The specific phenotype of depression in recent onset schizophrenia spectrum disorders

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The specific phenotype of depression in recent onset schizophrenia spectrum disorders: A symptom profile and network comparison to recent onset major depressive disorder without psychotic features

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ABSTRACT

The specific phenotype of depression in recent-onset schizophrenia spectrum disorders (SSD) and its relation to non-psychotic depression is unknown. Symptom profile and network analysis are complementary statistical techniques that may provide important insights into the presentation and relative importance of individual symptoms that give rise to depression. The aim of the current study was to characterise the profile and network of depressive symptoms in SSD and compare it to individuals with major depressive disorder (MDD) without psychotic features. This study involved analysis of baseline data pertaining to 109 individuals with comorbid SSD and depression and 283 with MDD without psychotic features. Study cohorts were the Psychosis Recent Onset GRoningen Survey (PROGR-S) and Youth Depression Alleviation (YoDA) trials, respectively. Profile and network analyses revealed that SSD and MDD differed in the profile and relative importance of individual depressive symptoms. While *reported sadness* was the primary hallmark of depression in both SSD and MDD, individuals with depression in SSD were more likely to sleep more, and have lower *lassitude* and *pessimism*. While *sadness* had great importance in MDD and SSD, in SSD but not MDD *lassitude*, *sleep*, *appetite*, *concentration difficulties*, *and inability to feel* were important in the network of depressive symptoms. The specific phenotype of depression might be different in SSD compared to MDD. Symptom inequivalence or underlying functional mechanisms in SSD might result in depression in SSD that is similar to MDD with atypical features.

1. Introduction

Schizophrenia spectrum disorders (termed SSD hereafter) are among the most burdensome psychiatric illnesses worldwide (Rossler et al., 2005). Despite increased availability of antipsychotic medications to treat positive psychotic symptoms, recovery rates have remained largely unchanged over recent decades (Jääskeläinen et al., 2013). Treating positive symptoms alone with conventional antipsychotics is insufficient to improve outcomes in SSD.

Co-occurring depression (based on diagnostic criteria) and clinically significant levels of depressive symptoms (or "caseness": meeting cut-off scores on severity scales indicating need for clinical management) significantly contribute to the burden of SSD. This is particularly the case in early illness stages, but depression is often overlooked in treatment and research (Cotton et al., 2012; Herniman et al., 2019). At least one quarter of individuals with SSD have comorbid depression, and nearly half have case-level depression (Herniman et al., 2019). Depression in SSD has been associated with serious adverse consequences: increased risk for non-remission of psychotic symptoms and future psychotic relapse, and greater risk concerns, including violence towards others, self-harm, and suicide (Conley et al., 2007). Depression in SSD is the most significant predictor of suicide, even more so than acting on command hallucinations (Crumlish et al., 2005; Dutta et al., 2010). Early assessment and treatment of depression might be an

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important strategy to improving outcomes in SSD (Herniman et al., 2019).

Despite the importance of early assessment and treatment of depression in SSD, there is an absence of research determining how the specific phenotype of depression in SSD compares to major depressive disorder without psychotic features (termed MDD hereafter). This precludes the development of tailored assessment and treatment of depression in SSD. This is the case for bipolar disorder, where assessment and treatments for depression need to be different to unipolar MDD (Kennedy et al., 2016; Yatham et al., 2018). Such a knowledge gap is surprising; preliminary evidence suggests that depression might be different in SSD, or in a sub-set of individuals with SSD, compared to DSM-defined diagnostic criteria for MDD. One study found that only about half of those with SSD who also had caseness for depression, actually met full diagnostic criteria for a DSM-defined depressive disorder (Herniman et al., 2017). Another more recent study found that individuals with SSD were three times more likely to experience atypical neurovegetative features such as *increased sleep* compared to individuals with MDD (Lange et al., 2021). Further research is needed to determine if there is a specific phenotype of depression and case-level depression in SSD, compared to MDD. This is of particular importance, as different phenotypes might differ in underlying pathophysiology (Milaneschi et al., 2020).

Symptom profile and network analysis are independent but complementary statistical techniques that may provide important insights into the specific phenotype of depression and caseness in SSD (Borsboom, 2017; Tabachnick and Fidell, 2013). Profile analysis determines the pattern and severity of individual depressive symptoms and therefore, informs the presentation of depression in SSD, and whether this deviates from MDD (Tabachnick and Fidell, 2013). It is more advantageous than trying to infer patterns from a series of univariate analyses of individual symptoms – without a test for the pattern itself (Atchison et al., 2007). This is used in neuropsychology, where the pattern of profiles on neuropsychological measures is used to assist diagnosis and treatment of neurological conditions (Atchison et al., 2007). Differences in symptom profiles between depression in SSD and MDD might implicate the need to tailor assessment of depression to SSD.

In network analysis, depression is conceptualised as a complex system of causally-interacting and self-perpetuating symptoms (Borsboom, 2017). It enables the identification of symptoms most central or important in perpetuating the network, based on the amount and direction of influence flowing from one symptom to another (Borsboom, 2017). Activation of a central symptom, which has several connections to other symptoms, can produce a cascade of activation through the entire network, resulting in a diagnostically valid disorder 'stuck' in a self-perpetuating state. A trigger could activate the central symptom of insomnia, which, in turn, could activate closely connected symptoms of fatigue, concentration difficulties, depressed mood, and pessimistic rumination, reinforcing insomnia (Borsboom, 2017). Thus, symptom profile and network analysis might yield important insights into the phenotype of depression in SSD, including the presentation and mechanisms that give rise to and maintain such disorder.

The aim of the current study was to characterise the profile and network of depressive symptoms and caseness in SSD and compare this to MDD. Given the absence of relevant research, we have no strong *a priori* hypotheses and, as such, the nature of this paper is exploratory.

