**Lower speech connectedness linked to incidence of psychosis in people at clinical high risk**

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**Abstract**

*Background*:

Formal thought disorder is a cardinal feature of psychotic disorders, and is also evident in subtle forms before psychosis onset in individuals at clinical high-risk for psychosis (CHR-P). Assessing speech output or assessing expressive language with speech as the medium at this stage may be particularly useful in predicting later transition to psychosis.

*Method*:

Speech samples were acquired through administration of the Thought and Language Index (TLI) in 24 CHR-P participants, 16 people with first-episode psychosis (FEP) and 13 healthy controls. The CHR-P individuals were then followed clinically for a mean of 7 years (s.d. = 1.5) to determine if they transitioned to psychosis. Non-semantic speech graph analysis was used to assess the connectedness of transcribed speech in all groups.

*Results*:

Speech was significantly more disconnected in the FEP group than in both healthy controls (p < .01) and the CHR-P group (p < .05). Results remained significant when IQ was included as a covariate. Significant correlations were found between speech connectedness measures and scores on the TLI, a manual assessment of formal thought disorder. In the CHR-P group, lower scores on two measures of speech connectedness were associated with subsequent transition to psychosis (8 transitions, 16 non-transitions; p < .05).

*Conclusion*:

These findings support the utility and validity of speech graph analysis methods in characterizing speech connectedness in the early phases of psychosis. This approach has the potential to be developed into an automated, objective and time-efficient way of stratifying individuals at CHR-P according to level of psychosis risk.

Key words: psychosis, schizophrenia, thought disorder, graph analysis, speech, ultra high-risk (UHR)

**1. Introduction**

Formal thought disorder (FTD) is a core feature of psychosis. Although originally conceptualized as being specific to schizophrenia, it can also occur in affective psychoses, non-psychotic illnesses and even in healthy controls, especially when provoked by ambiguous cues (Andreasen, 1979; Andreasen & Grove, 1986; McGuire et al, 1998; Kircher et al, 2001). Formal thought disorder appears to fall within a separate symptom dimension to positive and negative symptoms (Liddle 1987; Demjaha et al., 2009) and is unlikely to be unitary, with several different domains identified in studies employing factor analysis (Cuesta & Peralta, 1999; Roche et al., 2015a, 2015b). In patients with psychotic disorders, FTD is associated with poorer clinical status (Andreasen & Grove, 1986), reduced quality of life (Breier & Berg, 1999), an increase in the frequency and duration of hospital admission (Harrow & Marengo, 1986; Lenz et al., 2010; Wilcox et al., 2012), and reduced levels of employment and social functioning (Harrow & Marengo, 1986).

Recent research indicates that FTD is also present in an attenuated form in the clinical high-risk state for psychosis (CHR-P). These individuals can be identified using semi-structured clinical interviews such as the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 2005) or the Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2003). Around 20% of people with a CHR-P will develop a psychotic disorder within 2 years of presentation (Fusar-Poli et al., 2012, 2016). However, it is difficult to predict on clinical grounds which individuals will subsequently transition to psychosis and which will not. As a result, there is enormous interest in identifying biomarkers that may help predict clinical outcomes in this group (McGuire et al., 2015).

Given that formal thought disorder is linked to relatively poor clinical and functional outcomes in patients with psychosis, its presence in the CHR-P state might be associated with poor outcomes, particularly the onset of psychosis. Recent evidence indicates that higher scores on measures of thought disorder in CHR-P individuals are associated with later transition to psychosis (Bearden et al., 2011; DeVylder et al., 2014; Demjaha et al., 2012, 2017; Perkins et al., 2015). In a seminal study, Bearden and colleagues coded speech transcripts for FTD and linguistic cohesion. They found that both illogical thinking (positive FTD) and poverty of content of speech (negative FTD) predicted transition to psychosis amongst CHR-P participants (Bearden et al., 2011). Similarly, Demjaha and colleagues found that Thought and Language Index (TLI; Liddle et al., 2002) scores were higher in CHR-P patients compared with healthy controls. Although the TLI score alone was not associated with later transition, combining the negative component of the TLI score with attenuated and basic symptoms was linked with a higher incidence of psychosis during follow up (Demjaha et al., 2017).

Some of the challenges with using measures like the TLI are that they are time consuming, need extensive rater training and require subjective decisions to be made on a range of specific speech abnormalities that are present in passages of text. In recent years the availability of automated, objective measures of speech has provided a way to reduce these logistical demands. Analyses of the semantic coherence of speech using this approach has been associated with later transition to psychosis in CHR-P individuals (Elvevåg et al., 2007; Bedi et al., 2015; Corcoran et al., 2018; see Table 1 for a summary of current approaches to studying speech coherence in psychosis).

