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Research paper

Impact of age at onset on the phenomenology of depression in treatment-seeking adults in the STAR*D trial

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A B S T R A C T

Background: — Adolescence is characterized by biological, emotional, and behavioral changes. The onset of depression during this vulnerable time may confer specific risks. This study examined whether symptoms of depression were associated with age at onset (AAO), and whether AAO impacted depression symptom networks in adulthood.

Methods: — Data were from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. 3,184 depressed participants were included in analyses. A series of multiple regressions examined whether pretreatment differences in depression item-level symptom severity varied by AAO. Participants were divided into four groups based on AAO; GLASSO networks of depressive symptoms were estimated in each group and tests of differences between networks were performed.

Results: — Earlier AAO was associated with more severe symptom levels, with the exception of sleep—which increased with AAO, and loss of libido, psychomotor disturbance, and appetite-weight disturbance, which were invariant with AAO. In network analyses, the adolescent AAO symptom network significantly differed from the young adult and middle age AAO networks in structure and strength. In contrast, the child AAO network differed from the middle age AAO network in strength only.

Limitations: — Age at onset was recalled retrospectively and may be subject to bias. Future prospective studies should be conducted to address this limitation.

Conclusions: — Adolescence stands out as a time when onset of depression is associated with specific network characteristics. The unique severity of symptoms and network strength and structure caused by onset of depression during adolescence highlights the long-lasting impact of depression on the developing brain.

1. Introduction

1.1. Adolescent brain development

Adolescence is the developmental transition that bridges youth and adulthood. It is marked by behavioral features (sensation-seeking, parent-adolescent conflict, romantic interest), environmental influences (new independence and socioemotional maturity), paralleled by changes in the brain (myelination and pruning, hormonal influences) (Spear, 2000). This combination of changes in brain and behavior makes for a complicated time in a young person's life, leaving her vulnerable to the development of myriad psychological disorders such as depression (Casey et al., 2008).

A coordinated set of structural and functional neurobiological changes occur during adolescence. For example, we know that brain development is heterochronous—distinct structures and functions of brain regions and circuits mature at different rates (Giedd et al., 1999; Steinberg, 2005). Early adolescence is characterized by the development of circuits involved in arousal, motivation, and emotion. During this time, substantial myelination occurs, for example, the prefrontal cortex expands its connectivity to the whole brain, forming new linkages across distal regions. Later adolescence is characterized by pruning of excess linkages resulting in more efficient neural circuitry responsible for enhanced information processing (Steinberg, 2005). Together, adolescence is a unique time in neurodevelopment, which may explain why rates of mood and anxiety disorders increase precipitously during this time (Casey et al., 2008).

Thus, the long-term impact of a depressive episode on the brain and the concomitant psychological impacts are likely to depend on a myriad of factors, including the current stage of neurobiological maturation. Because having one depressive episode leaves an individual more likely to have future episodes (i.e., neural (Chan et al., 2016) and psychological (Burcusa and Iacono, 2007) scars), it may be that depressive episodes during sensitive neurodevelopmental periods fundamentally alter the presentation of depression, if it reemerges in adulthood.

1.2. Early onset depression and its relationship to depression in adulthood

Adults with earlier age at onset (AAO) depression differ from their later-AAO counterparts in several ways. They are at increased risk for more severe depressive illness, and more medical, psychiatric, and personality comorbidities (Alpert et al., 1999; Fava et al., 1996; Klein et al., 1999; Korczak and Goldstein, 2009; Ramklint and Ekselius, 2003; Zisook et al., 2004). Suicidality is more common the

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earlier the AAO (Korczak and Goldstein, 2009; van Noorden et al., 2011; Weissman et al., 1999; Zisook et al., 2004). Adolescent AAO is also associated with greater psychosocial impairment in adulthood (van Noorden et al., 2011; Weissman et al., 1999; Wilson et al., 2015; Zisook et al., 2004). While some studies indicate adolescent AAO depression is associated with greater risk for depression in adulthood (Lewinsohn et al., 2003; Pine et al., 1999; Weissman et al., 1999; Wilcox and Anthony, 2004; Wilson et al., 2015), other well-controlled research indicates that it does not (Copeland et al., 2009). Lastly, some research suggests that in addition to suicidality, irritability may be specifically associated with younger AAO (Parker et al., 2003; Ramklint and Ekselius, 2003).

