



Symptom clusters in adolescent depression and differential responses of clusters to pharmacologic treatment

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ABSTRACT

Objective: Symptoms of depression in adolescents are widely variable, but they are often interactive and clustered. The analysis of interactions and clusters among individual symptoms may help predict treatment outcomes. We aimed to determine clusters of individual symptoms in adolescent depression and their changes in the response to pharmacological treatment.

Method: A total of 95 adolescents, aged 12–17 years, with major depressive disorder were included. Participants were treated with escitalopram, and depressive symptoms were assessed at baseline (V1) and 1, 2, 4, 6, and 8 weeks (V6). The severity of depression was assessed using the Children's Depression Rating Scale-Revised. To construct network and clustering structures among symptoms, the Gaussian graphical model and Exploratory Graph Analysis with the tuning parameter to minimize the extended Bayesian information criterion were adopted.

Results: Exploratory Graph Analysis revealed that symptoms of depression comprised four clusters: impaired activity, somatic concerns, subjective mood, and observed affect. The main effect of visit with decreased symptom severity was significant in all four clusters; however, the degree of symptom improvement differed among the four clusters. The effect size of score differences from V1 to V6 was the highest in the subjective mood (Cohen's $d = 1.075$), and lowest in impaired activity ($d = 0.501$) clusters.

Conclusion: The present study identified four symptom clusters associated with adolescent depression and their differential changes related to antidepressant treatment. This finding suggests that escitalopram was the most effective at improving subjective mood among different clusters. However, other therapeutic modalities may be needed to improve other clusters of symptoms, consequently leading to increased overall improvement of depression in adolescents.

1. Introduction

Adolescence is the period when drastic changes in physical, emotional, and cognitive states in an individual occur. These are challenged by various developmental tasks, thus increasing the vulnerability of a person to depressive disorders (Steinberg, 2016). Indeed, the prevalence of depression increases rapidly during the adolescent period. Jane Costello et al. (2006) reported that the overall prevalence of

depression was increased up to 5.6% in adolescents aged 13–18 years, compared to 2.8% in children under 13 years. Other studies have reported that the lifetime prevalence of major depression in late adolescence ranges from 14.3 to 24.0% (Lewinsohn et al., 1998; Merikangas et al., 2010). In addition to the high prevalence, the treatment of adolescent depression is difficult because the symptom presentation of depression in adolescents is substantially different from that in adults, and the treatment response in adolescents is poorer than that in adults

Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EGA, Exploratory Graph Analysis; GGM, Gaussian graphical model; LASSO, least absolute shrinkage and selection operator; MDD, major depressive disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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(Rice et al., 2019). Moreover, only two selective serotonin reuptake inhibitors (SSRI), fluoxetine and escitalopram, have been approved by the U.S. Food and Drug Administration. In addition, all the antidepressants were labeled with black box warnings of an increased risk of suicidality in adolescents (US Food and Drug Administration, 2004) (Food and Administration, 2004), which makes the treatment of adolescent depression more challenging. Thus, it is important to understand the symptom characteristics in adolescent depression and how they change over the course of treatment.

The literature has shown that the heterogeneity in depressive symptom presentation is a major issue for characterizing these symptoms and defining suitable treatment. For example, the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) comprise nine psychologically distinct features, including emotional, vegetative, and cognitive functions, as well as additional specifiers that have differential features: anxious distress, mixed, melancholic, and atypical (American Psychiatric Association, 2013). Thus, individual symptom clusters of depression seem to represent distinct psychological problems. More importantly, treatment response varies depending on psychological symptoms. For instance, some antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRI), are more effective for physical complaints than SSRI (Kennedy et al., 2016). This heterogeneity may serve as a barrier when assessing treatment outcomes (Fried and Nesse, 2015; Olbert et al., 2014) because most are evaluated based on the sum score of rating scales encompassing multiple depressive symptoms (Fried and Nesse, 2015).

