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Research paper

Individual and common patterns in the order of symptom improvement during outpatient treatment for major depression

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ABSTRACT

Background: Research so far provided few clues on the order in which depressive symptoms typically remit during treatment. This study examined which depressive symptoms improve first, and whether symptoms changed before, simultaneous with, or after the core symptoms of depression (i.e., sad mood, loss of pleasure, and loss of interest).

Methods: Participants were 176 patients with Major Depressive Disorder (MDD) receiving outpatient treatment (a combination of pharmacotherapy and psychological interventions) for depression. Participants filled out the Inventory of Depressive Symptomatology - Self Report (IDS-SR) for 16 to 20 consecutive weeks. For each symptom, the timing of onset of a persistent improvement was determined for each single-subject separately.

Results: Which symptoms improved first differed markedly across patients. The core depression symptoms improved 1.5 to 2 times more often *before* (48% - 60%) than *after* (19% - 28%) depressive cognitions ('view of myself' and 'view of the future'), anxiety symptoms ('feeling irritable' and 'feeling anxious / tense') and vegetative symptoms ('loss of energy', 'slowed down', and 'physical energy'). Only improvements in suicidal thoughts were more likely to occur before (46% - 48%) than after (29%) improvements in the depression core symptoms.

Limitations: Not all 'core depression-non-core symptom' combinations could be tested because some symptoms did not improve in a sufficient number of patients.

Conclusions: Which improvements mark the start of symptom remission differed between patients. Improvements in the core depression symptoms 'sad mood', 'loss of interest', and 'loss of pleasure' were more likely to occur before than after improvements in non-core symptoms.

1. Introduction

While there is ample research on predictors of treatment response, the process of symptom remission in Major Depressive Disorder (MDD) is only partially understood. Examining the timing of improvement in individual depressive symptoms may provide clues to the mechanisms of symptom remission (Kendler et al., 2011), may help clinicians to recognize early signs of treatment response, and support decisions on targets for early intervention (Katz, 1998; Rabin et al., 1984).

When looking at depressive symptom remission, a distinction can be made between its core symptoms (i.e., sad mood and loss of interest/pleasure), and non-core symptoms that make up a rather heterogeneous

pool of additional criterion symptoms for depression (e.g., sleep, loss of energy) or symptoms known to co-occur with depression (e.g., anxiety, somatic symptoms). One or more of the core symptoms need to be present in order for a patient to have a depression according to formal DSM-criteria, while non-core symptoms do not necessarily need to be present in all patients and can be present in the absence of the core symptoms, e.g., as vulnerability markers for depression (also, prodromal symptoms).

Different theoretical models exist on how the remission of different types of symptoms evolves over time. According to compensation models, reductions in a patient's deficits or vulnerabilities for a disorder facilitates symptom remission (Cheavens et al., 2012). This premise may

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lead one to expect that symptoms associated with vulnerability for depression such as anxiety (Andreescu et al., 2007; Fava and Tossani, 2007), vegetative symptoms (Pede et al., 2017) or depressogenic cognitions (Beevers et al., 2003) may improve first and before the core symptoms of depression improve. In contrast, if symptom remission follows the principles of the ‘rollback phenomenon’ (Detre and Jarecki, 1971; Fava, 1999), vulnerability symptoms may be expected to improve *after* the core symptoms of depression. According to this model, symptom remission progresses through the same stages as the development of a disorder, though in a reverse order (Fava, 1999). This model is supported by studies showing that common prodromal symptoms, such as anxiety, vegetative symptoms, and depressogenic cognitions, (Andreescu et al., 2007; Beevers et al., 2003; Pede et al., 2017) are often reported as well after remission of depression (Conradi et al., 2011; Dozois, 2007; Yang et al., 2010), while the core symptoms sad mood and loss of interest/pleasure are less common after remission (Conradi et al., 2011; van Eeden et al., 2019).

Studies so far provided few clues on the order in which symptoms typically remit during treatment. Most studies examined depression as one construct instead of distinguishing between different symptoms when examining trajectories of symptom change during treatment (e.g., Gueorguieva et al., 2011; Stulz et al., 2010; Wardenaar et al., 2014). The studies that did differentiate between depressive symptoms typically showed that the average shape of the symptom trajectory over the course of treatment is similar across individual symptoms or symptom clusters (e.g., Bhar et al., 2008; Rabin et al., 1984). A broad range of symptoms have been found to improve during the early phases of treatment, including sleep (DiMascio et al., 1979; Katz et al., 1987; Kupfer et al., 1976; Sakurai et al., 2013), negative cognitions (Sakurai et al., 2013; Tang et al., 2005), anxiety (Katz et al., 1987), and sadness (Rabin et al., 1984; Sakurai et al., 2013; Tokuoka et al., 2016).