Given that semantic analysis relies on a large corpus of the language, its generalization to other linguistic and cultural settings is not trivial. Avoiding this limitation, another methodology was developed by representing spontaneous oral language as non-semantic word graphs. The idea behind this method is to characterize formal thought disorder by assessing topological changes in spontaneous word trajectories ([Mota et al., 2012, 2014](#_ENREF_3)). The initial studies in chronic psychosis patients applied graph analysis to speech samples from people with schizophrenia and bipolar disorder (Mota et al., 2012, 2014). Here, words are represented as nodes and the temporal connections between words are represented as edges. Speech connectedness measures such as the number of links or edges, the number of nodes in the largest connected component (LCC, in which all the pairs of nodes have a path) and the amount of nodes in the largest strongly connected component (LSC, in which all the pairs of nodes are linked and mutually reachable in both directions) can be generated as measures of how disorganized speech is, showing reliable differences between the speech of people with chronic schizophrenia, bipolar disorder, and healthy controls, allowing for quantitative and automated classification of schizophrenia with an accuracy higher than 90% (Mota et al., 2012, 2014). Even in first episode psychosis (FEP) patients, analysis based on 30 seconds oral reports collected in the first clinical interview was predictive of a future diagnosis of schizophrenia six months later (Mota et al., 2017). Moreover, representing word trajectories as graphs allow us not only to calculate the actual connectedness attributes but also to estimate how this could be achieved by chance comparing the original graph with randoms graphs modeled by shuffling the same set of words N times (Mota et al., 2017). At the early stages of the schizophrenia disorder, the comparison with random graphs distinguished the groups: as in schizophrenia group, 64% of participants produced oral reports as connected as random graphs modeled with the same original set of words, in the control group it occurred in 5% (Mota et al., 2017).

Importantly, in chronic and FEP patients, connectedness attributes were correlated with negative symptomatology severity (Mota et al., 2014; Mota et al., 2017), evidential by an R2 of 0.88 in FEP patients ([Mota et al., 2017](#_ENREF_2)). Moreover, also in typical children (6 to 8 years old), the same connectedness attributes that decrease according to negative symptoms severity increased according to better performance on intelligence quotient (IQ), the theory of mind abilities, reading tests ([Mota et al., 2016](#_ENREF_6)), and also exclusively with verbal short-term memory performance (Mota et al., 2019). This relationship between oral speech connectedness and development was better explained by educational level than by age for subjects without psychotic symptoms, but participants suffering from psychotic symptoms seem to be resistant to educational effects ([Mota et al., 2018](#_ENREF_4)).

As these previous studies were conducted in Brazil, using Portuguese oral reports, even considering that the method does not rely on a linguistic corpus of semantic relationship, syntactic differences between languages could impair the results. Automatic translation of original reports for 4 languages (Spanish, English, French, and German) preserved the classification accuracy (Mota et al., 2014). Furthermore, speech connectedness attributes applied to native English participants replicated connectedness differences between schizophrenia and bipolar disorder diagnosis, and the same attributes were correlated with social/functional outcomes, cognitive performance and psychometric evaluations of thought disorder, as well to brain dysconnectivity measured at resting state using functional MRI (Palaniyappan et al., 2019).

It is not yet clear whether graph analysis can detect the kind of subtle changes in expressive oral language that we see in people at CHR-P. The aim of the present study was to address this issue by testing whether measures of speech connectedness using graph analysis of speech samples differ between people with CHR-P, first episode psychosis (FEP), and healthy controls. We analyzed speech samples originally collected by Demjaha and colleagues (2017) using non-semantic graph analysis. We then tested whether there is an association between speech graph connectedness and measures of thought disorder estimated with the TLI. Finally we explored whether speech graph connectedness measures were associated with clinical and functional outcomes in the CHR-P group; specifically, whether reduced speech connectedness is associated with subsequent transition to psychosis.

\*\*\* TABLE 1 ABOUT HERE \*\*\*

**2. Methods**

*2.1. Participants*

People at CHR-P between the ages of 16 and 35 years were recruited from the Outreach and Support in South London (OASIS) service (Fusar-Poli et al., 2013). Participants were deemed eligible for the study if they met ultra-high risk criteria assessed with the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005). Transition to psychosis was defined as the onset of frank psychotic symptoms that did not resolve within a week. This corresponds to a severity scale score of 6 on Disorders of Thought Content subscale, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganized Speech subscales of the CAARMS.

People with FEP were recruited from the South London and Maudsley NHS Foundation Trust. Healthy controls with no previous or current history of psychiatric illness (as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders, First et al. 1997, and the Structured Clinical Interview for DSM-IV Personality Disorders, First et al. 1994) and no family history of psychosis, were recruited from the same geographical area by local advertisement and by approaching the social contacts of CHR-P individuals after receiving written permission. Healthy controls were matched to the CHR-P individuals and those with FEP for age and gender. Exclusion criteria for all groups comprised history of a neurological or medical disorder, history of head injury, or alcohol or illicit substance misuse or dependence. The mean chlorpromazine equivalent was calculated separately for antipsychotics. All participants were fluent in English and all apart from two were right handed. All participants gave written informed consent after receiving a complete description of the study. Ethical approval for the study was obtained from the Institute of Psychiatry Research Ethics Committee.