1.3. AAO in STAR*D

Three reports from Zisook and colleagues have utilized STAR*D to examine correlates of AAO in treatment-seeking adults with depression. A preliminary study utilized the first 1500 STAR*D participants dichotomized AAO into pre-adult (<18) and adult (>=18) (Zisook et al., 2004). The authors included gender, current age, and length of illness in their models. About a third of participants reported a pre-adult AAO. Early AAO was associated with sociodemographic characteristics such as female gender, single marital status, and lower educational attainment. Early AAO was associated with several clinical characteristics of depression including longer total duration of illness, longer and more frequent depressive episodes, more persistent suicidality, greater symptom severity, and a greater number of Axis I comorbid symptoms. With regard to individual symptoms, irritability and suicidal ideation were linked with pre-adult onset depression. The second report utilized the full STAR*D dataset of about 4000 participants and included similar analyses to the original study (Zisook et al., 2007b). Again, pre-adult onset of depression was associated with female gender, family history of depression, and greater suicidality. Other results, however, did not replicate.

In the most recent AAO analysis of STAR*D published in 2007, the authors compared specific subgroups of adults with depression according to their AAO (Zisook et al., 2007a). The subgroups were defined as child (<12), adolescent (12–17), early adult (18–44), middle age (45–59), and late adult onset (> = 60). Both clinical features and treatment outcomes were tested across the groups, and the authors reported that earlier AAO was associated with greater medical and psychiatric comorbidity, family history of depression, greater severity of current symptoms, poorer psychosocial adjustment, and increased past and present suicidality. Cognitive features associated with earlier AAO included more negative self-view, negative view of future, suicidal ideation, and sensitivity to interpersonal rejection. Thus, the STAR*D data have yielded mixed findings with regard to the impact of depression AAO on adult depression symptom patterns. Since the most recent report in 2007, however, there have been substantial advancements in multivariate analytic approaches that may uncover more nuanced patterns of results.

1.4. Psychological networks

One such multivariate approach is network analysis, which has gained popularity in recent years as a novel way to describe and visualize associations between psychological symptoms. In psychological networks, nodes represent symptoms, and edges represent partial correlations between symptoms (i.e. the unique association between symptoms, net of all other symptoms). Network analysis has already been employed in the study of depression, and even in the STAR*D dataset (Fried et al., 2016; Fried and Nesse, 2015, 2014). This work has demonstrated that network features are associated with important clinical outcomes. For example, a prior study in the STAR*D trial demonstrated that the symptoms most central in the network were also those that caused the most depression-related functional impairment (Fried and Nesse, 2014). Work using a Dutch sample found that more strongly connected networks were associated with poorer long-term outcomes following antidepressant treatment (Borkulo et al., 2015).

1.5. Motivation for the current study

The studies discussed above highlight the potential importance of AAO in the phenotype of depression if it presents in adulthood. In parallel, psychological network analysis is a novel and effective approach to examine global associations between symptoms in different groups of people. Thus, the aim of the present study is to examine how individual symptoms of depression are associated with AAO. We also utilize psychological network analysis as a tool to look at the impact of AAO on the structure of depressive symptom profiles.

2. Methods

2.1. STAR*D protocol

The data used for this study were from the NIH-supported Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Fava et al., 2003). STAR*D was a multisite sequential randomized controlled trial. All participants began s-citalopram and were subsequently randomized to a medication adjustment or psychotherapy when remission was not achieved. Full background, rationale, and procedures are described elsewhere (Fava et al., 2003).

2.2. Participants

To be enrolled in the STAR*D study, participants had to be 18–75 years old, meet DSM-IV criteria for a current major depressive episode, and have a Hamilton Rating Scale for Depression (HRSD (Hamilton, 1960)) score of at least 14 (considered at least moderate depression severity). Full inclusion/exclusion criteria are described elsewhere (Fava et al., 2003). A total of 4041 participants were enrolled in the STAR*D study. All participants provided written informed consent prior to enrollment. The final sample in these analyses included 3184 participants because complete pre-treatment HRSD and all covariate data was required. Our sample constituted 79% of the enrolled participants.

2.3. Outcome measures

We analyzed the clinician-rated HRSD (Hamilton, 1960), which was completed prior to the start of treatment. The HRSD is comprised of 17 items rated on three- or five-point scales. Several adjustments were made to this scale to render the data appropriate for network analysis. First, upon examination of the distributions of individual symptoms, the "Lack of Insight" item was highly skewed and kurtotic (skew = 4.80, kurtosis = 23.03). Since participants were enrolled in a treatment trial, they almost all shared a high level of insight into their disorder limiting variability in this item. Thus, this symptom was excluded from subsequent analyses. Second, since HRSD items are rated on several different ordinal scales, a linear transformation was employed to fit all symptoms on a five-point scale. This allowed for easier interpretation of analyses. Third, the three sleep items (early, middle, and late insomnia), the two psychomotor items (agitation and retardation), the appetite loss and weight loss items, and the two anxiety items (psychic and somatic anxiety) were collapsed into aggregate items of sleep disturbance, psychomotor disturbance, appetite-weight disturbance, and anxiety, respectively. This ensured that the edges in the estimated networks represent unique, not redundant, associations. The final HRSD was comprised of 11 symptoms.

