the schizoaffective group. Elevated depression scores and the relative infrequency of mood stabilizing medication imply predominance of the depressive type. In addition, patients with bipolar disorder were not included and thus the study could not address whether the same pattern of cognitive and social cognitive and neural deficit holds true across the schizophrenia-bipolar disorder continuum. In addition, it should be noted that diagnostic criteria for schizoaffective disorder changed with the introduction of DSM 5, which requires the presence of a major mood episode for the majority of the total duration of the active and residual portions of the illness (American Psychiatric Association, 2013). This means that our study data and previous findings may not apply fully to patients meeting new diagnostic requirements.

In conclusion, the present data reveal extensive overlap between patients with schizoaffective disorder and schizophrenia across demographic, symptomatic, cognitive and social cognitive functioning as well as in socially relevant brain network structures. These results do not undermine the clinical importance of mood disorder in the schizophrenia spectrum, but do support further critical analysis of the scientific value of traditional diagnostic distinctions and the possible amalgamation of psychosis syndromes.

Role of the funding source
The Canadian Institutes of Health Research provided financial support for the research and had no further role in the manuscript.

Contributors
Dr. Hartman managed the literature search, undertook the majority of the statistical analysis and wrote the majority of the manuscript. Dr. Heinrichs designed the study, wrote the protocol and also contributed to a significant portion of the literature search and statistical analysis. Ms. Farzaneh contributed to the literature search and statistical analysis of cortical thickness data. All authors contributed to and have approved the final manuscript.

Conflict of interest
The authors have no conflict of interest to declare.

Acknowledgement
We thank participating clinical sites and staff at St. Joseph’s Healthcare Hamilton (Schizophrenia Outpatient and Ceghlor Early Intervention clinics), the Hamilton Program for Schizophrenia, Schizophrenia Services Ontario (Hamilton chapter), Path Employment Services and the Wellington Psychiatric Outreach Program. This work was supported by the Canadian Institutes of Health Research (FRN102753).