*2.2. Measures and procedure*

Clinical high-risk status was determined by the CAARMS12/2006 (Yung et al., 2005). Participants were required to meet one or more of the ultra high-risk criteria: (i) attenuated psychotic symptoms, (ii) brief limited intermittent psychotic symptoms, i.e. a brief psychotic episode that resolved within seven days without treatment or (iii) genetic risk and deterioration syndrome, a recent decline in function combined with family history of psychosis in first-degree relative, or a diagnosis of schizotypal personality disorder. Thought disorder was assessed by the TLI (Liddle et al., 2002). The TLI requires participants to speak for one minute describing each of eight standard stimuli from the Thematic Apperception Test (TAT; Murray, 1943) or ﻿Rorschach test (Rorschach, 1942), after which their speech is assessed for ﻿the occurrence of eight types of abnormality. In the present study to generate excerpts of speech, participants were presented with eight pictures from the TAT and were asked to talk about the picture for one minute. If the participant stopped talking during the minute they were prompted to continue by the experimenter. Speech samples were recorded and transcribed then scored on the TLI by a trained assessor (SW) who was blinded to participant group status.

Functioning was assessed by the Global Assessment of Functioning (GAF; American Psychiatric Association, 2000). The Wide Range Achievement Test (WRAT; Wilkinson & Robertson, 2006) was used to assess intelligence quotient (IQ). The positive and negative syndrome scale (PANSS; Kay et al., 1987) was used to measure positive and negative symptoms in the CHR-P and FEP patient groups. The primary clinical rating measures for the study were therefore the TLI, the PANSS and the WRAT.

*2.3. Speech graph analysis*

 Speech graph analysis follows the method described by Palaniyappan et al., 2019. Speech graphs were constructed from each subject’s one-minute transcribed speech describing each of eight pictures from the TAT that are used as standard stimuli in the TLI. Separate graphs were produced from each subject’s eight one-minute speech samples. The original transcriptions used for the TLI were edited before being entered into the SpeechGraphs software (<https://www.neuro.ufrn.br/softwares/speechgraphs>; Mota et al., 2012; 2017). Filled pauses, such as “um” or “er”, were included but unfilled pauses and researcher’s prompts were removed. Contractions were not expanded upon. A line return was used to indicate where a sentence was not associated with the previous sentences, for example when the researcher had to prompt the participant to continue describing the picture.

Each one-minute excerpt of speech was converted into a graph using SpeechGraphs software, such that each word corresponded to a node and the temporal links between words were represented by edges. This produced an unweighted directed graph for each word trajectory (see example in Figure 1). Two graph connectedness measures were generated: the largest connected component (LCC) and largest strongly connected component (LSC). The LCC is the total number of nodes within the graph’s largest connected component, where nodes are linked by at least one undirected path (ignoring the directions of edges). The LSC is the total number of nodes within the graph’s largest strongly connected component, where any two nodes are linked by a directed path, traversable in both directions (see Figure 1; Mota et al., 2014; 2017). Thus, LCC can be calculated from undirected graphs whereas LSC requires a directed graph. Connectedness measures were calculated for moving windows of 30 words, which overlapped by 15 words with consecutive windows, to control for differences in verbosity between participants. The connectedness measures were averaged across all windows to produce mean values for LCC and LSC. 100 random shuffles of the words within each window determined how close to randomness the connectedness measures were. The connectedness measures for all the random graphs for each window were averaged to produce mean random values for LCC and LSC. Both the original and random LCC and LSC mean values were averaged across all eight sets of speech data to generate mean original and random LCC and LSC for each participant. Finally, the ratio of mean original LCC and LSC to mean random LCC and LSC were calculated respectively to produce LCCr and LSCr for each subject. A subject whose speech had random links with little goal-directedness would have a LCCr close to one, for example the text: “*Um. It’s a mother her daughter. Well if it’s not her mom it’s her sister. Um. A girl, a little girl and a baby doll, um with her. And an old lady, maybe it’s her nanny, who’s reading her a book and the girl, maybe she’s daydreaming”* has an LCCr of 1.04. A subject with no referential ties within their speech, unclear use of pronouns or comparators or random words temporarily linked, would have a LSCr close to one, for example the text: “They’re sitting together. I see two eh two girls. Sitting on the sofa. One’s holding a baby. and um. One’s standing, looking towards something. Um. Someone them. On the left. A woman’s looking down at the baby. The other holding the baby. Looking sad. Why is she looking sad?” has an LSCr of 2.46 (Palaniyappan et al., 2019). Generation of the random graphs and connectedness measures took less than two seconds per minute of speech.