2. Method

2.1. Design

This study comprised secondary analysis of baseline data pertaining to three participant groups: (1) SSD with DSM-defined depression (SSD + D); (2) SSD without DSM-defined depression but with case-level depression (SSD + C); and (3) unipolar MDD without psychotic features (MDD).

2.2. Participants

Data for the first and second participant groups, recent-onset SSD + D and SSD + C, were derived from Psychosis Recent Onset GRoningen Survey (PROGR-S; Liemburg et al., 2014). The eligibility criteria for PROGR-S has been described elsewhere (Liemburg et al., 2014). Participants resided in the Groningen province of the Netherlands and were referred to a psychiatric institution with a suspected recent-onset psychotic episode (<2 years) that was yet to be treated, or emergency treatment was recently initiated. Diagnoses were based on DSM-IV (American Psychiatric Association, 1994) and confirmed using Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990).

PROGR-S participants (recruited between 1997 and 2009) with complete Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) data and SSD were considered for eligibility (see Supplementary for details). Two subgroups were further defined: (1) SSD + D—DSM-IV-defined depression and MADRS score ≥20 (caseness); (2) SSD + C—no formal diagnosis of depression but meeting caseness. Caseness was defined as MADRS≥20 to make it concordant with the clinical-control group (MDD) with MADRS≥20 in their inclusion criteria (Berk et al., 2020; Davey et al., 2019).

The clinical-control group, recent-onset MDD without psychotic features, was derived from Youth Depression Alleviation (YoDA) trials (Berk et al., 2020; Davey et al., 2019). Eligibility criteria for YoDA trials have been described elsewhere (Davey et al., 2014; Quinn et al., 2018). Participants resided in the North-West regions of Melbourne, Australia, and were receiving treatment for MDD at the Youth Mood Clinic (YMC), Orygen, or at three *headspace* centres, all located in the North-West regions of Melbourne, Australia. Participants had MADRS≥20, and MDD was confirmed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). No additional exclusion criteria were applied to this participant group.

2.3. Procedure

Participants provided oral and written informed consent, including parent/guardian consent for participants <18 years. For PROGR-S, all procedures were conducted in accordance with local and international rules as confirmed by the local ethical committee of the University Medical Center of Groningen (Liemburg et al., 2014). For YoDA trials, all procedures were conducted in accordance with protocols approved by Melbourne Health's Human Research Ethics Committee (Berk et al., 2020; Davey et al., 2019).

2.4. Depressive symptoms

Depressive symptoms were measured using the MADRS (Montgomery and Åsberg, 1979), a 10-item interviewer-rated checklist, comprising a 7-point Likert scale ranging from 0 to 6, with specific anchors for each item (see Supplementary). Total scores range 0–60, with higher scores indicating more severe symptomatology.

Regular consensus meetings were held to maintain inter-rater reliability within parent studies (Davey et al., 2014; Liemburg et al., 2014; Quinn et al., 2018).

2.5. Statistical analyses

Data screening was undertaken to determine accuracy of data entry and assumptions (Tabachnick and Fidell, 2013). Descriptive statistics and frequency counts were obtained to characterise the samples.

2.5.1. Profile analysis

Profile analysis was conducted in IBM® SPSS® Statistics (Version 21) according to recommendations (Tabachnick and Fidell, 2013). A multivariate repeated-measures analysis of covariance (ANCOVA) was

conducted, with MADRS items as dependent variables, participant groups (SSD + D/SSD + C/MDD) as independent variables, and age and sex as covariates. Profile analysis tests for three facets within the symptom profile: (1) parallelism: tests if the pattern of depressive symptoms for each group is different from patterns of other groups; (2) flatness: tests if the combined item scores from all groups (SSD + D/SSD + C/MDD) differs from any item compared to all other items; (3) levels: tests if the overall severity of symptoms on the combined items is different between groups. In the case of a significant test, simple main effects and *post-hoc* analyses were conducted to determine where differences lie. Bonferroni correction was applied to adjust for multiple comparisons.

2.5.2. Network estimation

Network estimation and analyses were conducted in *R* (version 4.0.2) Pre-processing checks assessing collinearity were conducted using the *goldbricker algorithm* prior to network estimation to identify any overlapping nodes that likely reflect the same underlying latent construct. Regularized, partial correlation networks were then estimated according to recommendations (Epskamp et al., 2018; Epskamp and Fried, 2018). Graphical Gaussian Models (GGM) using Least Absolute Shrinkage and Selection Operator (LASSO; Tibshirani, 1996) with the Extended Bayesian Information Criterion (hyperparameter $\lambda = 0$; Chen and Chen, 2008) were used for network estimation of MADRS items and covariates (age, sex). LASSO shrinks trivially small correlations to zero, thereby removing spurious associations, and resulting in a sparse graphical model comprising only the strongest associations. The presented networks illustrate associations among symptoms, depicted by nodes (symptoms) and edges (regularized, partial correlations).

2.5.3. Network analysis

Strength centrality was calculated to determine the relative functional importance of each symptom in maintaining the networks. *Strength centrality* is the sum of the strength of associations between a symptom and all other symptoms to which it is connected, and the most reliable and stable centrality measure in symptom networks (Epskamp et al., 2018). Community analysis using well-recognised *spinglass algorithm* was conducted to determine clusters/structures of symptoms.

2.5.4. Network accuracy and stability

The accuracy and stability of edge-weights and strength centrality was examined using nonparametric and case-dropping subset bootstrapping procedures (Epskamp et al., 2018; Epskamp and Fried, 2018). Details and results of these are reported in Supplementary Material.

This approach to network estimation and analysis was conducted in SSD and then in MDD. Lastly, the Network Comparison Test (van Borkulo et al., 2015; van Borkulo et al., 2016) was conducted to test for differences in global strength (sum of the strength of all edges in the network) and network invariance (differences in the strength of connection of nodes between networks).