Some recent studies have investigated treatment outcomes focusing on the clusters of symptoms and found that these clusters differed in their responsiveness to treatment (Chekroud et al., 2017; Katzman et al., 2020). One way to characterize depressive symptoms is to identify network structures and clusters among individual symptoms because such symptoms may interact dynamically with one another (Fried, 2015). For instance, psychomotor agitation may induce sleep disturbances, which can result in fatigue and difficulty in concentration. Therefore, recent studies have analyzed the network structure among depressive symptoms and found dynamic associations among individual symptoms (Beard et al., 2016; Fisher et al., 2017; Fried and Cramer, 2017). Well-defined symptom clusters in network analysis may help predict treatment outcomes of depression. For instance, the central symptoms identified by the analysis of a symptom network can predict treatment outcomes in psychiatric disorders (Elliott et al., 2020; Goldberg et al., 2020; Papini et al., 2020). The density of the network among the individual symptoms at baseline was also reported to have associations with the course of treatment outcomes in depression (Schworen et al., 2018; van Borkulo et al., 2015).

Most of these studies regarding symptom network and clusters of depression were conducted in adults. Only a few previous studies utilized cluster-based network analyses for characterizing depressive symptoms in adolescents (Bondar et al., 2020; Mullarkey et al., 2019). For instance, Mullarkey et al. (2019) found that self-hatred, loneliness, sadness, and pessimism were the most central symptoms in adolescent depression. Bondar et al. (2020) also identified two symptom clusters among 17 individual symptoms in adolescent depression and found that the course of treatment outcomes was different between the two clusters. However, symptom clusters of depression and how these clusters predict treatment outcomes in adolescents are largely unknown.

Symptom clusters in psychiatric disorders have been conventionally investigated using factor analysis, which suggested that depressive symptoms might be clustered into some sub-factors rather than one dimension (Clara et al., 2001; Guo et al., 2006; Norton et al., 2013). Despite its usefulness, the conventional factor analysis is limited because it cannot provide information on the graphical associations among the individual symptoms or the symptom clusters. Therefore, the present study aimed to identify network structures and clusters of depressive symptoms in adolescents, which have interactive associations among the

individual symptoms, and examine how each cluster was differentially associated with the trajectory of treatment outcomes in adolescents with depression in a prospective clinical trial. To this end, we assessed depressive symptoms before, during, and after SSRI treatment and conducted a network analysis to identify symptom clusters and determine how these clusters predict SSRI treatment outcomes. We hypothesized that there would be symptom clusters in adolescent depression. We also predicted that different clusters would predict differential treatment outcomes. Given the paucity of research on symptoms clusters of adolescent depression, we did not formulate specific hypotheses.

2. Methods

2.1. Participants

The present study included 95 adolescents diagnosed with major depressive disorder (MDD), aged 12–17 years. The participants were recruited from the psychiatric outpatient clinic for children and adolescents at the Seoul National University Hospital, Republic of Korea from August 2015 to June 2018. Participants were enrolled if they met four inclusion criteria: diagnosis of MDD; depressive symptoms lasting for 4 weeks or more; a score of 40 or higher on the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski and Mokros, 1996); and a score of 4 or higher on the Clinical Global Impression-Severity scale (Guy, 1976). Detailed information on the participants and procedures is described in our previous study (Lee et al., 2020). Among the 95 participants, four adolescents were excluded because they dropped out from the study before the second visit. Eight additional participants dropped out during the study period; however, they were included in the analysis because they were evaluated at two or more visits and the data for the patients who dropped out were imputed by the method of last observation carried forward.

2.2. Ethical considerations

Before enrollment, all parents and participants were provided with detailed information about the study, and written informed consent was obtained from all participants. The study protocol was approved by the Institutional Review Board for Human Subjects of Seoul National University Hospital.

2.3. Procedures

All participants were administered escitalopram for 8 weeks. The dose of escitalopram was 5 mg/day for the first week, 10 mg/day for the second week, and titrated to a maximum dose of 30 mg/day based on the clinical evaluation of depressive symptoms. Concomitant psychotropic medication, as well as any indicated psychotherapy was not permitted during the study period. Participants visited the hospital at baseline (V1) and weeks 1, 2, 4, 6, and 8 (V6) of treatment and were assessed with the CDRS-R at each visit.