2.4. Age at onset

Before starting treatment, depression AAO was retrospectively reported by patients to an interviewer. The range of AAO was 0–74 years of age. Full details on the definition of AAO are reported elsewhere (Zisook et al., 2004). The current dataset was then split into quartiles based on AAO. Four groups emerged which we define as follows: (1) Child onset for ages 0–15; (2) Adolescent (adol) onset for ages 15–22; (3) Young Adult (YA) onset for ages 22–36; (4) Middle Age (MA) for ages 36–74. We acknowledge these age-ranges are somewhat arbitrary, but equal sample sizes were prioritized in order to reliably compare networks. This is because power to detect networks increases with sample size (van Borkulo et al., 2017), network stability and accuracy are impacted by sample size (Epskamp et al., 2018), and network comparisons are most accurate with equal sample size (van Borkulo et al., 2017). Furthermore, it has been suggested that "adolescence eludes precise characterization of its ontogenetic time course" (Spear, 2000). This sentiment is echoed in the literature as a myriad of cutoff ages have been utilized to dichotomize early and late onset of depression. Legal adulthood (18 years of age) is sometimes used (Zisook et al., 2007; Zisook et al., 2004), but has ranged to 21 (Klein et al., 1999), 25 (Parker et al., 2003), or even 26 (Ramklint and Ekselius, 2003). Our cutoff for adolescent depression of 22 is in the middle of this range, and parallels findings from neuroscience suggesting that the development of prefrontal cortex and other regions necessary for emotional regulation does not complete until the early to mid 20 s (Casey et al., 2008).

2.5. Covariates

AAO is invariably related to current age and number of past episodes. Given earlier AAO has been associated with greater severity and functional impairment (Weissman et al., 1999), although not ubiquitously (even within the STAR*D dataset; (Zisook et al., 2007a, b, 2004), length of current episode, and quality of life were also included as covariates. Current age, number of past episodes, and length of current episode were reported to an interviewer. Quality of life was self-reported by the patients via the Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott et al., 1993). Greater scores indicate better quality of life.

2.6. Statistical analyses

All analyses were conducted in R, version 3.5.1 (R Core Team, 2018). The significance level for all analyses was $\alpha \leq .05$.

2.6.1. General differences in symptom levels

A series of linear regressions were performed treating age a continuous variable to test whether AAO significantly predicted levels of symptoms. A series of ANOVAs were performed to test differences in covariates and baseline HRSD symptoms among the four AAO groups.

2.6.2. Network estimation

Network structures for each of the four AAO groups were estimated separately using the R package qgraph version 1.6.1 (Epskamp et al., 2012). Edge weights represent partial correlations between symptoms to reveal the unique associations between symptoms. In order to determine which partial correlations may be spurious and therefore should be removed from the network, the L1-regularization technique was employed. The L1-regularization technique minimizes the Extended Bayesian Information Criterion and shrinks edges to zero that may be false positives. These methods have been shown to yield accurate and stable network estimates (Foygel and Drton, 2010). This procedure finds a balance between parsimony and goodness-of-fit and yields a sparse network of pairwise interactions between symptoms.

2.6.3. Controlling for potential confounders

Several confounding variables differed between AAO groups, which could potentially impact differences between networks. Following the method proposed in Borkulo et al. (2015), we performed a series of regressions to remove variance due to four potential confounders in a stepwise manner. We controlled for variance due to current age, length of current episode, number of past episodes, and quality of life. Differences between original networks and controlled networks were examined to determine differences due to confounders (See Supplement). The networks resulting from controlling for covariates likely represent networks that are more specific to effects of AAO.

2.6.4. Differences in network structure

The R package, NetworkComparisonTest version 2.0.1 (NCT, (van Borkulo et al., 2017)) with 1000 permutations was used to compare networks among the four groups in two ways: network structure and global strength. NCT compares the distributions of the edge weights between two networks to test the null hypothesis of invariant network structure. NCT compares the overall connectivity of two networks to test the null hypothesis of invariant global strength.