3. Results

3.1. Participant flow

Of the 659 PROGR-S participants with complete MADRS data, 16.5% ($n = 109$) met inclusion criteria (see Supplementary materials for reasons for exclusion). Of these, 25 participants had a DSM-defined-MDD diagnosis and met caseness (MADRS≥20), and comprised SSD + D. There were 84 participants that did not have DSM-defined-MDD, but had caseness, forming SSD + C. There were 283 YoDA participants with MDD.

3.2. Demographic and clinical characteristics

As seen in Table 1, the average age of SSD + D and SSD + C participants was 26.56 ($SD = 5.72$) and 26.53 years ($SD = 6.00$), respectively, and 80% ($n = 20$) and 77.4% ($n = 65$) were male, respectively. In comparison, the average age of participants with MDD was 19.88 years ($SD = 2.69$; range = 15–25) and most were female (59.4%, $n = 168$). These differences (SSD + D/SSD + C/MDD) in age (F [2, 389] = 117.26, $p < 0.001$) and sex (χ^2[2, $n = 392$] = 43.97, $p < 0.001$) were significant. Age and sex were therefore controlled for in the profile and network analyses (see Supplementary Material for *post hocs* and results without covariates).

Table 1
Demographic characteristics of participants with recent onset schizophrenia spectrum disorders (SSD) and participants with recent onset major depressive disorder (MDD) without psychotic features.

Demographic	Statistic	SSD ($N = 109$)	SSD + D ($n = 25$)	SSD + C ($n = 84$)	MDD ($N = 283$)
Age (years)	*M* (*SD*)	26.54 (5.90)	26.56 (5.72)	26.53 (6.00)	19.88 (2.68)
Gender (female)	% (*n*)	22.0 (24)	20.0 (5)	22.6 (19)	59.4 (168)
Living situation		$n = 108$			$n = 282$
Living independently	% (*n*)	57.8 (63)	64.0 (16)	55.9 (47)	25.8 (73)
Living with parents/ family	% (*n*)	38.5 (42)	36.0 (9)	39.3 (33)	69.1 (197)
Special care facility	% (*n*)	1.8 (2)	0.0 (0)	2.4 (2)	1.8 (5)
Homeless	% (*n*)	<0.01 (1)	0.0 (0)	1.2 (1)	<0.01 (1)
Other	% (*n*)	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (4)
Education level		$n = 107$	$n = 25$	$n = 82$	$n = 282$
Did not complete or currently undertaking secondary school	% (*n*)	14.0 (15)	16.0 (4)	13.4 (11)	51.6 (146)
Completed secondary school	% (*n*)	86.0 (92)	84.0 (21)	86.6 (71)	48.1 (136)
Additional qualifications	% (*n*)	$n = 107$	$n = 25$	$n = 82$	$n = 282$
Vocational/trade/ tertiary certificate or diploma	% (*n*)	23.4 (25)	32.0 (8)	20.7 (17)	28.4 (80)
University degree	% (*n*)	0.0 (0)	0.0 (0)	0.0 (0)	8.2 (23)
Occupation		$n = 101$	$n = 24$	$n = 77$	$n = 282$
Unemployed	% (*n*)	48.5 (49)	62.5 (15)	44.2 (34)	22.7 (64)
Voluntary job	% (*n*)	8.3 (9)	8.3 (2)	9.1 (7)	<0.01 (1)
Student	% (*n*)	12.8 (14)	8.3 (2)	15.6 (12)	48.9 (138)
Paid job	% (*n*)	25.7 (28)	20.8 (5)	29.9 (23)	26.6 (75)
Other	% (*n*)	<0.01 (1)	0.0 (0)	1.3 (1)	<0.01 (4)

Notes. SSD = schizophrenia spectrum disorders; SSD + D = schizophrenia spectrum disorder with comorbid depressive disorder; SSD + C = schizophrenia spectrum disorder with caseness for depressive disorder. Most participants with SSD had a diagnosis of schizophrenia (57.8%, $n = 63$) and other schizophrenia spectrum diagnoses were: psychotic disorder not otherwise specified (NOS, 22.9%, $n = 25$), schizophreniform disorder (6.4%, $n = 7$), brief psychotic disorder (5.5%, $n = 6$), substance induced psychotic disorder (5.5%, $n = 6$), and delusional disorder (1.8%, $n = 2$).

3.3. Profiles of depressive symptoms

All variables were normally distributed, with the exception of *reduced sleep* and *reduced appetite* in SSD, and *reduced sleep* in MDD. However, it was considered inappropriate to transform such variables given the nature of the current analyses; that is, to determine the symptom profiles or distributions of all items. Multivariate repeated-measures ANCOVAs are nonetheless considered robust to violations of normality (Tabachnick and Fidell, 2013).

3.3.1. SSD

Fig. 1 shows the depression profiles. In SSD + D (blue line), the mean MADRS total-score was 27.28 (*SD* = 5.43). The most severe symptom was *reported sadness* (*M* = 3.84, *SD* = 0.85). The least severe were *reduced sleep* (*M* = 1.44, *SD* = 1.78) and *reduced appetite* (*M* = 1.32, *SD* = 1.49). Results were similar in SSD + C.

3.3.2. MDD

In MDD (Fig. 1, green line), the mean MADRS total-score was 32.71 (*SD*=5.66). The most severe symptom was *reported sadness* (*M* = 4.10, *SD* = 0.99). The least severe were *reduced appetite* (*M* = 2.22, *SD* = 1.72) and *suicidal thoughts* (*M* = 2.67, *SD* = 1.49).