Although it is tempting to conclude that these studies show that all symptoms change at roughly the same rate, a closer look at the data-analyses reveals that these studies do not inform us on the order in which symptoms improve. Between-subject heterogeneity in the presence of depressive symptomatology (de Vos et al., 2015; Fried and Nesse, 2015), the timing of symptom improvement (de Vos et al., 2015; Katz, 1998; Wardenaar and de Jonge, 2013), and order of symptom change (Katz et al., 1987; Katz, 1998) may have obscured the within-person order in which symptoms remit. That is, a similar timing of change across symptoms is to be expected when symptom trajectories are averaged across patients. This may be illustrated by a study finding a log-linear pattern of symptom improvement during treatment at the group-level, while observing linear, log-linear and one-step trajectories of depressive symptoms improvement at the individual level (Vittengl et al., 2013). Furthermore, some patients may experience sudden symptom gains early in treatment while such large symptom improvements may occur in the later phases of treatment in other patients (e.g., Lutz et al., 2013). These studies not only indicate that group-level analyses, such as growth mixture models or latent class growth curves, may blur individual patterns of change, but also indicate the presence of individual differences in the timing of symptom improvement. Studies examining the patient-specific timing of the onset and order of improvement in individual depressive symptoms are needed to better understand the process of symptom remission.

We therefore adopted a combination of an idiographic and nomothetic approach that addresses individual differences in the timing of individual symptom improvement by determining the timing of onset of improvement in each individual symptom per individual. The study was performed in a sample of patients with Major Depressive Disorder (MDD) receiving an outpatient treatment program for depression who provided weekly assessments of their depressive symptoms. We studied patients receiving care as usual, which comprised of a combination of both pharmacotherapy and psychological interventions, to maximize the chance of remission of depressive symptoms (Cuijpers et al., 2020) and to ensure generalizability of our findings to a typical depression

treatment setting. It was investigated for each symptom 1) how often it is the first to improve, and 2) how often it improves before, simultaneous with, or after the core depression symptoms (sad mood, loss of interest, and loss of pleasure) over the course of treatment. This allowed us to examine whether there are commonalities in the patterns of symptom remission that are either congruent with the compensation model or with the rollback phenomenon.

2. Methods

2.1. Study population

This observational study concerns a secondary analysis of data collected between January 2011 and March 2017 as part of Routine Outcome Monitoring (ROM) at the University Center of Psychiatry (UCP) of the University Medical Center Groningen (UMCG). Patients provided consent for the use of their (anonymized) data for scientific purposes. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

A first inclusion criterion for the current study was a diagnosis of MDD according to the DSM-IV or DSM-5 (not in remission) made by a psychiatrist or a psychiatrist in training of the UMCG. A second inclusion criterion was presence of moderate to very severe levels of depressive symptoms (Inventory of Depressive Symptomatology - Self Report (IDS-SR, Rush et al., 1996) ≥ 26) at intake and start of treatment. Patients with mild depressive symptoms were excluded to arrive at a homogeneous sample and to make sure that there was room for symptom improvement. Scores on the IDS-SR ≥ 26 are equivalent to QIDS-SR₁₆ ≥ 11 , HAM-D₂₄ ≥ 18 , and HAM-D₁₇ ≥ 14 (Rush et al., 2003). A third inclusion criterion was receiving outpatient treatment for depression. To arrive at an acceptable sample size, data from patients receiving either an outpatient group program or weekly individual treatment sessions were used. A final inclusion criterion was the presence of repeated assessments of the IDS-SR on a weekly basis over the course of treatment. As the out-patient group program was typically 16 weeks but could be several weeks longer in holiday periods, assessments after a time period of 20 weeks were excluded. Since the outpatient group program has a 2-week Christmas break, a maximum of 3 weeks of missing IDS-SR data was allowed. Patients who dropped out of treatment before 75% of treatment completion (12 weeks), were excluded from the analyses to ensure a follow-up period that was long enough to capture improvements in different symptoms.

IDS-SR data of 337 outpatients treated for MDD were available, of which 267 had an IDS-SR score ≥ 26 both at intake and the first day of treatment. Of these 267 patients, 91 patients were excluded from the analyses because they did not fill out the IDS over a period of at least 12 weeks or because their data included time-gaps of more than 3 weeks. This resulted in a final sample of 176 patients.