2.4. Assessment

To assess the depressive symptoms of participants, the CDRS-R was used, which was developed based on the Hamilton Depression Rating Scale. The CDRS-R consists of 17 items, which are rated based on interviewer observations with the adolescent and their parents. Each item is rated on a 5- or 7-point Likert scale, with higher scores representing higher degrees of individual symptoms. In the present study, patients with a decrease of 40% or more on the CDRS-R total score were defined as responders, and others were categorized as non-responders (Wagner et al., 2003).

2.5. Constructing a psychological network and clustering depressive symptoms

To construct the psychological network among depressive symptoms and analyze symptom clusters, we utilized the CDRS-R score data from every visit ($n = 521$). In the construction of the symptom network, a Gaussian graphical model (GGM) was adopted, and parameters were tuned to minimize the extended Bayesian information criterion (Epskamp et al., 2018). The psychological symptom network consists of nodes and edges between the pair of nodes. Each node represents individual symptoms on the CDRS-R and the edges between the pair of nodes indicate the association between them. The green edges represent positive associations, the pink edges show negative associations, and the thickness of the edges designates the strength of the associations. The “least absolute shrinkage and selection operator” (LASSO) technique, based on the GGM, was used to enable the construction of a conservative network model, which shrink some weak edges that had insignificant coefficients to zero.

For the clustering analysis, the Exploratory Graph Analysis (EGA) (Golino and Epskamp, 2017), which is the GGM combined with a clustering algorithm for weighted networks (walktrap; Pons and Latapy, 2006) was adopted. The EGA provides a visual network plot, including information on the number of clusters and which items cluster together (Golino et al., 2020). The EGA could recover the number of factors with a higher accuracy than the traditional factor analysis when the correlation between factors was high (0.70; Golino and Epskamp, 2017). The analyses for network structure and clustering were conducted using bootnet (version 1.4.3) and EGAnet (version 0.9.6) packages, respectively, in R (version 3.6.3; <https://www.r-project.org/>).

2.6. Centrality indices and comparisons among edge weights

A network structure analysis enables the identification of the centrality of individual symptoms in terms of the betweenness, closeness, and strength centrality. The betweenness of each node indicates the number of shortest paths bridging any two nodes that pass through the specific node, while closeness represents the inverse of the sum of the total length of all the shortest paths to the other nodes from any specific node. Finally, strength is the sum of the absolute edge weight of a specific node. We calculated the centrality indices of individual symptoms and compared the strength of edge weights among the pairs of nodes with 2500 rounds of case-dropping bootstrapping.

2.7. Analysis of changes in scores in each cluster

Finally, we adopted a linear mixed model to investigate changes in scores in each cluster as dependent variables. Sex, age group (early; 10–14 years old and late; 15–19 years old adolescence; (Staff, 2011) and visit were designated as fixed variables, interactions of sex $\times$ visit and age group $\times$ visit were considered as the independent fixed effects, and individuals were considered as random effects. The effect size (Cohen’s d) for the differences in mean scores in each cluster were calculated by the mean differences between V1 and V6 divided by the pooled standard deviation (Cohen, 2013). The linear mixed model analysis was conducted using SPSS (version 21.0; IBM, Armonk, NY, USA).

3. Results

3.1. Demographic characteristics

Table 1 shows the demographic characteristics of all participants. Among a total of 91 participants, 64 (70.3%) were female and 27 (29.7%) were responders. Generalized anxiety disorder (30.8%) was the most common comorbid diagnosis, followed by social anxiety disorder (16.5%).

Table 1
Demographic characteristics of participants.

Variables	Value
Sex, n(%)	
Male	27 (29.7)
Female	64 (70.3)
Age, years, mean (SD)	14.77 (1.63)
Age group, n(%)	
Early adolescent	39 (42.9)
Late adolescent	52 (57.1)
Responder	
Responder	49 (53.8)
Non-responder	42 (46.2)
Diagnosis, n(%)	
Generalized anxiety disorder	28 (30.8)
Social anxiety disorder	15 (16.5)
Panic disorder	5 (5.5)
Conduct disorder	5 (5.5)
Post traumatic stress disorder	4 (4.4)
Obsessive compulsive disorder	4 (4.4)
Others	16 (17.6)

3.2. Network structures and centrality of the symptom items

The structures of symptom network and clustering are presented in Fig. 1 and S1. The network structures consisted of four clusters: impaired activity, somatic concerns, subjective mood, and observed affect. The cluster of impaired activity included the symptoms of impaired schoolwork, difficulty having fun, and social withdrawal. The cluster of somatic concerns consisted of symptoms like sleep and appetite. The cluster of subjective mood encompassed symptoms of irritability, guilty, and suicidal ideation. Finally, observed mood cluster had depressed facial affect, listless speech, and hypoactivity.