2.6.5. Centrality analyses

Node strength represents how strongly a node is directly connected to all other nodes. Closeness represents how strongly a node is indirectly connected to all other nodes. Betweenness represents how important a node is on the path between other nodes. Expected influence is a metric similar to strength, accounting for negative associations between nodes. These four indices were calculated for each symptom of each network using qgraph (Epskamp et al., 2012). Qualitative differences between the groups were examined visually.

2.6.6. Network accuracy

The R package bootnet version 1.2 (Epskamp et al., 2018) was used to construct bootstrap confidence intervals around each network edge-weight. Bootnet was also to examine the stability of centrality indices using an m out of n bootstrap, where m cases are progressively dropped from the total sample n and correlations are computed between these reduced samples and the full sample.

3. Results

3.1. Symptom-Level differences

Results from analyses regressing symptom levels on AAO controlling for current age, length of current episode, number of previous episodes, and quality of life showed significant decreases in symptom severity with increasing AAO for energy loss ($\beta = -0.024$, $p = .03$), depressed mood ($\beta = -0.023$, $p = .002$), hypochondriasis ($\beta = -0.01$, $p = .02$), guilt ($\beta = -0.14$, $p < .0001$), suicidality ($\beta = 0.093$, $p < .0001$), anhedonia ($\beta = -0.0032$, $p = .007$), and anxiety ($\beta = -0.076$, $p < .0001$). There was no significant change in libido ($\beta = -0.043$, $p = .8$), psychomotor disturbance ($\beta = 0.0043$, $p = .6$), and appetite-weight disturbance ($\beta = 0.034$, $p = .5$) as a function of AAO. Sleep disturbance severity increased with increasing AAO ($\beta = 0.083$, $p < .0001$; Fig. 1; Table 1).

3.2. Group characteristics for network analyses

In our sample of 3184 individuals, 795 fell into each of the AAO groups (Fig. S1; Table 2). Significant differences were observed between the groups in current age ($F = 952.12$, $p < .0001$), such that current age increased with age at onset; length of current episode ($F = 11.92$, $p = .0006$), such that earliest and latest onset were associated with longer current episodes; and number of past episodes ($F = 132.21$, $p < .0001$) such that earlier AAO was associated with a greater number of past episodes. There were trending differences