2.2. Treatment

Patients included in the analyses received either a 16-week outpatient day clinic program for depression ($N = 134$) or psychological treatment at the outpatient clinic for depression on a weekly basis ($N = 42$). The 16-week program is a group-based program provided 4 days a week to 4 to 6 patients at a time. The program consists of the following group therapies: interpersonal therapy (IPT), rational emotive therapy (RET), psychomotor therapy, creative therapy and occupational therapy. This combination of therapies followed a behavioral activation approach with individual goalsetting and evaluation of goals on a weekly basis in the group and individually. In addition to group therapy, patients receive individual psychological counseling on a weekly basis. The group treatment and individual counseling sessions are provided by a clinical psychologist and a nurse-practitioner. The individual

psychological treatment provided at the outpatient clinic for depression consists of the same psychological treatments (IPT and CT) as the 16-week outpatient program in the form of weekly individually delivered sessions. Most treated patients used antidepressant medicines according to institutional guidelines (in line with national depression treatment protocols). A general rule was that the medication regime was not changed during treatment, unless the (resident) psychiatrist deemed it necessary.

2.3. Measures

Depressive symptoms were assessed with the 30-item IDS-SR (Rush et al., 1996). The IDS-SR was administered at intake (between 1 week and 3 months before start of treatment), on the first day of treatment, and on a weekly basis over the course of treatment. The IDS-SR assesses severity of depressive symptoms as well symptoms of anxiety and somatic symptoms over the past week. The items on anxiety and somatic symptoms were also included in the current study as they are common comorbid symptoms of depression. The core depression symptoms were assessed with the items assessing ‘feeling sad’ (item 5), ‘general interest’ (item 19), and ‘pleasure/enjoyment’ (item 21). All other items of the IDS-SR, except for item 9, 10, 13, and 14 were used to measure non-core symptoms of depression. ‘Diurnal variation of mood’ (item 9) and ‘quality of mood’ (item 10) were excluded because item 9 was previously shown to have issues with ordering of its response categories in IRT analyses (Wanders et al., 2015) and item 10 assessed the quality of mood rather than severity or frequency of a symptom. The questions on ‘weight loss’ (item 13) and ‘weight gain’ (item 14) were excluded as these questions covered the past two weeks instead of the past week. As either ‘a decrease in appetite’ (item 11) or ‘an increase in appetite’ (item 12) can be endorsed, and not both, these items were combined into a single ‘appetite disturbance’ item. Items were rated on a 4-point Likert scale ranging from 0 (representing symptom absence) to 3 (representing severe presence of a symptom). All items were analyzed separately and no subscales were used since it has been shown that the factor structure of depressive symptom scales can change when overall severity of depression changes (Fried et al., 2016).

2.4. Statistical analyses

First symptom improvements. To examine how often a specific symptom improved first, we determined the timing (onset) of a persistent improvement for each IDS-SR item within each patient. This approach corresponds with other studies on the onset of change (Katz et al., 1996–1997; Montgomery, 1995; Stassen et al., 1993). The onset of improvement was determined using two criteria. The first criterion was the moment a $\geq 50\%$ reduction in pretreatment symptom severity was reached, which is a commonly used criterion of treatment response (e.g., McClintock et al., 2011; Riso et al., 1997; Rush et al., 2006). For individual items, this corresponded to a decrease from a score of 3 or 2 (severe/present most of the time) to a score of 1 (mild/present half of the time), or from a score of 1 (mild/present half of the time) to a score of 0 (normal/absent). The symptoms had to show this 50% decrease

relative to both the intake symptom score and the symptom score on the first day of treatment. The second criterion was that the 50% symptom reduction persisted (i.e., did not revert) over the course of treatment, to make sure that the improvement was a persistent change in mean levels instead of a fluctuation.

A sample proportion was calculated of the number of times a symptom improved first. Only patients who had an IDS-SR score ≥ 1 (mild/present half of the time) on a symptom at intake and the first day of treatment were included in these analyses. Confidence intervals (99% CI's) for the proportions were calculated. For symptoms with CI's that did not overlap, we examined whether the sample proportions significantly differed from one another using two-sample tests of proportions.