The centrality indices of individual symptoms are shown in Fig. S2. Depressed feelings were the most central symptom with the highest scores on all centrality indices. Low self-esteem also demonstrated high scores on the closeness and betweenness centralities. Finally, comparisons of edge weights among the pairs of symptom nodes are shown in Fig. S3. The pairs of Depressed Facial Affect–Listless Speech, Difficulty Having Fun–Social Withdrawal, Depressed Feelings–Suicidal Ideation, and Impaired Schoolwork–Low Self–Esteem presented higher edge weights than other pairs of symptoms.

3.3. Trajectory of mean scores in the four clusters

Fig. 2 and Table 2 show the changes in mean scores in the four clusters during the study period. The main effect of a visit was significant with decreasing symptom severity alongside visits in all four clusters in all participants and the responder subgroup; however, the degree of symptom improvement differed among the four clusters. The effect size of score differences between V1 and V6 was the highest in the subjective mood cluster in all participants (Cohen’s $d = 1.075$), whereas it was the lowest in impaired activity in all the participants ($d = 0.501$). In the responder subgroup, the effect size of score differences between V1 and V6 was also the highest in the subjective mood cluster ($d = 2.139$), with the lowest effect in observed affect ($d = 1.081$). In the non-responder group, the main effect of visits was significant in improving symptoms in the somatic concern and observed affect clusters, whereas impaired activity and subjective mood did not show improvements.

4. Discussion

The present study investigated the network structures and clusters among symptoms in adolescent depression and changes in cluster-based symptom severity during an open trial of treatment with escitalopram. The cluster analysis revealed that the symptoms included in the CDRS-R encompassed four clusters: impaired activity, somatic concerns, subjective mood, and observed affect. Among the four clusters identified,

