Depressive Symptoms in Patients with Brain Metastasis: Predictive Factors

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Abstract

Introduction: Depressive symptoms are common in patients with brain metastases before radiotherapy. Neurocognitive functioning appears to be impaired by the effects of depressive symptoms but also by the effects of radiotherapy mediated by depressive symptoms. The aim of this study was to identify predictive factors that make patients with brain metastases vulnerable for developing depressive symptoms before radiotherapy. Patients with poor neurocognitive functioning, cerebellar metastases, maladaptive coping strategies and neurotic traits were expected to have more depressive symptoms. **Methods:** The sample consisted of patients with brain metastases. Neurocognitive tests were administered to measure the neurocognitive functioning. Depressive symptoms, coping strategy and personality traits were measured through the Hospital Anxiety and Depression Scale, Utrechtse Coping Lijst – 90, and the NEO Five Factor Inventory. Based on the location of the metastases patients were divided in to two groups (Cerebellar involvement; Non-cerebellar involvement). In addition, based on coping strategy, patients were again divided into two groups (Maladaptive coping strategy; Adaptive coping strategy). **Results:** Patients with poor neurocognitive functioning, cerebellar involvement and maladaptive coping strategies did not have more depressive symptoms. However, patients with neurotic traits were found to have more depressive symptoms. **Conclusion:** Neurotic traits can be considered a risk predictor for developing depressive symptoms in individuals with BM before undergoing radiotherapy.

*Keywords***:** *Brain metastases, depressive symptoms, neurocognitive functioning, cerebellar involvement, maladaptive coping strategy, neurotic traits*

Depressive symptoms in patients with brain metastasis: Predictive Factors

Brain metastases (BM) are the most common type of brain tumors among adults. Prognosis is poor with a high mortality rate (Schroeder, 2020). BM can cause a decline in neurocognitive functioning (NCF), which often leads to a lower quality of life (Marotta et al., 2020; Wefel et al., 2016). Therefore, a minimally impaired NCF is a critical clinical outcome for patients with primary brain tumors and BM. In addition, it is prioritized as an integrated endpoint, alongside survival, tumor response and quality of life (RANO group, 2013). Consequently, health care professionals aim to keep the NCF as high as possible. Predictors of this decline in NCF were found to be tumor characteristics, psychological factors, and radiotherapy (Cerulla et al., 2020)

BM are also associated with psychiatric comorbidity such as depression and anxiety. Radiotherapy can also lead to depressive symptoms or worsen any pre-existing symptoms (Wong et al., 2016). Depressive symptoms may in turn lead to a decline in NCF. This effect can occur directly, as well as through mediating the effects of radiotherapy on NCF (Bedillion, 2019). However, the cause of depressive symptoms observed before radiotherapy is still unknown (Gibson & Graber, 2020). Therefore, it is important to investigate predictive factors for developing depressive symptoms before radiotherapy in patients with BM. In this way, efforts can be made to keep the depressive symptom low, in order for NCF to remain as high as possible.

Within the neuropsychological literature, depressive symptoms are found to be associated with NCF. Research in patients with Huntington disease and multiple sclerosis have shown that patients with depressive symptoms also reported poor NCF (Kalron et al., 2018; Smith et al., 2012) However, research in patients with cancer show mixed results. In the recent study, Tibbs et al. (2020) investigated NCF and depressive symptoms in patients with brain tumors. It was concluded that those with high levels of depressive symptoms scored lower on NCF. Moreover, neurocognitive processes such as executive functioning, attention, memory, and information processing speed are often investigated. Most studies concluded that patients with high depressive symptoms showed a shorter attention span, problems in verbal and non-verbal memory and lower processing speed (Janelsins et al., 2018; Tibbs et al., 2020) Contradictingly, Gerstenecker et al. (2015) and Schimmel et al. (2019) found no association between depressive symptoms and NCF in patients with brain metastasis.