The order of improvement. To examine how often each of the symptoms improved before, simultaneous with, or after the core depression symptoms, we used the data on the timing of improvement in each of the symptoms. For each individual, the timing of the first improvement in each of the symptoms was compared to the timing of the first improvement in ‘feeling sad’, ‘general interest’, and ‘pleasure/enjoyment’ (i.e., the core depression symptoms). The analyses were performed for each of the core symptoms separately. For each ‘core depression symptom – non-core symptom’ combination, the following sample proportions were calculated: improvement in a symptom before a core symptom (a difference of ≥ 1 week), simultaneous improvement (in the same week), and improvement in a symptom after a core symptom (a difference of ≥ 1 week). Thus, these analyses included only the patients who showed an improvement in both symptoms of the tested ‘core depression symptom – non-core symptom’ combination. The observed proportions were compared with the expected cell proportion (33%) under the null hypothesis of no difference in proportion improved before, simultaneous, or after a core symptom using a one-sample test of proportions. A sample-size calculation showed that a sample size of 66 participants was needed for sufficient power of 80% to show that a specific symptom improved in 50% of the individuals before a core depression symptom compared to an expected cell proportion of 33%, when tested two-sided (alpha of 0.05).

Sensitivity analyses. To examine whether the results would hold in treatment responders only, the analyses were repeated in a group having at least a 50% reduction in the IDS-SR total score from start of treatment to post-treatment. To evaluate the robustness of the results against method artifacts, we also repeated the analyses using a less strict criterion cut-off for the onset of improvement ($\geq 25\%$ instead of $\geq 50\%$) and using a less strict definition of a persistent improvement (improvement for at least 4 weeks instead of the full course of treatment) in two additional sensitivity analyses.

3. Results

3.1. Sample characteristics

Of the 176 participants, 60% were female. The mean age was 41.1 ($SD = 12.6$). Depressive symptoms (IDS-SR total scores) were on average severe at intake and the first week of treatment (see Table 1). Depressive symptoms were on average mild at post treatment. At post-treatment,

Table 1
Depressive symptoms at intake, start of treatment, and post-treatment.

	Intake	Start of treatment	Post-treatment
IDS-SR total score (M/(SD))	44.9 (8.8)	42.4 (9.5)	21.9 (14.4)
IDS-SR severity			
No depression (N/(%))	0 (0%)	0 (0%)	61 (35%)
Mild (N/(%))	1 (1%)	0 (0%)	56 (32%)
Moderate (N/(%))	38 (22%)	62 (35%)	38 (21%)
Severe (N/(%))	80 (45%)	71 (40%)	12 (7%)
Very severe (N/(%))	57 (32%)	43 (24%)	9 (5%)

Note: No depression = IDS-SR < 14, Mild = IDS-SR < 26, Moderate = IDS-SR < 39, Severe = IDS-SR < 49, Very severe = IDS-SR ≥ 49

Table 2
Individual symptom presence and symptom improvement.

	Presence at baseline	Improved at any moment	Improved first
MOOD	N (%)	N (% of N present)	N (% of N present)
Feeling sad	175 (99%)	122 (70%)	21 (12%; CI 6% - 20%)
Reactivity of mood	159 (90%)	115 (72%)	17 (11%; CI 5% - 19%)
General interest	159 (90%)	108 (68%)	24 (15%; CI 9% - 24%)
Pleasure/enjoyment	166 (94%)	114 (69%)	21 (13%; CI 7% - 21%)
SLEEP			
Falling asleep	118 (67%)	67 (57%)	14 (12%; CI 5% - 22%)
Sleep during the night	134 (76%)	42 (31%)	7 (5%; CI 2% - 12%)
Waking up too early	64 (36%)	29 (45%)	3 (5%; CI 1% - 16%)
Sleeping too much	76 (43%)	43 (57%)	14 (18%; CI 9% - 32%)
COGNITIONS			
View of myself	157 (89%)	95 (60%)	9 (6%; CI 2% - 12%)
View of my future	171 (97%)	89 (52%)	12 (7%; CI 3% - 14%)
Suicidal thoughts	128 (72%)	89 (70%)	20 (16%; CI 8% - 26%)
Interpersonal sensitivity	140 (80%)	65 (47%)	11 (8%; CI 3% - 16%)
ANXIETY			
Feeling irritable	151 (86%)	94 (60%)	14 (9%; CI 4% - 18%)
Feeling anxious or tense	155 (88%)	91 (59%)	14 (9%; CI 4% - 17%)
Panic / phobic symptoms	103 (59%)	55 (53%)	13 (13%; CI 6% - 23%)
VEGETATIVE			
Appetite disturbance	112 (63%)	71 (63%)	15 (13%; CI 6% - 24%)
Concentration/deciding	170 (97%)	100 (59%)	17 (10%; CI 5% - 17%)
Energy / fatigability	165 (94%)	86 (52%)	5 (3%; CI 1% - 8%)
Interest in sex	136 (77%)	53 (39%)	7 (5%; CI 2% - 12%)
Feeling slowed down	140 (80%)	99 (71%)	10 (7%; CI 3% - 15%)
Feeling restless	113 (64%)	66 (58%)	2 (2%; CI 0% - 8%)
Physical energy	168 (96%)	87 (52%)	6 (4%; CI 1% - 9%)
SOMATIC			
Aches and pains	142 (81%)	52 (37%)	7 (5%; CI 1% - 12%)
Other bodily symptoms	131 (74%)	52 (40%)	9 (7%; CI 2% - 15%)
Constipation / diarrhea	88 (50%)	44 (50%)	13 (15%; CI 7% - 27%)