3.3.3. Comparison of profiles

The test of parallelism using Wilks' Lambda was significant, $F(18, 758) = 5.60$, $p < 0.001$, partial $\eta^2 = 0.117$, indicating the pattern of symptoms was different between groups (SSD + D/SSD + C/MDD). Visual inspection of profiles (Fig. 1) indicated SSD + D and SSD + C exhibited similar profile patterns, but different to MDD. The test of parallelism was conducted with only SSD + D and SSD + C and then only in SSD + D and MDD. There were no significant differences in symptom patterns between SSD groups, $F(9, 97) = 1.07$, $p = 0.394$, partial $\eta^2 = 0.090$. Symptom patterns were significantly different between SSD + D and MDD, $F(9, 296) = 4.44$, $p < 0.001$, partial $\eta^2 = 0.119$.

The flatness test using Wilks' Lambda was significant within the combined-group (SSD + D/SSD + C/MDD), $F(9, 379) = 22.85$, $p < 0.001$, partial $\eta^2 = 0.352$, indicating differences in severity across individual symptoms. Pairwise comparisons between the most severe symptom *reported sadness* and other symptoms were examined. In the combined-group, *reported sadness* was significantly greater than all depressive symptoms (all $p < 0.050$) except *concentration difficulties* ($p = 0.135$). In SSD + D, *reported sadness* was significantly greater than *reduced sleep*, *reduced appetite*, and *pessimistic thoughts* (all $p < 0.050$), but not greater than *apparent sadness*, *inner tension*, *concentration difficulties*, *lassitude*, *inability to feel* and *suicidal thoughts* (all $p > 0.050$). In SSD + C, *reported sadness* was greater than *apparent sadness*, *reduced sleep*, *reduced appetite*, *lassitude*, *pessimistic thoughts* and *suicidal thoughts* (all $p < 0.050$), but not greater than *inner tension*, *concentration difficulties*, and *inability to feel* (all $p > 0.050$). In MDD, *reported sadness* was greater than all other depressive symptoms (all $p < 0.050$). Since mean differences between *reported sadness* and other symptoms were sometimes greater in SSD + D compared to MDD, non-significant pairwise comparisons in SSD + D were likely due to small sample size ($n = 34$ required with power = 0.80, effect-size = 0.05, alpha = 0.05). Like MDD, *reported sadness* is greater, albeit non-significantly, than all other depressive symptoms in SSD + D.

The test of levels was statistically significant across all groups (SSD + D, SSD + C, MDD), $F(2, 136) = 45.60$, $p < 0.001$, partial $\eta^2 = 0.191$, indicating differences in overall depression severity. In SSD + D and SSD + C, there were no differences in the level of severity on the combined depressive items, $p = 0.692$. SSD + D had significantly lower levels of overall severity (*M* = 2.65, *SE* = 0.12, 95%CI = 2.43, 2.88) compared to MDD (*M* = 3.30, *SE* = 0.04, 95%CI = 3.23, 3.37; $M_{diff} = -0.65$, *SE* = 0.13, $p < 0.001$, 95%CI = −0.950, −0.346). SSD + D had significantly lower levels of *reduced sleep* ($M_{diff} = -1.83$, *SE* = 0.37, $p < 0.001$, 95%CI = −2.720, −0.947), *lassitude* ($M_{diff} = -0.64$, *SE* = 0.26, $p = 0.045$, 95%CI = −1.266, −0.009), and *pessimistic thoughts* ($M_{diff} = -1.19$, *SE* = 0.24, $p < 0.001$, 95%CI = −1.763, −0.613) compared to MDD. SSD + C had significantly lower levels of overall severity (*M* = 2.50, *SE* = 0.07, 95%CI = 2.36–2.64) compared to MDD ($M_{diff} = -0.80$, SE = 0.09, $p < 0.001$, 95%CI = -1.003, −0.592). The SSD + C group had significantly lower levels of *apparent sadness* ($M_{diff} = -1.09$, *SE* = 0.17, $p < 0.001$, 95%CI = −1.504, −0.665), *reported sadness* ($M_{diff} = -1.09$, *SE*

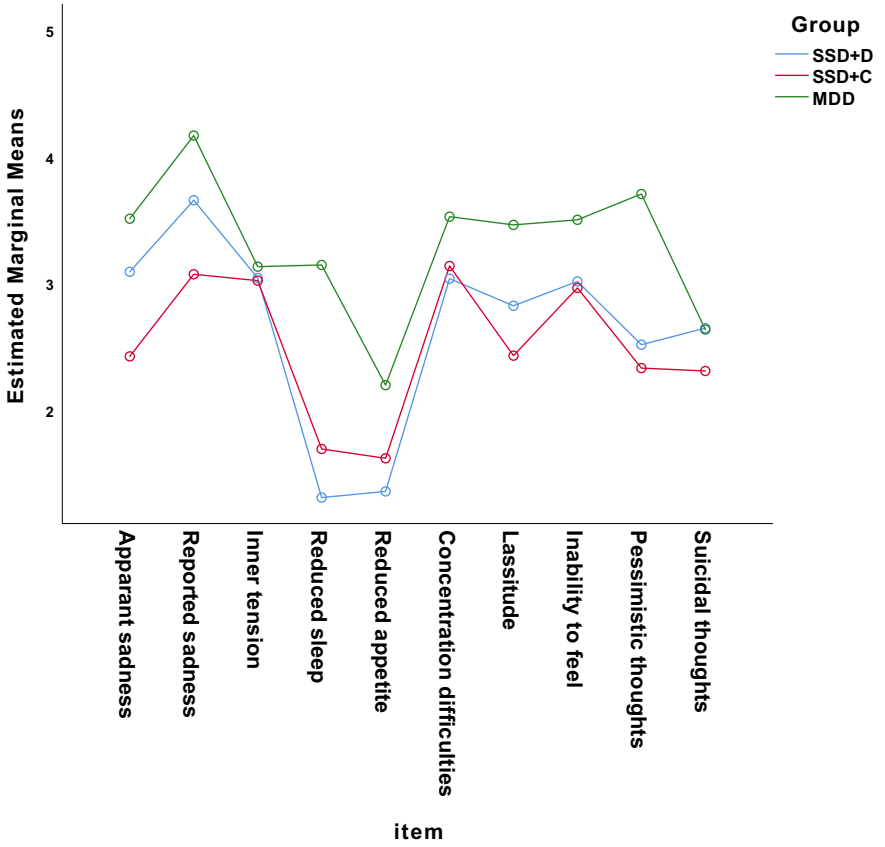

Fig. 1. Depressive Symptom Profiles in Individuals with Schizophrenia Spectrum Disorder plus Major Depressive Disorder (SSD + D), SSD plus Caseness for Depressive Disorder (SSD+C), and Major Depressive Disorder (MDD).