\*\*\* FIGURE 1 ABOUT HERE \*\*\*

*2.4. Statistical analysis*

 All statistical analysis was performed in SPSS version 25.0 (Chicago, Illinois, USA). Initial tests were run to explore homogeneity of variance and normality of variables. Levene’s test for homogeneity of variance was used to test for equal variance and the Shapiro-Wilk test was used to determine normality of variables. Speech graph connectedness (LCC, LSC, LCCr and LSCr) were not normally distributed so Kruskal-Wallis test was used to assess for significant differences in speech graph connectedness between the three groups. Non-parametric analysis of covariance using Quade’s method (Quade, 1967), was used to test for group differences in speech graph connectedness, controlling for the effects of IQ. Spearman’s rank-order correlations were used to assess associations between speech connectedness and both clinical ratings and TLI scores. Correlations that survived correction for multiple comparisons using false discovery rate (Benjamini-Hochberg, p<0.05) are reported. Speech graph connectedness were also ranked and one-way ANCOVAs were run on the ranks. In this way, one-way ANCOVA was used to test whether the individual positive and negative TLI measurements, and the PANSS negative measurement had significant effects on the relationship between group and individual speech graph measures, i.e. whether there would be changes in differences between any of the groups when the covariate was accounted for. There was significant multicollinearity between the TLI total and TLI positive scores, so TLI total was not included in this analysis. Pairwise comparisons were run to explore whether differences between specific groups changed when incorporating the TLI or PANSS negative symptom scores, with Bonferroni adjustment for multiple comparisons. Multinomial logistic regression was additionally used to investigate whether speech connectedness measures could predict group membership (healthy controls, CHR-P or FEP).

**3. Results**

 Complete TLI and speech graph measure data were available from 24 CHR, 16 FEP, and 13 healthy controls. Sociodemographic and clinical characteristics of the three groups are displayed in Table 2. Between-group differences were seen in IQ and education level, with higher values in the control group than either patient group. No between-group differences were found for age, gender or ethnicity. We examined participants’ clinical records to assess the clinical diagnoses given to those in the FEP group and those who transitioned to psychosis in the CHR-P group. The proportion of participants given a diagnosis of schizophrenia did not differ between the FEP group (0.615) and the CHR-P transition group (0.625). The proportion of affective psychoses also did not differ between the FEP group (0.38) and the CHR-P transition group (0.375). This means that any speech graph differences between FEP and CHR-P groups are not likely due to the preponderance of schizophrenia thought disorder in the FEP group versus a higher preponderance of risk of affective psychoses in the CHR-P group.

\*\*\* TABLE 2 ABOUT HERE \*\*\*

*3.1. Group differences in speech connectedness*

The Shapiro-Wilk test revealed that none of the speech graph connectedness measures were normally distributed: LCC (W=.91, p=.001); LSC (W= .88, p<.001); LCCr (W=.91, p= .001); LSCr (W=.91, p=.001) and Levene’s test revealed unequal variance between groups for all speech graph measures. Kruskal-Wallis tests showed significant differences between the three groups in terms of LCC (χ2(2)=11.81, p=.003 with large effect size, η2=.23), LCCr (χ2(2)=10.46, p=.005 with large effect size, η2=.20) and LSCr (χ2(2)=11.73, p=.003 with large effect size, η2=.23), but no significant difference in LSC (χ2(2)=5.53, p=.063 with moderate to large effect size, η2=11). Medians of all speech graph connectedness measures for each group and significant differences are displayed as raincloud plots (Allen et al., 2019) in Figure 2: speech connectedness was lowest in FEP patients and highest in controls, with that in CHR-P individuals in between. Pairwise comparisons (see Table S1) using Dunn-Bonferroni indicated that specifically, LCC, LCCr and LSCr were significantly lower in the FEP group than in the control group, each with a large effect size. LCC, LCCr and LSCr were also significantly lower in the FEP group than in the CHR-P group, with large, medium and large effect sizes, respectively. There were no significant differences in any of the measures between the CHR-P and control groups. Given that we found significant group differences in IQ and significant correlations between speech graph connectedness and IQ (see below), we tested for group differences in speech graph connectedness using non-parametric analysis of covariance (Quade, 1967), controlling for the effects of IQ. When adjusting for IQ there were still significant differences between the three groups in terms of LCC (F(2,50)=4.22, p=.02), LCCr (F(2,50)=3.27, p=.046) and LSCr (F(2,50)=3.29, p=.045). There were no statistically significant differences between groups when the same analyses were run for LSC (p>.8). [remains non-significant]