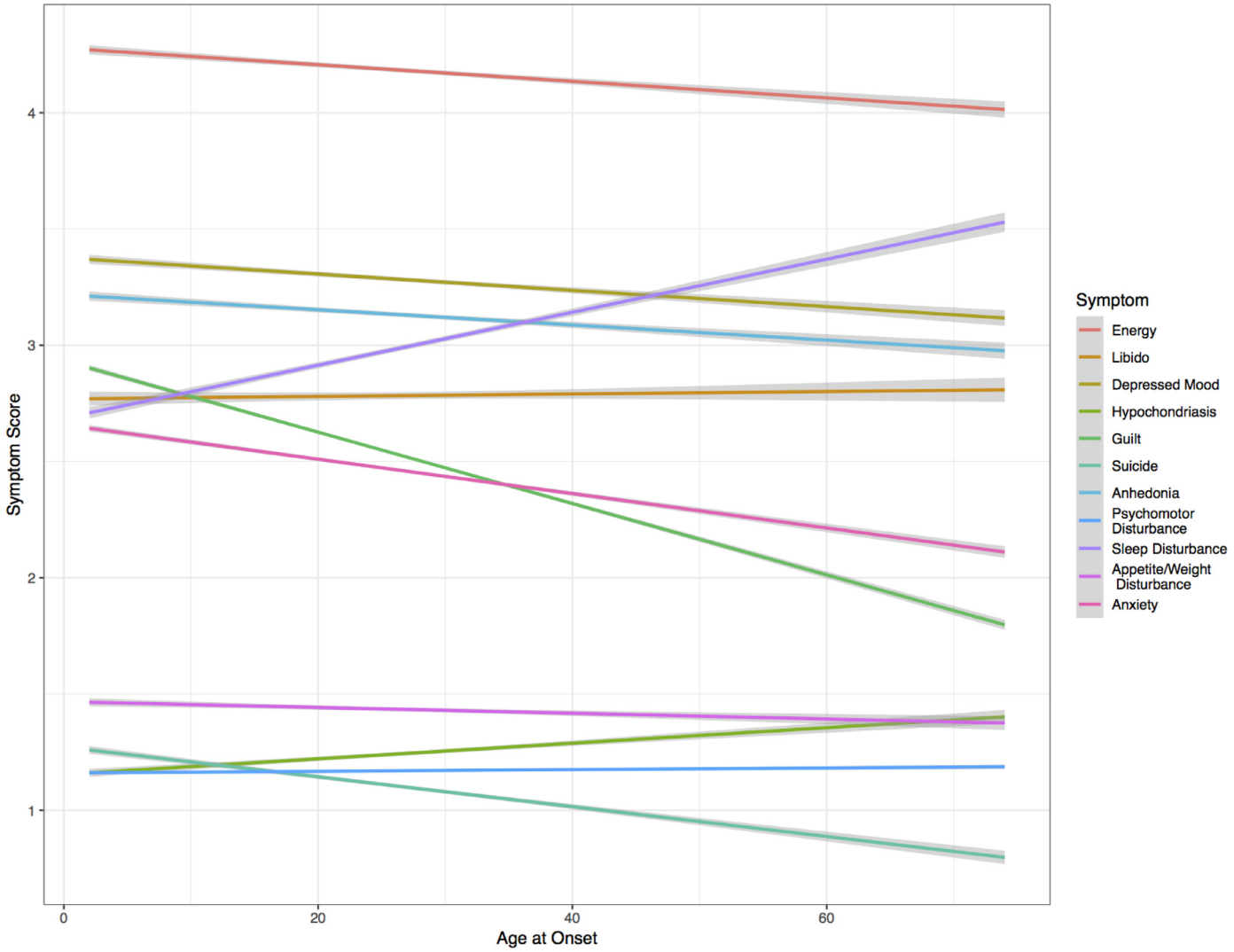

Fig. 1. Regression slopes for each symptom as a function of age at onset, controlling for current age, length of current episode, number of past episodes, and current quality of life. Standard error regions are shaded in grey. Note that sleep disturbance increases in severity as a function of AAO, whereas nearly all other symptoms decrease in severity as a function of AAO. .

Table 1
Linear regression (adjusting for current age, length of current episode, number of previous episodes, and quality of life).

Symptom	Beta	F-value	p-value
Energy	−0.024	4.83	.03
Libido	−0.043	.0044	.8
Depressed mood	−0.023	9.86	.002
Hypochondriasis	−0.01	4.99	.02
Guilt	−0.14	121.25	<0.0001
Suicide	−0.093	27.08	<0.0001
Anhedonia	−0.0032	7.23	.007
Psychomotor disturb	0.0043	.21	.6
Sleep	0.083	42.06	<0.0001
Appetite-weight	0.034	.39	.5
Anxiety	−0.076	47.53	<0.0001

between the groups in quality of life ($F = 3.43$, $p = .06$) such that quality of life marginally improved with later age at onset (Table 2).

3.3. Connectivity

Networks were estimated from pretreatment symptom data, controlling for current age, length of current episode, number of past episodes, and quality of life (Fig. 2). Global strength and network structure were compared pairwise using the NetworkComparisonTest (Table 3). The adolescent AAO differed marginally from the young adult AAO network and significantly from the middle age AAO network in both strength (YA: $p = .07$, MA: $p = .002$), and structure (YA: $p = .08$, MA: $p = .001$). The child AAO network differed significantly from the middle age AAO network in strength but not structure (strength: $p = .047$, structure: $p = 0.13$). The child network did not differ from the adolescent (strength: $p = .52$, structure: $p = .63$) or young adult networks (strength: $p = .24$, structure: $p = .54$). The young adult and middle age networks did not differ in strength ($p = .55$) or structure ($p = .49$).

Visual inspection of the relative centrality of nodes within the AAO networks (left side of Fig. 2) illustrated that depressed mood was most central in the adolescent AAO network relative to other AAO networks. Centrality analysis indicated that guilt and sleep were nodes greatest in closeness and betweenness in the adolescent AAO network (Figure S3). The adolescent AAO network also contained the greatest number of edges (8) while the middle age AAO network contained the fewest (4).

4. Discussion

It has been suggested that the age at which an individual develops a

Table 2
Group characteristics. Means (standard deviations) by Child (0–15 years), Adolescent (15–22 years), Young Adult (22–36 years), and Middle Age (36–74 years) onset groups (N = 795/group).