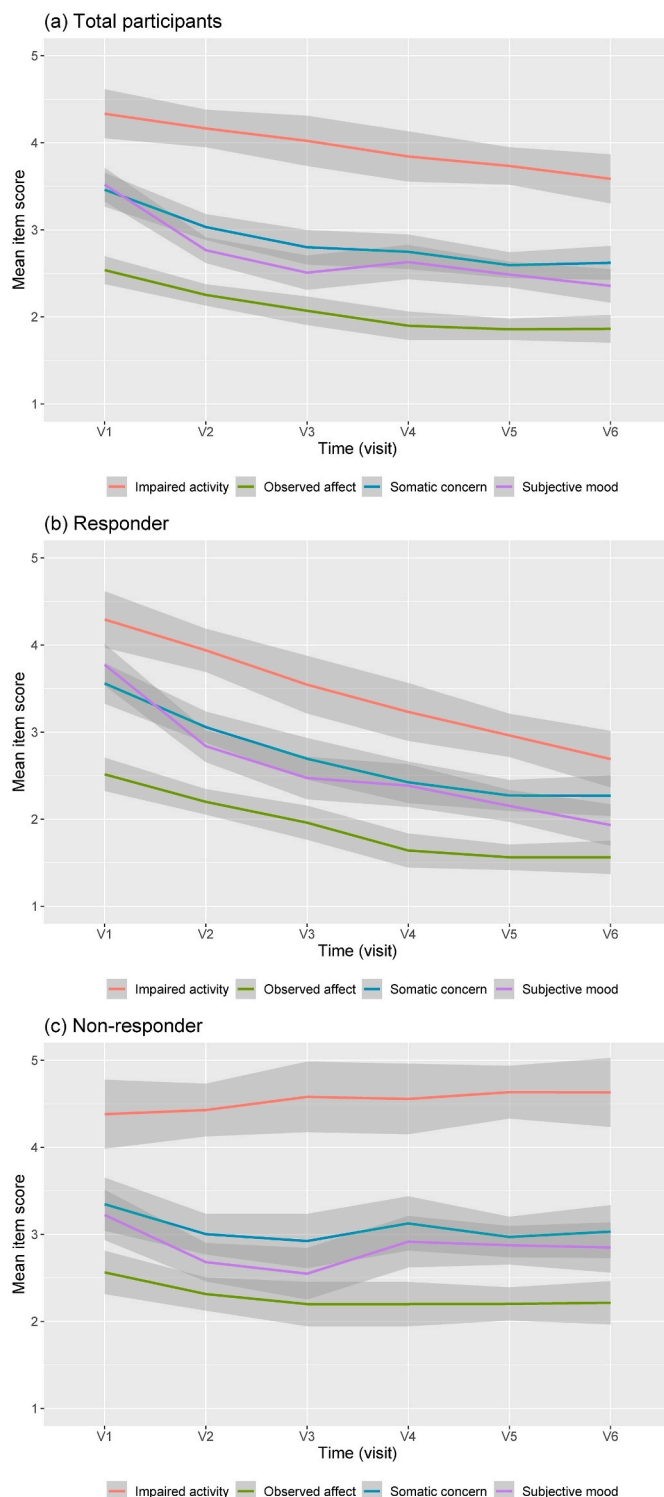


Fig. 1. Symptom clusters of depression assessed using the Children's Depression Rating Scale. Circles indicate individual nodes of symptoms and lines represent the edges. Circles with the same colors comprise the same cluster. The thickness of the lines indicates the weights of the edges.

the effect size of improvement was the highest in the cluster of subjective mood comprising depressed feelings, excessive guilt, low self-esteem, morbid and suicidal ideations, and excessive weeping. Moreover, the subgroup analysis found that subjective mood showed the biggest improvement among the four clusters in the responder groups, whereas it did not improve significantly in the non-responder group,

unlike the clusters of somatic concern and observed affect.

Given the lack of research utilizing cluster-based or network analyses for characterizing depressive symptoms in adolescents, our results of symptom clusters were compared to previous studies using conventional factor analysis. Although different analytic approaches were used, our symptom clusters had similarities with previous findings of factor structures of the CDRS-R (Guo et al., 2006; Poznanski et al., 1984; Uher et al., 2012). The items on the original CDRS-R are categorized according to four groups: mood, somatic, subjective, and behavior. Another factor analysis of the CDRS-R reported the factor structures consisting of observed, depressive mood, anhedonia, morbid thoughts, and somatic symptoms, which are similar to those in our observed clusters; however, while these studies revealed multiple symptom domains of depression in adolescents, they did not investigate the trajectory of each symptom domain with the treatment course. Our study identified that these symptom clusters had different trajectories of response to pharmacologic treatment. This finding has a significant clinical implication suggesting that symptom clusters should be considered during treatment of adolescent depression.

Recently, a secondary analysis using data from the Treatment for Adolescents with Depression Study (TADS) evaluated symptom clusters of depression from the CDRS-R and investigated the change of each symptom cluster based on treatment allocation (Bondar et al., 2020). They identified two clusters of depressive symptoms: cluster 1 included depressed mood, difficulty having fun, irritability, social withdrawal, sleep disturbance, impaired schoolwork, excessive fatigue, and low self-esteem, and cluster 2 comprised increased appetite, physical complaints, excessive weeping, decreased appetite, excessive guilt, and morbid and suicidal ideations. They also reported that the symptoms in cluster 1 improved significantly more in the group treated with fluoxetine or fluoxetine plus cognitive behavioral therapy (CBT) than in the control group, whereas cluster 2 did not show significant differences in improvement between the treatment and control group. Their findings also suggest that the improvement induced by treatment may differ based on the symptom clusters in adolescent depression, which is consistent with results of the present study. Meanwhile, the cluster composition in the study of Bondar et al. (2020) was substantially different from that in our study, although both studies utilized the same assessment tool (CDRS-R). This differential composition of clusters may be caused by the different analysis strategy for composing the clusters between our study (EGA) and the previous study that used Ward's method with Euclidian distances for hierarchical agglomerative clustering. Nevertheless, all the symptoms of impaired activity cluster in our study were included in the cluster 1 in the study of Bondar et al. (2020), which suggests the common features of adolescent depression in both studies, despite differential analysis techniques. To confirm these findings, future studies are needed because the differences among individuals enrolled in the study could contribute to the differences in cluster composition.