\*\*\* FIGURE 2 ABOUT HERE \*\*\*

*3.2. Correlations with clinical ratings and TLI scores*

For these analyses, in view of the small sample sizes, the FEP and CHR-P groups were combined in a single patient group. Spearman’s rank-order correlations between speech graph connectedness and clinical ratings and TLI scores are shown in Table 3. Within the combined patient group, LSC and LSCr were significantly correlated with total TLI score. LCC, LCCr and LSC were significantly associated with the TLI negative scores. No correlations between speech graph connectedness measures and PANSS total, PANSS positive or PANSS negative scores survived correction for multiple comparisons using false discovery rate. LSC and LSCr were significantly correlated with WRAT IQ (see Table 3; *rs* .52 and .466 respectively, p<0.01). However, there was no difference between the transition and non-transition groups on median IQ (112 versus 102; Mann-Whitney U=.238) or median years of education (13 versus 14; Mann-Whitney U=.528). There were no associations between speech graph connectedness measures and gender or ethnicity, but subject age was weakly correlated with LCC (*rs*=.348, p = .012) and with LCCr (*rs*=.372, p=.007). There were no significant correlations between speech connectedness measures and medication dose (rs all p > .60), or with level of functioning (GAF score) at baseline (rs all p>.107) and follow-up (rs all p>.076). Multicollinearity tests found no collinearity between TLI positive, TLI negative and PANSS negative scores (VIF<1.4). Significant correlations reported above survived correction for multiple comparisons using false discovery rate (Benjamini–Hochberg procedure, p<0.05; see Table 3).

\*\*\* TABLE 3 ABOUT HERE \*\*\*

*3.3. Effect of TLI scores on group differences*

 To explore group differences in speech graph connectedness measures after adjusting for TLI positive or TLI negative scores, we ran one-way ANCOVAs on the ranked dependent variables (LCC, LCCr, LSC and LSCr) with TLI positive or TLI negative scores as a covariate. We also included WRAT IQ as a covariate as well. One-way ANCOVAs revealed that after adjustment for TLI positive scores and WRAT IQ LCC (F(2,48)=4.92, p=.011), LCCr (F(2,48)=3.83, p=.029) and LSCr (F(2,48)=3.46, p=.039) were significantly lower in the FEP than CHR-P group. There were no statistically significant differences between groups when the same analyses were run for LSC (p>.9). One-way ANCOVAs revealed that after adjustment for TLI negative scores and WRAT IQ LCC (F(2,48)=3.21, p=.049) was significantly lower in the FEP than CHR-P group. There were no statistically significant differences between groups when the same analyses were run for LCCr (p>.1), LSC (p>.9) or LSCr (p>.09). All significant effects in these ANCOVAs were smaller compared with the effect sizes in the group comparisons with speech graph connectedness measures alone.

*3.4. Effect of negative symptoms on group differences*

 Given the importance of negative symptoms and negative thought disorder in clinical and functional outcomes in patients with psychosis, we assessed group differences in speech graph connectedness modeling PANSS negative symptoms and WRAT IQ as covariates. Due to missing PANSS data these tests were done on a reduced number of participants (14 CHR-P and 8 FEP). Ranked dependent variables (LCC, LCCr, LSC and LSCr) and PANSS negative symptom scores and WRAT IQ as covariates were used in one-way ANCOVAs. One-way ANCOVAs revealed that after adjustment for PANSS negative scores and WRAT IQ, there were no significant group differences for LSC (p=.374) and LSCr (p=.499), but that LCC (F(1,18)=5.91, p=.026) and LCCr (F(1,18)=5.49, p=.031) were significantly lower in the FEP than the CHR-P group.

*3.5. Speech connectedness is associated with subsequent transition to psychosis*

 Eight of the 24 (33.3%) CHR-P individuals developed a psychotic disorder subsequent to assessment. The Shapiro-Wilk test revealed that within the CHR-P group, all the speech connectedness attributes were normally distributed: LCC, W= .95, p=.228; LSC, W=.94, p = .159; LCCr, W=.98, p=.908; LSCr, W=.962, p=.473. Levene’s test revealed equal variance between groups for LSC (F=.02, p=.878) and LSCr (F=.53, p=.473) but unequal variance between groups for LCC (F=5.85, p=.024); LCCr (F=6.23, p=.021). For the measures with equal variance (LSC and LSCr) we used ANCOVA, while non-parametric ANCOVA (Quade’s method) were used for the measures with unequal variance (LCC and LCCr). In all cases, WRAT IQ was used as a covariate. ANCOVA revealed that both LSC and LSCr were reduced in the CHR-P subjects who later developed psychosis compared to those who did not after controlling for IQ (LSC, F(1,21)=6.97, p=.015; with an effect size partial η2=.249; LSCr, F(1,21)=10.8, p=.004; with an effect size partial η2=.34) . There were no significant differences in LCC or LCCr between transitioned and non-transitioned groups when controlling for IQ (LCC, p>.1; LCCr, p>.19). The median speech connectivity measures in the CHR-P group according to subsequent onset of psychosis are displayed as raincloud plots in Figure 3.