= 0.16, $p < 0.001$, 95%CI = −1.470, −0.717), *reduced sleep* (M_{diff} = −1.45, $SE = 0.25$, $p < 0.001$, 95%CI = −2.053, −0.847), *lassitude* (M_{diff} = −1.03, $SE = 0.18$, $p < 0.001$, 95%CI = −1.459, −0.603), and *inability to feel* (M_{diff} = −0.54, $SE = 0.18$, $p = 0.008$, 95%CI = -0.962, −0.112) but not *inner tension*, *reduced appetite*, *concentration difficulties*, *and suicidal thoughts* compared to MDD (all $p > 0.050$).

3.4. Networks of depressive symptoms

The SSD + D and SSD + C groups were combined for network analyses. Profiles were similar, and sample size of SSD + D ($n = 25$) was too small for network estimation; *a priori* calculations confirmed $n \geq 78$ was necessary for networks comprising twelve nodes, 10 symptoms and two covariates (Epskamp et al., 2018). As stated above, all variables were normally distributed, with the exception of *reduced sleep* and *reduced appetite* in SSD, and *reduced sleep* in MDD. However, nonparanormal transformation cannot be conducted on ordinal variables, and polychoric correlations were used in accordance with current guidelines (Epskamp et al., 2018; Epskamp and Fried, 2018). Collinearity was not identified in either SSD or MDD, so all nodes were entered into the network models.

3.4.1. SSD

In SSD (Fig. 2), of the possible 66 edges, 40.9% ($n = 27$) were estimated >0.00. The strongest edge was *reduced sleep–reduced appetite* (regularized, partial *r*[*r* hereafter] = 0.41), and weakest *reduced appetite–suicidal thoughts* (partial $r = 0.02$).

Three communities were identified: (1) *negative affect and thinking and gender*; (2) *deficit symptoms and age*; and (3) *somatic symptoms*. Fig. 3 presents the strength centrality indices in SSD and MDD. Of symptoms, *lassitude* had the greatest strength centrality (1.07), then *reported sadness*, *apparent sadness*, *reduced appetite*, *reduced sleep*, *concentration difficulties*, *suicidal thoughts*, and *inability to feel* (1.04, 0.99, 0.56, 056, 0.28, 0.09, respectively; Fig. 3, left panel).

3.4.2. MDD

As seen in Fig. 4, 53.0% ($n = 35$) of the possible edges were estimated >0.00. The strongest edge was *apparent sadness* and *reported sadness* (r = 0.31), and weakest *lassitude* and *pessimistic thoughts* ($r < 0.01$).

As seen in the bottom right panel of Fig. 2, three communities were identified: (1) *negative affect and thinking and age*; (2) *physiological arousal and gender*; and (3) *somatic symptoms*. As seen in Fig. 3(right panel), *reported sadness* had the greatest strength centrality (2.56)–much more so than all other depressive symptoms.

3.4.3. Comparison of networks

There was no difference in global strength of networks between SSD and MDD (3.08 *versus* 2.89), $S = 0.19$, $p = 0.867$, or network invariance, $M = 0.24$, $p = 0.505$. Given this, we did not test for specific differences in edge strength (van Borkulo et al., 2015).

4. Discussion

This is the first study to characterise and compare the phenotype of depression in recent-onset SSD to recent-onset MDD without psychotic features, and to simultaneously apply the complementary techniques of profile and network analysis. Both indicated that the phenotype of depression in SSD and MDD might be different, specifically regarding severity and endorsement of symptoms, and how symptoms might interact with one another.

In SSD and MDD, the depressive profile was characterised by greater *reported sadness* than all other depressive symptoms. In comparison to MDD, the overall severity of depression was lower in SSD. This was specifically due to the relative absence of *reduced sleep* and lower severity of *lassitude* and *pessimistic thinking* in SSD. Though depression in SSD might involve relatively absent *reduced sleep*, it can also involve *increased sleep*. This speculation is somewhat supported by networks showing that *reduced sleep* was negatively associated with several other symptoms in SSD, but not in MDD (except for *lassitude–reduced sleep* association). For example, *reported sadness* and *inability to feel* were associated with *reduced sleep* in MDD but *less reduced sleep* and therefore, potentially *increased sleep*, in SSD. This interpretation is consistent with one recent study, which found that individuals with SSD were three times more likely to experience *increased sleep* compared to individuals with MDD (Lange et al., 2021). In the current study, *reduced* (*or increased*) *sleep* was also among the most central symptoms in SSD, but