Although the present study did not include information on the mechanism of action that explained the greatest improvements in the subjective mood cluster, it is important to explore the hypothetical mechanism. Considering the mechanism of action of escitalopram, an SSRI, is important, because it was prescribed to our participants and we did not allow any psychotherapeutic approaches, such as CBT. The efficacy of psychotropic agents on depression are known to be substantially different according to symptom profiles and the medication's mechanism of action. For instance, a meta-analysis reported that the effect size of SSRIs was the largest for depressed mood on the Hamilton Rating Scale for Depression, whereas it was very low or even negative for early insomnia, agitation, and gastrointestinal somatic symptoms (Hieronymus et al., 2016). Our findings can be considered consistent with this previous study, which presented the biggest effect of SSRIs on subjective mood. Conversely, SNRIs, such as duloxetine and venlafaxine, are suggested to better relieve somatic symptoms such as pain and fatigue accompanied by depression, while vortioxetine is more effective in

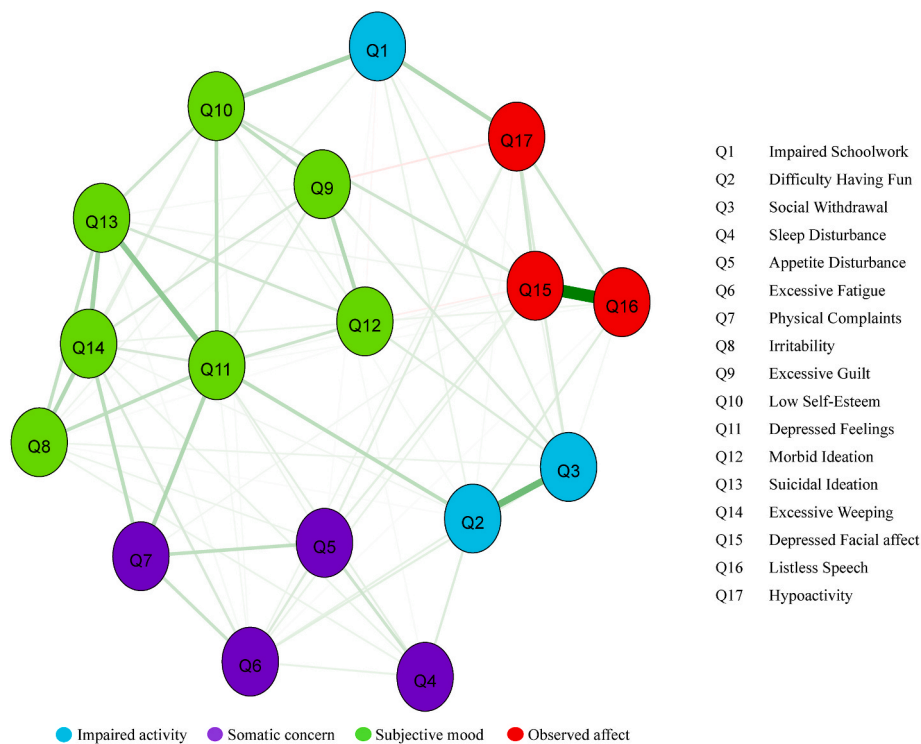


Fig. 2. The trajectory of mean scores in the four clusters.

Table 2
The estimates of mixed model and effect size of differences between V1 and V6.