Variable	Child	Adol	Young Adult	Middle Age	F-value	p-value
Current age (years)	35.59 (12.5)	35.84 (12.6)	40.42 (10.8)	53.25 (9)	952.12	<0.0001
Length curr ep (days)	990.44 (2327)	697 (1485)	647.29 (1070)	716.66 (1159)	11.92	.0006
No. past ep	7.9 (10)	5.94 (9.2)	5.26 (10)	2.63 (4.6)	132.21	<0.0001
Quality of life	41.25 (15)	42.1 (15.1)	41.8 (15.1)	42.84 (15.7)	3.43	.06
Age at onset (years)	11.52 (3)	18.62 (2)	28.87 (4.1)	47.65 (8.6)	16,211	<0.0001
Total HRSD	26.67 (5.9)	26.38 (6.11)	26.47(5.9)	25.7 (5.8)	8.92	.003

psychiatric disorder can have long-standing downstream consequences for their life, beyond simply the years of impaired functioning. This study utilized a large representative sample and applied network analyses to enhance our understanding of the implications of AAO for the phenomenology of depression in adulthood. If a depressive episode first emerges in childhood or late adolescence (up to age 22), the presentation of a subsequent depressive episode in adulthood appears to be fundamentally altered. Importantly, these effects were significant beyond the effects of other factors including age, number of past episodes, current quality of life, and length of current episode. In general, earlier AAO is associated with more severe symptoms and a distinct structure of associations between symptoms. The role of depressed mood within the constellation of symptoms is a distinguishing feature of earlier AAO.

4.1. Age at onset and symptom severity

The multiple regression analyses examining the impact of AAO on symptom-severity are in line with the extant literature demonstrating that earlier AAO is associated with greater overall depression severity in adulthood (7). However, our approach builds upon the current literature by treating AAO as a continuous variable, utilizing the entire scope of AAO, and examining HRSD items individually. Three findings stood out. First, we replicated extant literature suggesting that early AAO is associated with greater suicidality (Korczak and Goldstein, 2009; van Noorden et al., 2011; Weissman et al., 1999; Zisook et al., 2004). Second, symptoms of libido and appetite/weight disturbance were not impacted by depression AAO. These symptoms, which are broadly associated with appetitive behavior, appear to be unrelated to the age at which depression emerges. One possible explanation is that the timing of the impact of depression on brain regions linked to symptoms of feeding and movement may not matter for how these symptoms present if depression (re-)emerges later. Finally, sleep was the only symptom that increased in severity with AAO. In general, the onset of sleep problems increases with age (Ancoli-Israel and Ayalon, 2006) suggesting that this finding may not be related to depression per se, but rather an epiphenomenon of sleep difficulties over age. This suggests that patients might benefit from more sensitive detection of depression when treatment providers probe specifically for sleep problems if later AAO is reported. Taken together, it appears that not all depression symptoms (at least those prominently indexed by the HRSD) are similarly impacted by AAO.

4.2. The adolescent onset network: distinct associations between symptoms

The adolescent AAO network was significantly greater in global strength centrality and different in structure than the middle age AAO network. In contrast, the child AAO network was only different in global strength centrality from the middle age AAO network. Thus, the overall structure of the adolescent AAO network was the sole network that was different from the adult AAO networks. This result can be largely explained by the pattern of stronger associations from the depressed mood node to other nodes such as sleep disturbance, anhedonia, and guilt specifically in the adolescent AAO network. These symptoms, while not necessarily the most severe in the adolescent AAO group, may serve as important treatment targets, as they are closely linked to the strongest node in the network (see work of Fisher and others (Fisher et al., 2017), for an examination of how researchers are attempting to use network analysis to inform treatment).

From a network perspective, depression is conceptualized as a set of mutually reinforcing symptoms (Freeman, 1978). It is clear from the visual inspection of the networks that the depressed mood node plays a more central role in the network than the two adult AAO networks (particularly salient in the left side of Fig. 2). The specific experience of depressed mood in someone with adolescent AAO could have a more damaging effect by directly activating more symptoms such as sleep disturbance and guilt, than in someone with non-adolescent AAO. Furthermore, as guilt and sleep disturbance were greatest in both closeness and betweenness in the adolescent AAO network, these symptoms have stronger indirect effects on other nodes within the network. They facilitate the fast activation of the network, and they are responsible for activating the most distal nodes (Freeman, 1978). Given that the adolescent AAO network is also most strongly connected, spreading effects can be amplified. These results may be clinically relevant as prior research has demonstrated that stronger networks are associated with more persistent and difficult to treat depression (Borkulo et al., 2015).