Note: Presence at baseline = IDS-Score ≥ 1 both at intake and at the first week of treatment. Improved at any moment = improved at any moment over the course of treatment. Improved first = improved at the first moment any of the symptoms improved. % of N present = N improved first / N presence at baseline. 99% CI's for binomial distributions are presented.

56% ($N = 99$) of the sample achieved a 50% reduction (responders) in their IDS-SR total scores.

3.2. Symptom presence at baseline

The presence of individual IDS-SR symptoms at baseline (IDS-SR item-score ≥ 1 at intake and first week of treatment) can be found in Table 2. Symptom presence varied across symptoms from 34.7% to 99%. Symptoms that were present in fewer than 50% of the sample were 'waking up too early', 'sleeping too much', and 'constipation/diarrhea'.

3.3. Symptom improvement at any time

Most symptoms had improved by the end of treatment in at least half of the sample (range: 31% - 75%, see Table 2). The core symptoms improved in at least 68% of the sample. Symptoms that improved in less than half of the sample having these symptoms were 'sleep during the night', 'early morning awakening', 'interpersonal sensitivity', 'interest in sex', 'aches and pains', and 'other bodily symptoms'.

3.4. The first symptom improvements

Which symptoms improved first differed markedly across patients. No symptom improved first in more than 18% of the sample having these symptoms (range 2% - 18%, see Table 2). Symptoms that improved first most often (in $\geq 15\%$ of the sample) were 'general interest', 'sleeping too much', and 'suicidal thoughts'. 'General interest' improved significantly more often first than the three symptoms that were rarely ($\leq 5\%$) among the firsts to improve: i.e., 'feeling restless' ($Z = 3.40$, $p < .01$), 'energy/fatigability' ($Z = 3.36$, $p < .01$), and 'physical energy' ($Z = 3.19$, $p < .01$). Similarly, 'sleeping too much' improved significantly

more often first than 'feeling restless' ($Z = 4.03$, $p < .01$), 'energy/fatigability' ($Z = 4.12$, $p < .01$), and 'physical energy' ($Z = 3.92$, $p < .01$). Finally, 'suicidal thoughts' improved significantly more often first than 'feeling restless' ($Z = 3.99$, $p < .01$), 'energy/fatigability' ($Z = 4.16$, $p < .01$), and 'physical energy' ($Z = 3.97$, $p < .01$).

3.5. Sensitivity analyses first symptom improvements

To check the robustness of the findings on the first symptom improvement, we repeated the analyses three times: (1) using a cut-off criterion of an improvement of at least 25% instead of 50%, (2) using a criterion of persistence of a 50% improvement for at least 4 weeks, and (3) using the original criteria but in treatment responders only ($\geq 50\%$ symptom reduction, $N = 99$). In these sensitivity analyses, again none of the symptoms were consistently among the first symptoms to improve; no symptom improved first in more than 26% of the sample having this symptom. Also, similar trends were found in the type of symptoms that improved more often first than other symptoms, although some of the original differences were no longer significant (Tables in supplementary material). Notably, when we changed the criterion of an improvement from 50% to 25% symptom reduction, the symptom 'sad mood' stood out as improving significantly more often first than several non-core symptoms (i.e., 'feeling restless', 'aches and pains', 'sleep during the night', 'self-criticism', 'interpersonal sensitivity', 'energy/fatigability', and 'physical energy').

3.6. The order of symptom improvement

Of the tested symptoms, only improvements in 'suicidal thoughts' were more likely to occur before improvements in 'general interest' and 'pleasure/enjoyment' (see Table 3). None of the other tested symptoms

Table 3

The order of improvement in non-core symptoms with regard to the core symptoms.