Participants	Statistical value	Impaired activity	Somatic concern	Subjective mood	Observed affect
Total	Score at V1; mean(SD)	4.34 (1.34)	3.46 (2.46)	3.53 (3.53)	2.54 (4.54)
	Score at V6; mean(SD)	3.58 (1.44)	2.64 (2.95)	2.37 (3.93)	1.86 (4.76)
	Effect size ^a	0.501	0.803	1.075	0.743
	Estimates ^b (p value)				
	sex (male)	0.646 (0.045)	−0.299 (0.164)	−0.266 (0.239)	0.258 (0.164)
	group (younger)	−0.495 (0.105)	−0.175 (0.391)	0.109 (0.611)	−0.26 (0.14)
	visit	−0.130 (<0.001)	−0.155 (<0.001)	−0.159 (<0.001)	−0.118 (<0.001)
Responder	Score at V1; mean(SD)	4.29 (1.39)	3.56 (2.97)	3.79 (3.92)	2.52 (4.98)
	Score at V6; mean(SD)	2.69 (0.94)	2.27 (0.67)	1.94 (0.63)	1.55 (0.51)
	Effect size*	1.241	1.619	2.139	1.081
	Estimates** (p value)				
	sex (male)	0.804 (0.021)	0.033 (0.893)	−0.084 (0.757)	0.601 (0.005)
	group (younger)	−0.977 (0.004)	−0.275 (0.238)	−0.242 (0.351)	−0.012 (0.954)
	visit	−0.366 (<0.001)	−0.227 (<0.001)	−0.318 (<0.001)	−0.149 (<0.001)
Non-responder	Score at V1; mean(SD)	4.40 (1.29)	3.35 (2.95)	3.22 (3.00)	2.56 (4.83)
	Score at V6; mean(SD)	4.62 (1.20)	3.07 (2.06)	2.87 (3.98)	2.21 (4.85)
	Effect size ^a	0.198	0.279	0.538	0.416
	Estimates ^b (p value)				
	sex (male)	0.29 (0.547)	−0.817 (0.025)	−0.793 (0.016)	−0.07 (0.812)
	group (younger)	−0.116 (0.8)	0.001 (0.998)	0.568 (0.068)	−0.491 (0.085)
	visit	0.066 (0.089)	−0.073 (0.029)	−0.044 (0.076)	−0.082 (0.002)

^a Effect size for the differences of scores between V1 to V6 (Cohen's d).
^b The estimates of mixed model (only the estimates for the main effects of sex, age group and visit were presented).

relieving cognitive dysfunction (Green et al., 2017; Kemp et al., 2008; Kennedy et al., 2016). In addition, dopaminergic antidepressants like bupropion were more effective in patients with anhedonia and loss of motivation (Perlman et al., 2019). These findings suggest that the assessment of treatment effects should be based on the individual symptoms or symptom clusters rather than the sum score of all depressive symptoms (Chekroud et al., 2017; Uher et al., 2009). When assessing the depressive symptoms of youths, clinicians could be helped by checking the sum scores of the individual clusters suggested in this

study for finding individualized treatment strategy to improve the treatment outcomes.

In the present study, impaired schoolwork, difficulty having fun, and social withdrawal were clustered together in impaired activity. Contrary to subjective mood, the mean scores in the impaired activity cluster were the highest at baseline among the four clusters and the improvement with treatment was also the lowest. These findings imply that this cluster is less responsive to pharmacological treatment in a clinical setting, which is important to consider. First, the weak response of the impaired

activity cluster may be associated with the effect of SSRIs as discussed above. Future studies including other psychotropic agents, such as SNRIs or norepinephrine-dopamine reuptake inhibitors, are needed for the comparison of different types of medication. Second, the present study was performed during a relatively short period of 8 weeks. It is possible that the natural course of treatment response in the impaired activity cluster requires more time for recovery than the subjective mood cluster, which can be confirmed with a longer follow-up period. Third, recently the behavioral activation like physical activity has been widely studied as an effective intervention for the adolescents' depression (Bailey et al., 2018; Carter et al., 2016). However, most of previous studies were also examined by the sum scores of depressive symptoms. Thus, future studies considering the improvement of the symptom clusters by the intervention of physical activity might reveal the mechanisms of the improvement in the depression symptoms of adolescents.