\*\*\* FIGURE 3 ABOUT HERE \*\*\*

*3.6. Speech connectedness is predictive of group membership*

Multinomial logistic regression showed three of the four speech connectedness measures predicted group membership (healthy controls, CHR-P or FEP) significantly better than chance (LCC, accuracy 56.0%, B(CHR-P)=0.93, SE(CHR-P)=0.44, B(FEP)=1.38, SE(FEP)=0.56, p=0.015; LCCr accuracy 50.0%, B(CHR-P)=34.54, SE(CHR-P)=18.91, B(FEP)=56.57, SE(FEP)=23.81, p=0.028; LSCr accuracy 51.9%, B(CHR-P)=1.78, SE(CHR-P)=0.78, B(FEP)=2.90, SE(FEP)=1.10, p=0.005). LSC did not significantly predict group membership better than chance (LSC accuracy 50.0%, B(CHR-P)=0.28 SE(CHR-P)=0.25, B(FEP)=0.76, SE(FEP)=0.34, p=0.053).

**4. Discussion**

 The results showed that automated and unbiased speech connectedness measures, estimated from non-semantic graph analysis of speech, were significantly lower in FEP patients than in healthy controls, with those in CHR-P patients at an intermediate level. Significant correlations were found between speech connectedness measures and scores on the TLI, a measure of the severity of formal thought disorder. The magnitude of the group differences was reduced by covarying for TLI measures, suggesting that these were related to group differences in the severity of formal thought disorder. Finally, CHR-P individuals who subsequently transitioned to psychosis had lower scores on two measures of speech connectedness (LSC and LSCr) than CHR-P individuals who did not develop psychosis, after controlling for effects of IQ.

 To our knowledge, this is the first study to assess speech using non-semantic speech graph analysis in CHR-P individuals and English speakers recently diagnosed with FEP. Previous work has examined speech connectedness in people with chronic schizophrenia or bipolar disorder (Mota et al., 2012; Mota et al., 2014; Palaniyappan et al., 2019), or in Portuguese speakers diagnosed with FEP (Mota et al., 2017). Our finding that speech graph connectedness measures are lower in people with FEP than both CHR-P individuals and controls is consistent with evidence that patients with FEP have lower scores on speech connectedness measures than controls (Mota et al., 2017). This is further strengthened by LCC, LCCr and LSCr significantly distinguishing between healthy controls, CHR-P and FEP, however this should be replicated in a larger sample. We did not find differences in speech graph connectedness measures between CHR-P individuals and healthy controls. This may reflect the high level of heterogeneity within the CHR-P population (Fusar-Poli et al., 2016). In particular, it is possible that alterations in speech connectedness are specific to the subgroup of CHR-P subjects that subsequently develops psychosis. This would be consistent with our finding that this subgroup had lower LSC and LSCr values than CHR-P subjects who did not become psychotic.

 The correlations between measures of speech graph connectedness and scores on the TLI provide evidence of concurrent validity for the speech graph analysis approach. The group differences in speech connectedness were diminished when we included TLI scores as a covariate, suggesting that these were at least partly driven by differences in thought disorder.

We found that CHR-P subjects who subsequently transitioned to psychosis had lower scores on LSC and LSCr than those who did not. This is consistent with reports that measures of semantic coherence (derived from latent semantic analysis) coupled with differences in syntax (e.g., reduced usage of possessive pronouns) may predict transition to psychosis in CHR-P subjects (Corcoran et al., 2018). Our findings suggest that speech graph analysis may also be useful as a means of stratifying this patient group, however this work will need replication and calculation of sensitivity, specificity, positive predictive value and negative predictive value with a larger sample. Speech graph analysis is quick and simple to administer and provides an automated and objective measure of thought disorder. However, while this work and previous research have built sufficient justification for the potential of speech connectivity measures as a clinical tool, it must be noted that more work needs to be done to produce a predictive model that can discriminate on an individual level, rather than at the group level previously shown (Mechelli et al., 2017; Fusar-Poli et al., 2018).

 The speech graph connectedness measures that we studied (LCC, LCCr, LSC and LSCr) were highly inter-correlated (rs ranged from .0327 to .964). Nevertheless, they may reflect different components of thought disorder. LCCr has been associated with random links and low goal directedness, as these features produce LCCr scores close to one (Palaniyappan et al., 2019). Supporting this suggestion is evidence that LCC and LCCr, but not LSCr, were significantly correlated with the TLI negative score, which includes weakening of goal and poverty of speech (Liddle et al., 2002). In contrast, LSCr may capture aspects of syntactic processing as reductions in referential ties produce LSCr scores close to one (Palaniyappan et al., 2019). The speech graph connectedness measures that we found to be associated with transition to psychosis were LSC and LSCr which may reflect a reduced use of referential ties; for example, a reduction in, or unclear use of pronouns or comparators, so that the listener is not clear to whom or to what the speaker is referring to. Previous work has shown that a reduction in referential cohesion, i.e. fewer references to objects, people or events previously introduced in discourse, was associated with transition to psychosis in adolescent CHR-P subjects (Bearden, et al.,, 2011).