In addition, the localization of the metastases might also play a role in the occurrence of depressive symptoms. The majority of BM are found in the frontal lobes (31.3%) and the cerebellum (24.6%) (Schroeder

et al. 2020). Since the cerebellum occupies 12.6% of the total brain volume, a disproportionately high number of BM are found there. The cerebellum is known for its involvement in motor functions and motor learning (De zeeuw & ten Brink, 2015). However, recent research has shown that the cerebellum may play a role in affective and emotion processing as well (Ballard et al., 2019). The cerebellum may act as a relay station in the limbic system, which in turn is important for emotion regulation. This could be due to white matter pathways between the prefrontal cortices and structures such as the parietal lobe and temporal lobe. Despite this evidence, its involvement in non-motor processes remain underestimated (Hilber et al., 2019). Animal models of deficiencies or lesions in the cerebellum have reinforced the idea that the cerebellar system could be integrated in neural networks involved in emotional processing. Lupo et al. (2018) investigated the involvement of the cerebellar system in emotion processing in patients with cerebellar lesions and adults with psychiatric mood disorders. They found that these two patient groups showed the same neural alterations. This indicates a cerebellar involvement in the neural network system of mood disorders. Thus, playing a possible role in developing depressive symptoms in patients with cerebellar BM.

Psychological factors such as coping strategy and personality traits are also associated with depressive symptoms. Coping can be defined as cognitive and behavioral efforts to cope with specific external and/or internal challenges that are perceived as taxing or exceeding the person's resources (Lazarus & Folkman, 2000, p. 141). A distinction can be made between adaptive and maladaptive coping strategies (Carver et al., 1989). An adaptive coping strategy refers to positive coping responses which may benefit people in general in certain situations. Maladaptive coping strategies are more negative coping responses that are eventually dysfunctional for the person. Studies have shown that a high score on maladaptive coping strategies is related to psychopathology such as anxiety and depression in adults with depressive symptomatology (Bohlmeijer et al., 2010). Furthermore, Ghanem et al. (2020) concluded that patients with breast and gastric cancer using a maladaptive coping strategy showed more depressive symptoms than patients using an adaptive coping strategy. Early psychological intervention in those with a maladaptive coping strategy was also stated to modulate the onset of depression, especially in those at higher risk for depression.

Besides coping strategies, particular personality traits may also make patients vulnerable to developing depressive symptoms. Personality traits are clusters of personal characteristics that define how a person reacts and adapts in various situations. One of the most well-known personality models is the The Five

Factor Model (McCrea and Costa, 1990). It includes five personality domains: neuroticism, extraversion, agreeableness, conscientiousness, and openness (Markon et al., 2005). Neuroticism is represented by the tendency to experience negative emotions. A high degree of neurotic traits may lead to psychological distress and vulnerability to stress, which increases the predisposition to depressive symptoms (Banjongrewadee et al., 2020). The meta-analysis of Kotov et al. (2010) concluded that depressive symptoms are associated with higher levels of neuroticism and a lower level of conscientiousness and extraversion in patients with depression or anxiety. However, agreeableness and openness were unrelated to depressive symptoms in that analysis. Bonsaksen et al. (2019) suggest that those with high neurotic traits may present less adaptive coping strategies when facing stressful events, leading to more emotional distress. In short, coping strategies and personality traits are stable factors that are often associated with depressive symptoms. However, research in patients with BM is lacking and therefore relevant.

To conclude, depressive symptoms are common in patients with brain tumors and BM. Even though extensive research has been done, it is still difficult to differentiate the cause of depressive symptoms in patients with brain tumors and BM before radiotherapy. Moreover, research is controversial and poor in this patient population. Since depressive symptoms in turn mediate the effects of cancer treatment on cognition, it is important to investigate predictive factors that make patients with BM at risk for developing depressive symptoms before radiotherapy.

Therefore, the main aim of the current study is to identify 'which factors make patients with BM vulnerable to developing depressive symptoms?'. Thereby the relationship between depressive symptoms in patients with BM and (1) pre-radiotherapy NCF, (2) cerebellar BM, (3) coping strategies, and (4) personality traits will be investigated (Figure 1). In line with other research in cancer populations, it is expected that patients with depressive symptoms will experience poor NCF within the domains of executive functioning and attention, memory, and processing speed. Secondly, we expect that patient with cerebellar BM experience more depressive symptoms. Since several studies have shown that people with maladaptive coping strategies and high levels of neurotic traits have more depressive symptoms, we expect that patient with maladaptive coping strategy experience more depressive symptoms and that patients with a high score on neurotic traits experience more depressive symptoms. Evidence for these relationships can make early screening for these factors a useful tool to inform the patient of possible consequences of radiotherapy on their depressive

symptoms and in turn on their NCF. More importantly, healthcare professionals can use early interventions to stabilize or prevent depressive symptoms in this patient population.