Non-core symptoms	Comparison with <i>Sad Mood</i>			Z	p
	Improved before <i>Sad Mood</i>	Improved at the same time as <i>Sad Mood</i>	Improved after <i>Sad Mood</i>		
View of myself (N (%))	19 (22%)	15 (17%)	52 (60%)*	5.35	<.01
View of my future (N (%))	23 (27%)	17 (20%)	44 (52%)*	3.71	<.01
Suicidal thoughts (N (%))	31 (40%)*	21 (27%)	25 (32%)	1.30	.20
Feeling irritable (N (%))	21 (26%)	14 (17%)	46 (57%)*	4.49	<.01
Feeling anxious or tense (N (%))	21 (26%)	21 (26%)	39 (48%)*	2.84	<.01
Concentration/deciding (N (%))	31 (35%)	19 (22%)	38 (43%)*	1.97	.049
Energy / fatigability (N (%))	20 (27%)	13 (17%)	42 (56%)*	4.17	<.01
Feeling slowed down (N (%))	25 (29%)	12 (14%)	48 (56%)*	4.53	<.01
Physical energy (N (%))	15 (19%)	17 (21%)	49 (60%)*	5.19	<.01

Non-core symptoms	Comparison with <i>Interest</i>			Z	p
	Improved before <i>Interest</i>	Improved at the same time as <i>Interest</i>	Improved after <i>Interest</i>		
View of myself (N (%))	21 (29%)	9 (12%)	43 (59%)*	4.64	<.01
View of my future (N (%))	17 (23%)	22 (29%)	36 (48%)*	2.70	<.01
Suicidal thoughts (N (%))	32 (48%)*	15 (23%)	19 (29%)	2.62	<.01
Feeling irritable (N (%))	19 (26%)	21 (28%)	34 (46%)*	2.31	.02
Feeling anxious or tense (N (%))	26 (37%)	14 (20%)	30 (43%)*	1.70	.09
Concentration/deciding (N (%))	26 (35%)	13 (17%)	36 (48%)*	2.70	<.01
Energy / fatigability (N (%))	20 (28%)	9 (13%)	42 (59%)*	4.62	<.01
Feeling slowed down (N (%))	20 (29%)	13 (19%)	37 (53%)*	3.47	<.01
Physical energy (N (%))	17 (26%)	10 (15%)	39 (59%)*	4.45	<.01

Non-core symptoms	Comparison with <i>Pleasure</i>			Z	p
	Improved before <i>Pleasure</i>	Improved at the same time as <i>Pleasure</i>	Improved after <i>Pleasure</i>		
View of myself (N (%))	24 (30%)	6 (8%)	49 (62%)*	5.42	<.01
View of my future (N (%))	26 (33%)	21 (26%)	33 (41%)*	1.51	.13
Suicidal thoughts (N (%))	33 (46%)*	18 (25%)	21 (29%)	2.26	.02
Feeling irritable (N (%))	24 (31%)	17 (22%)	36 (47%)*	2.50	.01
Feeling anxious or tense (N (%))	26 (36%)	10 (14%)	37 (51%)*	3.15	<.01
Concentration/deciding (N (%))	29 (34%)	10 (12%)	47 (55%)*	4.20	<.01
Energy / fatigability (N (%))	19 (29%)	9 (14%)	38 (58%)*	3.62	<.01
Feeling slowed down (N (%))	25 (31%)	12 (15%)	43 (54%)*	3.88	<.01
Physical energy (N (%))	19 (25%)	12 (16%)	44 (59%)*	4.66	<.01

Note: The highest observed cell proportion indicated with an * was tested against the expected cell proportion (33%) using a one-sample test of proportions. Sample size differs for each 'core symptom /non-core symptom' combination since each analysis only includes those individuals that showed an improvement in both symptoms of the 'core symptom /non-core symptom' combination.

improved more often before any of the three core depression symptoms. Rather, several symptoms improved significantly more often *after* the core symptoms.

Regarding depressive cognitions, improvements in 'view of myself' were more likely to occur after improvements in all three core symptoms (see Table 3). 'View of the future' was also more likely to improve after the core depression symptoms 'sad mood' and 'general interest'. 'View of myself' and 'view of the future' improved about twice as often after sad mood and general interest than before these core symptoms.

Regarding symptoms of anxiety, improvements in 'feeling irritable' were more likely to occur after all three core symptoms. 'Feeling irritable' improved twice as often after 'sad mood' compared to before. Improvements in 'feeling anxious or tense' were more likely to occur after sad mood and pleasure/enjoyment.

Regarding vegetative symptoms, improvements in 'energy/fatigability', 'feeling slowed down', and 'physical energy' were more likely to occur after all three core symptoms. These symptoms improved 1.5 to 2 times more often after than before the core depression symptoms. Furthermore, improvements in 'concentration' were also more likely to occur after the three core symptoms.