The depression symptom networks of adults whose depression first emerged during childhood and adolescence were broadly similar to one another. Child and adolescent AAO depression networks did not differ significantly in strength or structure from those with adolescent AAO depression. These results parallel those of a prior STAR*D report, which suggested that clinical features of depression may not differ between child and adolescent AAO (Zisook et al., 2007a). Contrary to the findings of Zisook and colleagues, however, the child and adolescent AAO networks did emerge as different from the young adult and middle age AAO networks. The AAO groups we constructed, while somewhat arbitrary, align closely to neurobiological work suggesting that brain maturation continues through late adolescence and into the early-twenties (Casey et al., 2008).

4.3. Extending the "Scar hypothesis"

Once depression occurs for the first time, it is more likely to recur (Belsher and Costello, 1988). This is highly relevant because depression recurrence is associated with negative personal (Wittchen et al., 1998) and societal (Kupfer et al., 1996)consequences. For this reason, researchers have attempted to develop a theory that explains how and why depression recurs (Lewinsohn et al., 1999). One explanation is the "scar hypothesis," which posits that depression recurs due to an underlying biological vulnerability that is activated after the first episode (Burcusa and Iacono, 2007). In this way, the onset of depression early in life (during childhood or adolescence) may fundamentally alter brain development, which in turn may leave a specific "scar", rendering the individual at greater risk for depression episodes later.

However, research on the scar hypothesis findings have been inconsistent: early depression onset has not been consistently predictive of increased risk of recurrence compared to later onset (e.g. Lewinsohn et al., 2003 found it was, while Copeland et al., 2009 found