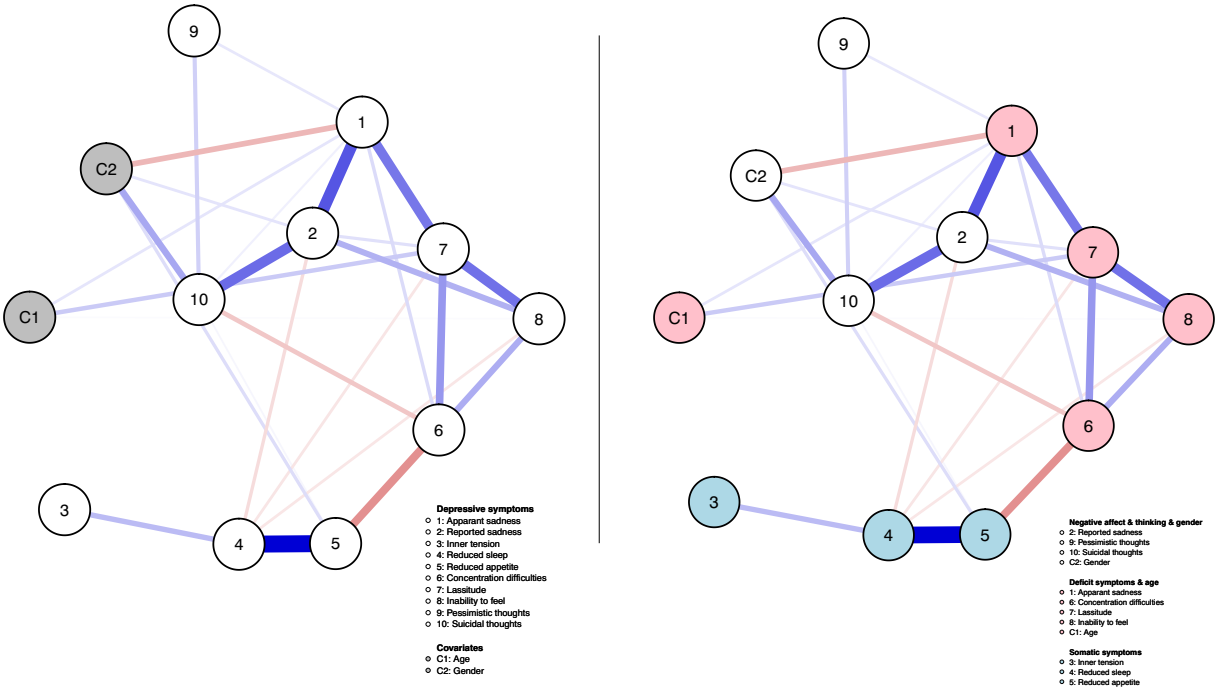

Fig. 2. Depressive Symptom Network in Individuals with Schizophrenia Spectrum Disorder.

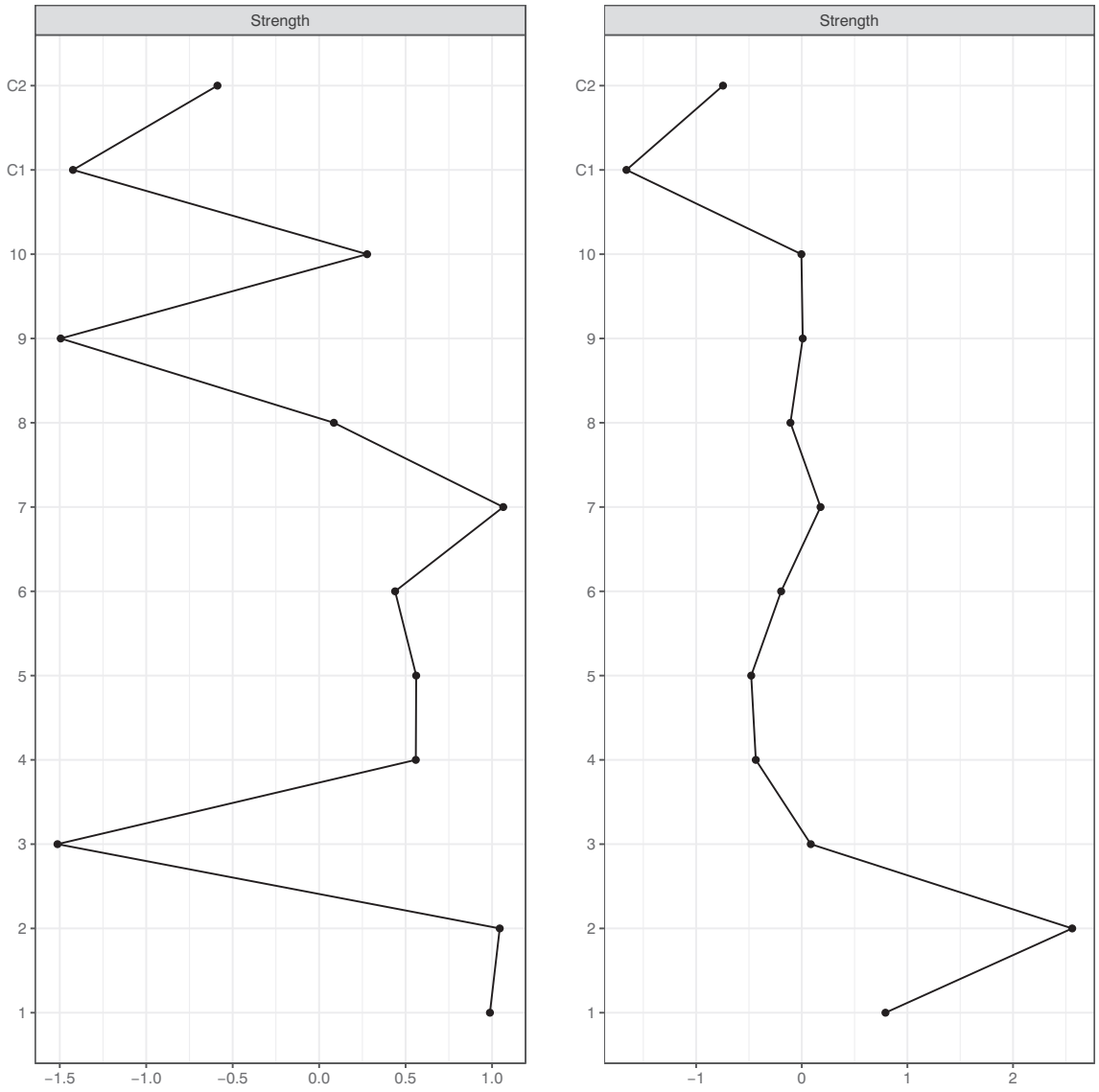

Fig. 3. Strength Centrality Z-scores for Individuals with Schizophrenia Spectrum Disorder (Left Panel) and Major Depressive Disorder without Psychotic Features (Right Panel).