The order of improvement could not be tested for 12 out of the 21 'core depression – non-core symptom' combinations because the number of individuals showing an improvement in both symptoms under investigation was not sufficient ($N < 66$), either because of low prevalence at baseline and/or persistence of these symptoms. All four sleep

related symptoms, all three somatic symptoms, 'interpersonal sensitivity', and the symptoms 'panic/phobia', 'appetite disturbance', 'interest in sex', and 'feeling restless' were symptoms that could not be tested for this reason.

3.7. Sensitivity analyses the order of improvement

Similar results on the order of improvement were found when repeating the analyses using a different criterion of an improvement (25%), or using a different criterion for the duration of the improvement (4 weeks), or using only a sample of treatment responders ($\geq 50\%$ symptom reduction). In most sensitivity analyses, the same symptoms improved significantly more often after the core symptoms than expected (see supplementary material). A few differences were observed across the analysis reruns. Improvements in 'concentration' were not more likely to occur after the three core symptoms in the sample of treatment responders. 'View of my future' did not improve more often after 'general interest' in treatment responders and when we examined the onset of an improvement of at least 25%. Across the original and sensitivity analyses, the symptoms that improved most consistently after all three core symptoms were 'view of myself', 'energy/fatigability', 'feeling slowed down', and 'physical energy'.

4. Discussion

The current study showed individual differences and commonalities in the depressive symptoms that improve first and the order of symptom improvement during treatment for Major Depressive Disorder (MDD). While group-level studies on the course of symptom improvement found that the rate of improvement is similar across individual symptoms (Bhar et al., 2008; Rabin et al., 1984), this study shows that symptoms often do not improve at the same moment in time at the individual level. One pattern of improvement was most common: improvements in many non-core symptoms were more likely to occur *after* improvements in core depression symptoms ('feeling sad', 'general interest', 'pleasure/enjoyment'). In fact, the core symptoms improved 1.5 to 2 times more often before than after depressive cognitions ('view of myself', 'view of the future'), symptoms of anxiety ('feeling irritable', 'feeling anxious / tense'), and symptoms related to energy ('energy / fatigability', 'feeling slowed down', and 'physical energy'). Only improvements in 'suicidal thoughts' were more likely to occur before than after core depression symptoms.

On the one hand, our findings indicate that there is no 'general rule' (Cattell, 1966; Nesselroade, 1991) that applies to all or most individuals with MDD regarding which symptoms change first. This adds to literature indicating that depression is a heterogeneous syndrome with variability in the presence of symptoms (de Vos et al., 2015; Fried and Nesse, 2015) and time-course of symptoms (de Vos et al., 2015). Apparently, the process of remission can start with improvement in different symptoms. This may explain why previous studies found early improvements (i.e., after 2 weeks of treatment) in a broad variety of symptoms during treatment with duloxetine (Tokuoka et al., 2016), citalopram (Sakurai et al., 2013), imipramine (Dunbar et al., 1991; Katz et al., 1987), amitriptyline (Katz et al., 1987), and placebo (Tokuoka et al., 2016). The found individual differences in which symptoms resolve and in the timing thereof may partly explain why previous studies have so far not found specific effects of pharmacological and psychological treatment on individual symptoms (Bekhuis et al., 2018; Bhar et al., 2008; Katz et al., 1987; Tokuoka et al., 2016).

On the other hand, the results indicate that the course of individual symptom improvement is not completely random: core depression symptoms often improve more quickly than the other symptoms of depression. This may imply that the core symptoms of depression and suicidal thoughts are more fleeting while depressive cognitions, symptoms of anxiety, and lack of energy may be harder to change. This aligns with studies showing that reduced energy, anxiety, and depressive cognitions are common prodromal symptoms (Andreescu et al., 2007; Beevers et al., 2003; Pede et al., 2017) as well as residual symptoms (Conradi et al., 2011; Dozois, 2007; Yang et al., 2010), and that suicidal ideations and core depression symptoms are uncommon residual symptoms (Conradi et al., 2011; McClintock et al., 2011; van Eeden et al., 2019).

Furthermore, the present results provide a new piece of evidence for the 'rollback phenomenon' (Detre and Jarecki, 1971; Fava, 1999); the hypothesis that remission of symptoms may progress in the reverse order of the development of a disorder (Fava, 1999). We indeed showed that symptoms commonly reported during prodromal phases of depression (i.e., depressive cognitions, symptoms of anxiety, or lack of energy), often improve only after the core mood symptoms have improved. However, more research examining both the order in which symptoms develop and in which symptom remit over time is needed to fully investigate the existence of the rollback phenomenon.