 A limitation of the present study was the small sample size. This partly reflects the logistical demands associated with collecting and transcribing speech samples from patients. The study was conducted before the availability of digital technology and automated methods that now make it easier to collect speech data. It will be important to replicate the findings in larger samples of patients, and to use measures of thought disorder other than speech graph analysis, such as latent semantic analysis and syntactic analysis. Although there was no significant relationship between speech connectedness and the dose of antipsychotic medication, since 6 of the FEP group but only 4 of the

CHR-P patients (and non of the controls) were taking antipsychotics, we cannot exclude the possibility that the group differences between the FEP and the other groups were related to effects of treatment. However, this would not explain the correlations between TLI scores and the graph metrics, or the differences within the CHR-P group in relation to transition. A further caveat is that the FEP versus healthy controls and CHR-P group comparisons could be partially driven by group differences in IQ, given that we found significant correlations between speech graph connectedness measures and IQ as well as group differences between them. This supports previous findings that connectedness varies with both IQ in normal childhood development (Mota et al., 2016) and with educational level (Mota et al., 2018). However, the main findings of the study remained significant even when controlling for IQ as a covariate. We also did not find differences between IQ and years of education when we compared CHR-P participants who transitioned to psychosis with those who did not transition, meaning that differences in IQ and education are unlikely to be the reason for differences in speech connectedness measures for these comparisons.

 These findings may be informative for future research. It is important to replicate our results in a large multicenter study with a diverse population. Theoretically speech graph connectedness can differ between languages and different syntax so it would be useful to assess these measures in different languages using a common protocol. The approach used in this paper could also be applied to written output, given that thought disorder manifests in writing as well as speech output (Rezaii et al., 2019). Other future directions could include examining the acoustic and phonetic aspects of speech to see if they are important factors in determining transition to psychosis (Compton et al., 2018) and using neuroimaging to link speech graph measures to underlying brain mechanisms.

In conclusion, our data suggest that speech connectedness are lower in FEP patients than healthy controls and CHR-P patients, and are correlated with the severity of formal thought disorder. We also found evidence that in people at high risk of psychosis, lower speech connectedness was associated with an increased incidence of psychosis. These findings highlight the potential utility of speech analysis measures as an automated and objective measure of formal thought disorder, and in predicting clinical outcomes in individuals at CHR-P.

**Ethics statement**

 Ethical approval for the study was obtained from the Institute of Psychiatry Research Ethics Committee. This study was carried out in accordance with the Declaration of Helsinki. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

**Author contributions**

TJS and PM designed the study. TJS, BT, DO, NM, SEM and KD analyzed the data. TJS and BT wrote the first draft of the manuscript. AS, SW, DS, FD, LV, GR, AdM, PFP and PM contributed to the primary study that provided data for this analysis, including acquisition of funding, recruitment of participants, and/or collection of data. All authors contribute to the interpretation of results and to the manuscript.

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**Conflicts of interest statement**

 The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Table 1**. Current approaches to studying speech coherence in psychosis. LSA, latent semantic analysis; SZ, schizophrenia; CHR-P, clinical high-risk for psychosis.

|  |  |  |
| --- | --- | --- |
| Methods | Results | References |
| LSA- incoherence (grammatical and semantic inaccuracies) | Reduced semantic coherence predicted transition to psychosis in CHR-P individuals | (Bedi et al., 2015; Corcoran et al., 2018) |
| LSA- derailment (shifts among unrelated topics) | Reduced semantic coherence in SZ patients vs controls | (Bar et al., 2019) |
| LSA- tangentiality (irrelevant answer to question) | Reduced coherence in SZ patients vs controls, greatest in patients with formal thought disorder | (Elvevåg et al., 2007) |
| Referential coherence (ambiguous pronoun use) | Predictive feature for classifying patients with SZ vs controls. Reduced referential cohesion predicted transition to psychosis in CHR-P individuals | (Iter et al., 2018; Bearden et al., 2011) |
| Connectedness of speech graphs | Reduced connectedness in SZ and first episode psychosis patients vs controls. Reduced connectivity also predicted SZ diagnosis 6 months in advance | (Mota et al., 2014; 2017) |