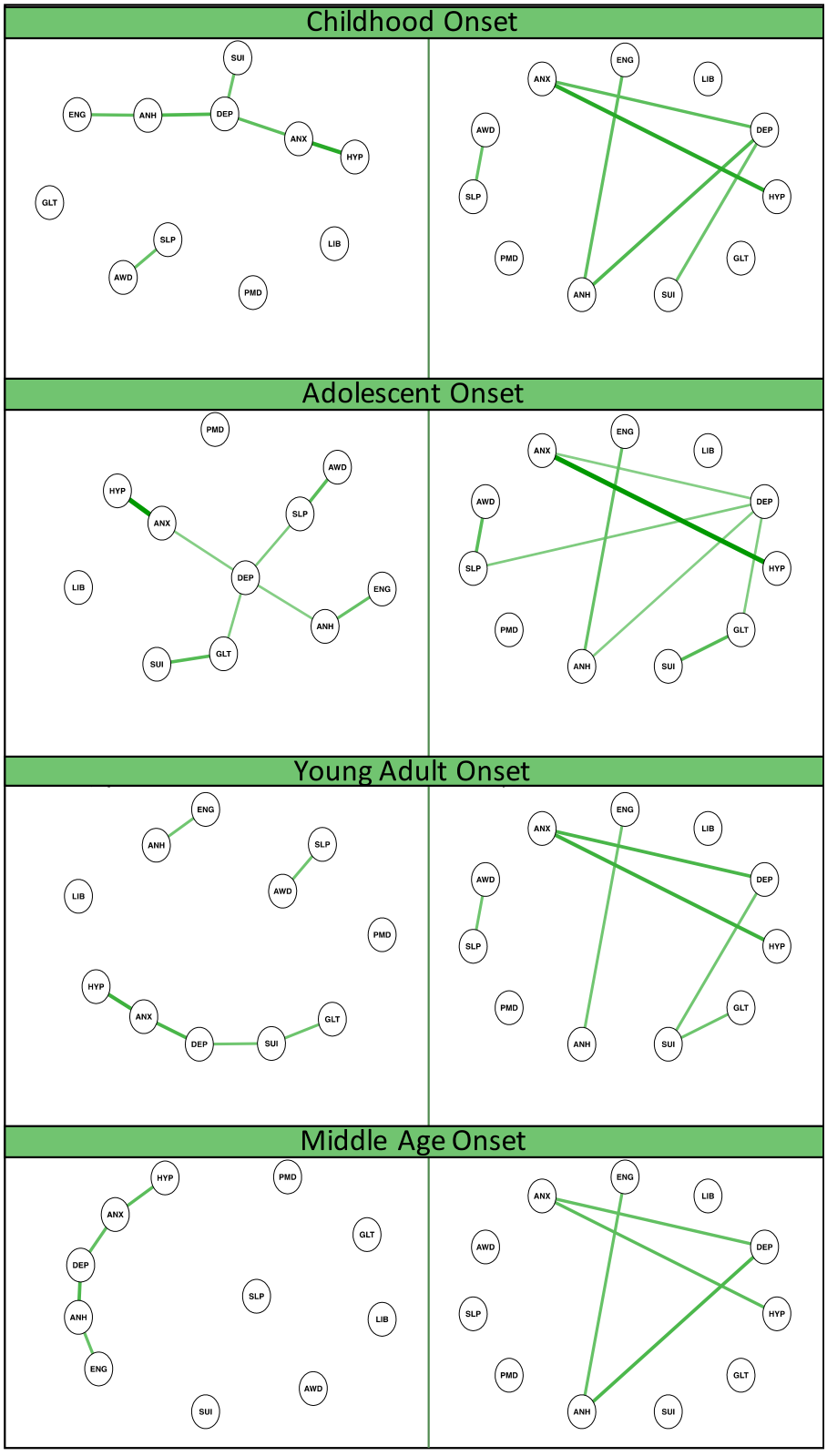

Fig. 2. Network Structures of Child (0–15 years), Adolescent (15–22 years), Young Adult (22–36 years), and Middle Age (36–74 years) onset groups (N = 795/group). Networks controlled for variance due to current age, length of current episode, number of past episodes, and quality of life. Green colored lines represent positive partial correlations; thicker lines indicate greater partial correlations. Figures on the left column depict networks where the distance between nodes represents how strongly related the nodes are. Figures on the right column depict networks where the layout is standardized and the distance between nodes is arbitrary. Note the centrality and connectedness of the depressed mood node in adolescent AAO compared with the other age groups (ENG = loss of energy, LIB = loss of libido, DEP = depressed mood, HYP = hypochondriasis, GLT = inappropriate guilt, SUI = thoughts of death or dying, ANH = anhedonia, PMD = psychomotor disturbance, SLP = sleep disturbance, AWD = appetite-weight disturbance, ANX = anxiety). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

it was not). Other work suggests that early depression onset is associated with significantly greater psychosocial impairment in a variety of domains, including interpersonal relationships, school performance, quality of life (Geller et al., 2001). Thus, given the findings of Geller et al., in concert with the results described in this study, perhaps these "scars" associated with early onset are more subtle and nuanced than previously described, and are expressed in the phenomenology of depression in adulthood. The current study suggests that early onset depression re-emerges as phenomenologically different in adulthood compared to later onset depression. These phenomenological differences were observed in unequal symptom severity, and differential symptom networks.

Table 3
Results from the NetworkComparisonTest.

Strength Invariance Test				
	Child	Adolescent	Young Adult	Middle Age
Child	–			
Adolescent	p = .52	–		
Young Adult	p = .24	p = .07	–	
Middle Age	p = .047	p = .002	p = .55	–
Network Structure Invariance Test				
	Child	Adolescent	Young Adult	Middle Age
Child	–			
Adolescent	p = .63	–		
Young Adult	p = .54	p = .08	–	
Middle Age	p = .13	p = .001	p = .49	–

5. Limitations

This study was not without limitations. First, our key independent variable, AAO, was recalled retrospectively and may be subject to bias. Adults may not be very precise in reporting the exact age their depression began, especially if it was far in the past (Klungsøyr et al., 2013). However, when AAO was used as a continuous variable, we were able to avoid some of the validity issues raised when creating dichotomized variables (e.g. misreporting AAO as 18 when it was truly 17 is an issue in some studies). Our analyses were not immune to these issues when individuals were categorized into the four groups. Nonetheless, retrospective memory research indicates that individuals are capable of accurately reporting the timing of past events with the help of idiographic "temporal landmarks" put into context by interviewers, and that bias in retrospective recall may not be significant (Shum, 1998). Second, intraindividual networks based on quartiles yielded somewhat arbitrary cutoffs for AAO. As with all between-group designs, results may not generalize to the individual. Third, in this study design, we statistically controlled for important confounding variables, but it is possible that some unexamined variable may in fact explain more variance in symptoms than AAO.

6. Conclusions

Our results demonstrate that AAO cannot be ignored as a clinically relevant variable for adult depression. Our findings suggest that onset of depression earlier in life, and particularly during adolescence leaves a specific scar that affects the severity, structure, and presentation of depression in adulthood. In particular, adult depression symptom severity is greatest when the AAO is during childhood or adolescence. Furthermore, the role of depressed mood appears to modulate other symptoms most strongly in individuals with adolescent AAO depression. These results may inform research identifying the pathophysiology of depression, and demonstrate that age at onset may be an important factor in fully describing current episodes of depression in patients and in future research.

CRediT authorship contribution statement

Lara Michelle Baez: Formal analysis, Writing - original draft, Writing - review & editing. **Aaron Shain Heller:** Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.10.036.

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