Noteworthy is that several dynamic network studies have shown that anhedonia and positive affect are most strongly predictive of others depressive symptoms or mood states at a later moment in time (Bos et al., 2017; Bringmann et al., 2015; Fisher et al., 2017; de Vos et al., 2017; Wigman et al., 2015). Based on the network theory (Borsboom, 2017), it can be expected that interventions reducing anhedonia and positive affect may cause other symptoms to transition to a healthy state.

As lowered positive affect and anhedonia are indicators of loss of pleasure and loss of interest, our study indicates that reducing these symptoms may indeed be followed by other symptoms transitioning to a more healthy state.

The implication for clinical practice is that it is important to monitor whether sad mood, loss of interest/pleasure, and suicidal thoughts improve as such changes often go together with or are followed by persistent improvements in other depressive symptoms. This may ultimately result in remission of depressive symptoms, as indicated by our sensitivity analyses showing similar sequences of improvement in treatment responders. The importance of monitoring core depression symptoms is also evidenced by studies showing that early improvements in sad/depressed mood strongly predict depressive symptom remission at 8 weeks of duloxetine treatment (Tokuoka et al., 2016), and 14 weeks of treatment with citalopram (Sakurai et al., 2013). Furthermore, a mega-analysis showed that 'depressed mood' is a more sensitive measure for detecting the efficacy of antidepressants than a sum score of depressive symptoms (Hieronymus et al., 2016). Another implication may be that clinicians could consider targeting the core depression symptoms first in treatment. Symptoms of anxiety and depressive cognitions may merit specific treatment if they remain after treatment response (Schoevers et al., 2008), which may reduce the chance of a depressive relapse (Bockting et al., 2005).

The current study focused on the order of depressive symptoms improvement in a naturalistic setting, without examining what caused the improvement in depressive symptoms. Some symptoms may have been more sensitive to contextual changes than others. Furthermore, we cannot exclude the possibility that the received interventions had an impact on which symptoms improved first, although previous studies showed that the time course of individual symptom remission did not depend on the type of treatment (e.g., Stassen et al., 1993; Tokuoka et al., 2016). The results may only generalize to patients receiving similar treatments as offered in the current study, namely a combination of pharmacotherapy and psychological interventions. Different results could have been obtained if all patients in the sample had had exactly the same treatment. Future studies may focus on replicating our results in samples of MDD patients that are more homogeneous in terms of the received types of treatment.

A limitation of the study is that we could not test all 'core symptom-non-core symptom' combinations because some symptoms were either not present or did not improve in a sufficient number of participants (e.g., sleep symptoms and somatic symptoms). Furthermore, data on some patient characteristics (e.g., comorbidities and type of antidepressant medication) were not available because the data was collected as part of routine outcome monitoring. When interpreting the results, one should bear in mind that this study focused on symptom improvement that persisted until the end of treatment or for four weeks. We cannot rule out that symptom changes that did not persist (i.e., 'flickering' or 'instability') preceded more enduring improvements in depressed mood. Future studies that include more frequent assessments during treatment are needed to examine this possibility. Another limitation of the study is that we had to assume equivalence between the changes of different items of the IDS-SR. A change on one item may reflect a larger decrease in severity than change on another item because of differences in the answering categories. Future studies are encouraged to use other symptom assessments that yield item changes reflecting equivalent change in severity. A final limitation of the study is that the sample size of the group receiving the outpatient group program and the group receiving only individual treatment sessions was not large enough to test differences of the findings between these two groups.

A strength of the study is that we used a combination of an idiographic and nomothetic approach that is relatively easy to interpret. Another strength of the study is that it was performed in a sample of MDD patients with high rates of response to treatment. By including symptoms only in the analyses when they were present at baseline, we minimized the issue that the greatest improvement can be expected in

those symptoms that are most frequently reported. In contrast to previous studies, our analytic approach addressed individual differences in both symptom presence and timing. This allowed us to reveal that symptoms often do not improve at the same time and that core depression symptoms are more likely to improve before non-core symptoms.

CRedit authorship contribution statement

Evelien Snippe: Conceptualization, Methodology, Formal analysis, Project administration, Writing - original draft, Writing - review & editing. **Bennard Doornbos:** Conceptualization, Methodology, Writing - review & editing. **Robert A. Schoevers:** Resources, Writing - review & editing. **Klaas J. Wardenaar:** Methodology, Writing - review & editing. **Marieke Wichers:** Conceptualization, Supervision, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

None.

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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.2021.04.097](https://doi.org/10.1016/j.jad.2021.04.097).

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