not in MDD, suggesting that *sleep disturbances* are not relatively absent, but potentially important in SSD. The use of the MADRS might impact assessed severity, as it does not capture *increased sleep* (or *increased appetite*), and might therefore under-score individuals with such symptoms. Nonetheless, depressive profiles comprising *sadness* in combination with *increased sleep or appetite* are consistent with conceptualisations of MDD with atypical features (APA, 2013; Lamers et al., 2012). Thus, while *reported sadness* might be the primary hallmark of depression in both SSD and MDD, the presentation of depression might be different in SSD, with greater likelihood of atypical features (Lange et al., 2021).

Differences in underlying mechanisms might contribute to differences in presentation of depression in SSD and MDD. In depression in SSD, the symptom network was characterised by greater centrality of *lassitude* as well as *sadness* (*reported* and *apparent*), *reduced sleep* (*or increased*), *reduced appetite* (*or increased*), *concentration difficulties*, *suicidal thoughts*, and *inability to feel* compared to *inner tension*, and *pessimistic thinking*. This was in contrast to MDD, in which only *sadness* (*reported* and *apparent*) had great centrality. The additionally important symptoms in SSD could be due to a relatively greater loading of biological disturbances compared to MDD. Immunological (*e.g.*, interleukin-6[*IL-6*]) and metabolic (*e.g.*, higher body mass index[BMI]) disturbances might contribute to MDD with atypical features (Lamers et al., 2012; Milaneschi et al., 2017), and such disturbances might map onto *fatigue/lassitude*, *increased sleep* and *increased appetite*. These immunological disturbances might also contribute to SSD (Khandaker et al., 2015; Upthegrove et al., 2014), and metabolic disturbances are common in SSD, at least due to anti-psychotic medication side-effects (Reynolds and Kirk, 2010; Tschoner et al., 2007). Thus, it is speculated that a relatively greater loading of biological disturbances or mechanisms in SSD might result in depression presenting similarly to MDD with atypical features. This further suggests that depressive symptoms might be inequivalent between SSD and MDD. While *lassitude* was greater in severity in MDD, *lassitude* might have an in-equivalently greater functional impact on depression in SSD compared to MDD.

Like functional mechanisms, differences in depression structure or symptom interactions might contribute to differences in presentation. In depression in SSD, the network comprised three sub-networks of interrelated symptoms: (1) *negative affect and thinking*, including *reported sadness*, *pessimistic thoughts*, and *suicidal thoughts*; (2) *deficit symptoms*, including *apparent sadness*, *inability to feel*, *lassitude*, and *concentration difficulties*; and (3) *somatic symptoms*, including *inner tension*, *reduced*

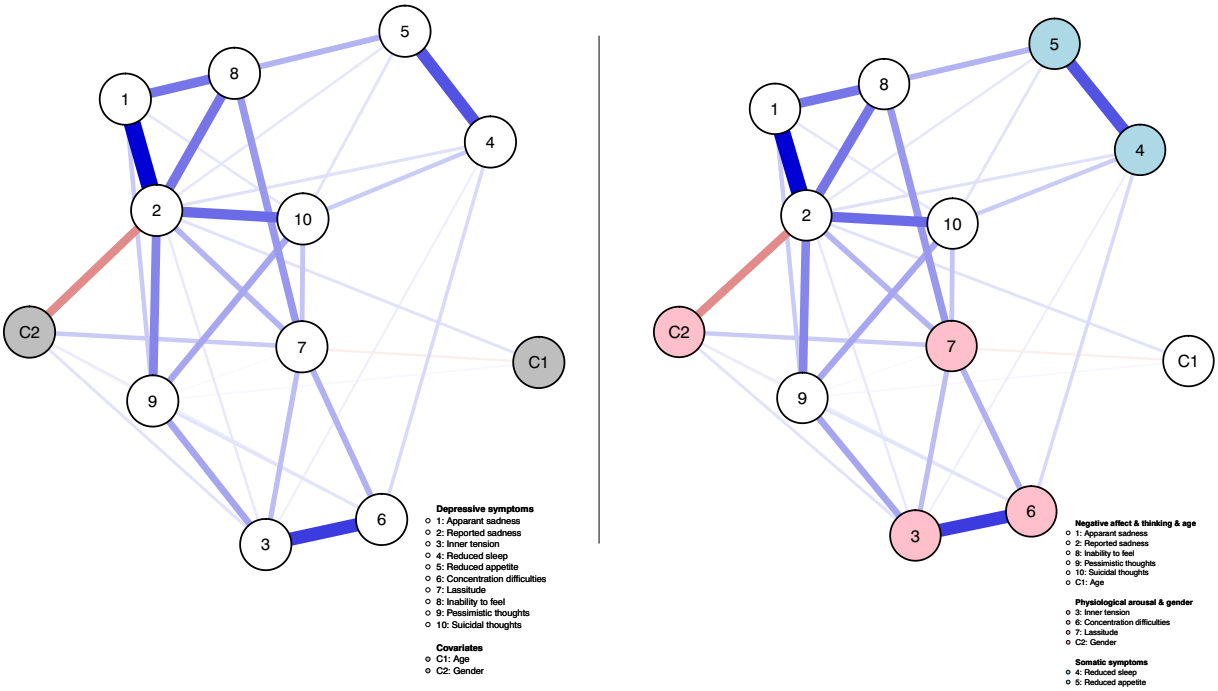

Fig. 4. Depressive Symptom Network in Individuals with Schizophrenia Spectrum Disorder.