Finally, these three symptoms are assumed to be a school-related phenomenon, considering the cultural background of collectivism and the school system in Korea (Hong and Min, 2018; Perret et al., 2021). Korea has a collectivistic culture that emphasizes interpersonal harmony with peers rather than individual interests (Chong et al., 2006; Kashima et al., 1995; Shin and Yu, 2012). In addition, the schooling in Korea has compulsory class-based lessons with long school hours, typically from 08:00 to approximately 16:30 or even to 22:00. Therefore, adolescents spend most of their time in a classroom with the same peers, allowing for high levels of peer pressure. Thus, it may be difficult to recover interpersonal relationships once adolescents are excluded from a peer group. Bullying or social isolation are often reported to occur from peers in the same class in Korea (Koo et al., 2008). Peer rejection is a major source of depression in adolescents (Platt et al., 2013). Finally, the emphasis on school performance in Korea (Ang et al., 2009; Crystal et al., 1994) may also contribute to depression. Our findings of small improvements in this cluster suggest that addressing school-related problems, such as peer relationships and worry about schoolwork, should be considered when adolescents are treated for depression, alongside biological treatments.

In the present study, feelings of depression were identified as the most central symptom associated with the highest scores on closeness and betweenness. Our findings are consistent with those of the DSM-5, adopting feelings of depression as a core diagnostic criterion, which suggests that asking adolescents if they are experiencing any feelings of depression is essential to assess their overall depression state. In addition, depressed feelings were strongly connected to suicidal ideation. Thus, the evaluation of suicidal ideation is needed during the assessments of adolescent depression when the levels of their depressed feelings are high. Alongside depressed feelings, self-esteem presented the second highest score on closeness and betweenness. Notably, self-esteem was strongly connected to impaired schoolwork, although it was included in other clusters. These findings imply that low self-esteem, especially related to impaired schoolwork, is also a central symptom in adolescent depression. Thus, if the adolescents are experiencing low self-esteem, checking their schoolwork are needed during the assessment interview.

5. Limitations

The present study has some limitations. First, the sample size is small. To estimate the network structure of individual symptoms more accurately, a larger sample size is necessary because the number of estimation parameters increases rapidly alongside the number of symptoms (namely, $17 \times 16/2 = 136$ for the network structures among 17 nodes). Although we have repeated measures data and used LASSO and bootstrapping to overcome this limitation, future studies with a larger sample size are needed to confirm our present findings. Second, symptom network and clustering may be sensitive to the composition of the population; however, our sample included a limited population, which was recruited from tertiary psychiatric clinics at the university hospital. This might limit the generalizability of our findings to other

populations, such as the community sample. Thus, future studies including other populations are needed to confirm our findings. Finally, the present study adopted a restricted study design to prevent other psychotropic or other psychotherapeutic modalities. For instance, other psychotropic agents, such as SNRIs, may have differential effects on the trajectory of symptom clusters; however, other antidepressants are not approved for use in adolescent populations, which limits their use in additional studies. Thus, the underlying mechanisms of treatment response in each symptom cluster cannot be explained due to the lack of comparisons among different treatment modalities. Future studies including other psychotropic agents might help to reveal the underlying mechanisms of differential improvement based on the clusters in adolescent depression.

6. Conclusion

Our present study identified four symptom clusters of adolescent depression: impaired activity, somatic concerns, subjective mood, and observed affect. These symptom clusters differed significantly in the treatment response to escitalopram, with the greatest improvement observed in subjective mood, while the lowest response was in the impaired activity cluster. These findings suggest that symptom clusters should be considered in the treatment of adolescent depression. Future studies including other psychosocial interventions or medications with cluster analysis are needed to reveal the mechanism underlying the differential improvement of symptom clusters. This study emphasizing the approach of examining improvement in clusters of depression symptoms by treatment strategy could help individualize treatment decisions by prioritizing treatment strategies that have higher demonstrated impact for each individual patient's primary depression symptom clusters.

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CRediT authorship contribution statement

Kyoung Min Kim: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Kyung Hwa Lee:** Conceptualization, Formal analysis, Writing – review & editing. **Haebin Kim:** Conceptualization, Data curation, Writing – review & editing. **Ok Kim:** Writing – original draft, Writing – review & editing. **Jae-Won Kim:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have no potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychires.2024.02.001>.

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