**Table 2**. Sociodemographics and clinical characteristics of first episode psychosis (FEP), clinical high-risk for psychosis (CHR-P) and healthy control groups. WRAT, Wide Range Achievement Test; CPZ eqv., chlorpromazine equivalent; ns, non-significant.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  FEP  (n=16) |  CHR-P  (n=24) | Healthy controls (n=13) |  P value |
|  |  |  |  |  |
| Age, years: mean, (s.d.) | 24.5 (3.7) | 25.2 (4.8) | 26.5 (5.2) | ns |
| Gender (male/female) | 13/3 | 15/9 | 8/5 | ns |
| WRAT IQ: mean (s.d.) | 98.6 (14.8) | 103.3 (11.8) | 115.6 (5.2) | 0.001 |
| Years of education, years: mean, (s.d.) | 13.4 (1.8) | 13.0 (2.8) | 18.4 (4.2) | >0.001 |
| Ethnicity, n White | 6 | 14 | 10 | ns |
|  Black | 7 | 5 | 2 |  |
|  Asian | 0 | 1 | 0 |  |
|  Mixed race | 1 | 4 | 1 |  |
| Medication mg/day CPZ eqv.: mean (s.d.) | 150 (83.7) | 140 (42.4) | - | ns |
| TLI total: mean (s.d.) | 3.48 (2.9) | 1.79 (1.4) | 0.37 (0.5) | <0.001 |
| TLI positive: mean (s.d.) | 2.88 (3.0) | 1.44 (1.28) | 0.37 (0.5) | <0001 |
| TLI negative: mean (s.d.) | 0.58 (0.86) | 0.27 (0.6) | 0 (0) | 0.005 |
| Transition to psychosis |  |  |  |  |
|  Yes | - | 8 | - |  |
|  No | - | 16 | - |  |

**Table 3**. Spearman’s correlations between speech graph connectedness and clinical measures for all patients (FEP plus CHR-P). LCC, largest connected component; LCCr, ratio of largest connected component by random connectedness; LSC, largest strongly connected component; LSCr, ratio of largest strongly connected component by random connectedness; TLI, Thought and Language Index; PANSS, Positive and Negative Syndrome Scale; WRAT, Wide Range Achievement Test; Rs, Spearman’s rho; p, p-value; \*\*p<0.01; \*p<0.05. Significant correlations (\*) survived correction for multiple comparisons using false discovery rate (Benjamini–Hochberg procedure, p<0.05).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | LCC | LCCr | LSC | LSCr |
|  | *rs* | p | *rs* | p | *rs* | p | *rs* | p |
| TLI Total | -0.383 | 0.015 | -0.342 | 0.031 | **-0.587\*\*** | 0.001 | **-0.521\*\*** | 0.001 |
| TLI Positive | -0.142 | 0.381 | -0.121 | 0.457 | -0.374 | 0.017 | -0.335 | 0.035 |
| TLI Negative | **-0.452\*\*** | 0.003 | **-0.457\*\*** | 0.003 | **-0.513\*\*** | 0.001 | -0.389 | 0.013 |
| PANSS Total | -0.048 | 0.828 | -0.152 | 0.489 | -0.108 | 0.624 | 0.013 | 0.954 |
| PANSS Positive | 0.033 | 0.880 | -0.077 | 0.727 | -0.102 | 0.642 | 0.071 | 0.749 |
| PANSS Negative | -0.242 | 0.265 | -0.208 | 0.341 | -0.340 | 0.112 | -0.302 | 0.162 |
| WRAT IQ | 0.318 | 0.045 | 0.285 | 0.074 | **0.520\*\*** | 0.001 | **0.466\*\*** | 0.002 |
| Years of education | 0.239 | 0.137 | 0.277 | 0.084 | 0.281 | 0.078 | 0.317 | 0.046 |

**Figure 1**. Example speech from a participant describing one of the pictures from the Thematic Apperception Test. Speech is represented as a directed speech graph, each unique word corresponds to a red node in the graph and each temporal link between words is represented as an edge. The light-grey shaded area denotes the set of nodes in the largest connected component (LCC) and the lilac shaded area corresponds to the set of nodes in the largest strongly connected component (LSC).



**Figure 2**. Raincloud plots showing median LCC, LSC, LCCr and LSCr measures for FEP, CHR-P and HC groups with significant differences between groups indicated as \* = p < .05; \*\* = p < .01. Half violin plots show probability density functions and dots show the raw data. LCC, largest connected component; LSC, largest strongly connected component; LCCr, ratio of largest connected component to random connectedness; LSCr, ratio of largest strongly connected component to random connectedness; FEP, first-episode psychosis; CHR-P, clinical-high-risk for psychosis; HC, healthy controls.



**Figure 3**. Raincloud plots showing median LCC, LSC, LCCr and LSCr measures for CHR-P patients who transitioned to psychosis and CHR-P patients who did not transition to psychosis, with significant differences between groups indicated as \* = p < .05. Half violin plots show probability density functions and dots show the raw data. LCC, largest connected component; LSC, largest strongly connected component; LCCr, ratio of largest connected component to random connectedness; LSCr, ratio of largest strongly connected component to random connectedness.