sleep, and *reduced appetite*. This was different to MDD. While MDD also comprised sub-networks pertaining to *negative affect and thinking* and *somatic symptoms*, there were some compositional differences, and a sub-network pertaining to *physiological arousal* rather than *deficit symptoms*. Such differences might indicate qualitative differences among certain symptoms. For example, *inability to feel* or *anhedonia* was subsumed within the sub-network of *deficit symptoms* in SSD, but within *negative affect and thinking* in MDD. *Anhedonia* might arise in the context of *deficit-like symptoms*–or express a *deficit-or-negative-like* quality–in SSD, whereas *inability to feel* might arise in the context of *negative affect and thinking*–or express a *negative, affect-like* quality–in MDD. These speculations are consistent with distinctions between *anticipatory* and *motivational* (motivation to pursue rewards) and *consummatory anhedonia* (pleasure experienced in anticipation or response to rewards; Strauss and Gold, 2012), and hypotheses that *anticipatory* and *motivational anhedonia* might be consistent with *negative symptoms*, and *consummatory anhedonia* with *depressed mood* (Upthegrove et al., 2017). While discussing all differences in network structure is beyond the scope of this discussion, such differences might reveal qualitative differences in the presentation of depression in SSD.

4.1. Implications, limitations, and future research

The phenotype of depression might be different in SSD compared to MDD. However, replication studies overcoming the current limitations are needed before firm conclusions can be made. First, the SSD and MDD cohorts were derived from studies conducted in different countries with different recruitment procedures, inclusion criteria, researchers, and treatment as usual. While the current study controlled for age and sex, results could have still been influenced by these and other important unmeasured confounders, including negative symptoms and the effects of antipsychotic medications in SSD. Since negative symptoms were not measured and antipsychotic medications were not prescribed in the MDD cohort, these were unable to be controlled for in the current analyses. However, *post hoc* analyses indicated that antipsychotic medications and negative symptoms unlikely contributed to the current results showing that individuals with SSD were sleeping significantly more than individuals with MDD (see Supplementary materials). Second, in the SSD cohort, the sample size was relatively small. This meant that only a small subsample had a formal diagnosis of depression in SSD, preventing adequate power in some of the pairwise comparisons. Third, in the SSD cohort, while the network was considered sufficiently stable for interpretation (Epskamp et al., 2018; Epskamp and Fried, 2018), it is important to note that such stability was only just above sufficient threshold, and results should be considered with this in mind. Finally, only the MADRS was used in the current study; it is possible that depressive symptoms might differ between MDD and SSD in important ways that are not captured by the MADRS. Thus, further replication studies in larger samples derived from the same setting and employing larger or more than one depression measure are needed before firm conclusions can be made about differences in the phenotype of depression between SSD and MDD.

If the current results are replicated, this would imply that the conceptualisation, assessment, and potentially treatment of depression might benefit from specific tailors to the context of SSD. Indeed, depressive symptoms in SSD are diagnostically conceptualised as relating to a distinct, superimposed comorbid disorder, and associated research has consequently been grounded in the indiscriminate application of models pertaining to unipolar MDD without psychotic features—without evidence indicating that this is a valid approach (Sandhu et al., 2013; Upthegrove et al., 2017). There is now robust evidence that depressive symptoms are highly common in and associated with symptoms of SSD (Herniman et al., 2019). Thus, rather than being conceptualised, assessed, and treated as a comorbidity akin to MDD, depressive symptoms in SSD might be better conceptualised as intrinsic to SSD – at least in the acute psychotic phase – and tailored accordingly (Sandhu et al., 2013; Upthegrove et al., 2020). Assessment scales used to examine depressive symptoms should capture the phenotype that is common in SSD, which must include assessment of atypical symptoms. Many scales do this poorly, including the MADRS and Calgary Depression Scale for Schizophrenia (the only instrument designed to assess depression specifically in SSD). The Quick Inventory of Depression Symptomatology (QIDS; Rush et al., 2003) and the Bipolar Depression Rating Scale (BDRS; Berk et al., 2007) have symmetrical assessment items for atypical depression and might be preferred.

Treatments might benefit from focusing at the individual-symptom

level, specifically on *sadness*, as well as *lassitude*, *sleep*, *appetite*, *concentration difficulties*, and *inability to feel*. Whether mechanisms underlying depressive symptoms in SSD are similar to those in MDD, and whether treatments for MDD are appropriate for SSD, are unknown and important questions for future research. There is limited evidence of efficacy for antidepressant medications in SSD (Gregory et al., 2017; Helfer et al., 2016). Citalopram, a Selective Serotonin Reuptake Inhibitor (SSRI), might nonetheless have the greatest efficacy in SSD due to its anti-inflammatory effects (Gregory et al., 2017), though further research is needed. Cognitive behavioural therapy (CBT; including CBT for psychosis, depression, and insomnia) and behavioural activation might be promising psychological interventions for depression in SSD. CBT and behavioural activation are gold-standard treatments for low mood, sleep disturbances, and symptoms associated with behavioural withdrawal (likely including *sadness*, *lassitude*, *sleep*, and *inability to feel*) in MDD (Ekers et al., 2008). While there is no research on the efficacy of these interventions specifically targeting depression in SSD, there is evidence implicating their efficacy in the improvement of positive symptoms, negative symptoms, sleep disturbances, and neurocognitive difficulties in SSD (Choi et al., 2016). Undoubtedly, controlled trials are needed to examine the efficacy of psychopharmacotherapies and psychotherapies for the treatment of depression specifically in individuals with SSD.

4.2. Conclusions

The specific phenotype of depression might be different in recent-onset SSD compared to recent-onset MDD without psychotic features. Underlying functional mechanisms in SSD might result in depression in SSD that presents similarly to MDD with atypical features, and the assessment of depression might benefit from specific tailors to the context of SSD.

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Declaration of competing interest

None relevant to this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.11.048.

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