Figure 1

Graphical Overview of the Sub-Questions and Variables Included

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Method

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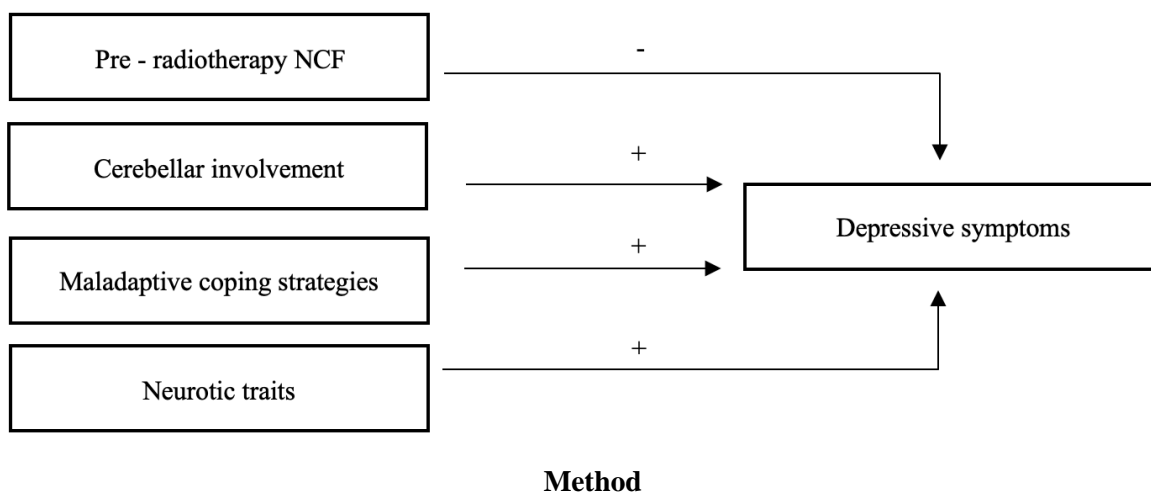
Participants

The data of this study was obtained from the larger studies COIMBRA (Cohort for patient-reported Outcomes, Imaging and trial inclusion in Metastatic BRAin disease) and APRICOT (Assessing and Predicting Radiation Influence on Cognitive Outcome using the cerebrovascular stress Test). Both studies were conducted at the UMC Utrecht. The sample consisted of patients ($\geq$ 18 years) referred by the radiotherapy department to undergo stereotactic radiotherapy (SRT) and whole brain radiotherapy (WBRT) for either brain metastases or as prophylactic cranial irradiation. The purpose of the COIMBRA cohort was providing evidence on clinical and environmental factors associated with treatment outcome, quality of life, cognition, and survival. In addition, it will also contribute to data on natural disease progression, treatment response, disease recurrence and complications in patients with BM. The purpose of APRICOT was identifying risk factors for radiation induced cognitive changes in patients with brain metastasis.

Procedure

Informed consent was obtained before participation. Informed consent for the use of standardized and routinely collected clinical data, was mandatory for participation in the COIMBRA cohort. In addition, patients in COIMBRA could also give informed consent for 1) prospective collection of patient and caregiver

reported outcome measures, 2) assessing cognitive performance through neurocognitive assessments, 3) Undergoing experimental MRI sequences in addition to routine scans, with a maximum total scan time of 60 minutes, 4) approval to be randomized and, when allocated to the intervention arm, to be approached for undergoing experimental interventions, 5) Serve as control in a randomized trial without further notified.

Patients in APRICOT were recruited from patients in the COIMBRA cohort that consented to complete the QoL-questionnaires and participate in the neurocognitive assessment. The APRICOT study consisted of an additional MRI and a neurocognitive assessment. However, patients in COIMBRA who did not want to undergo additional MRI could still participate in the neurocognitive assessment.
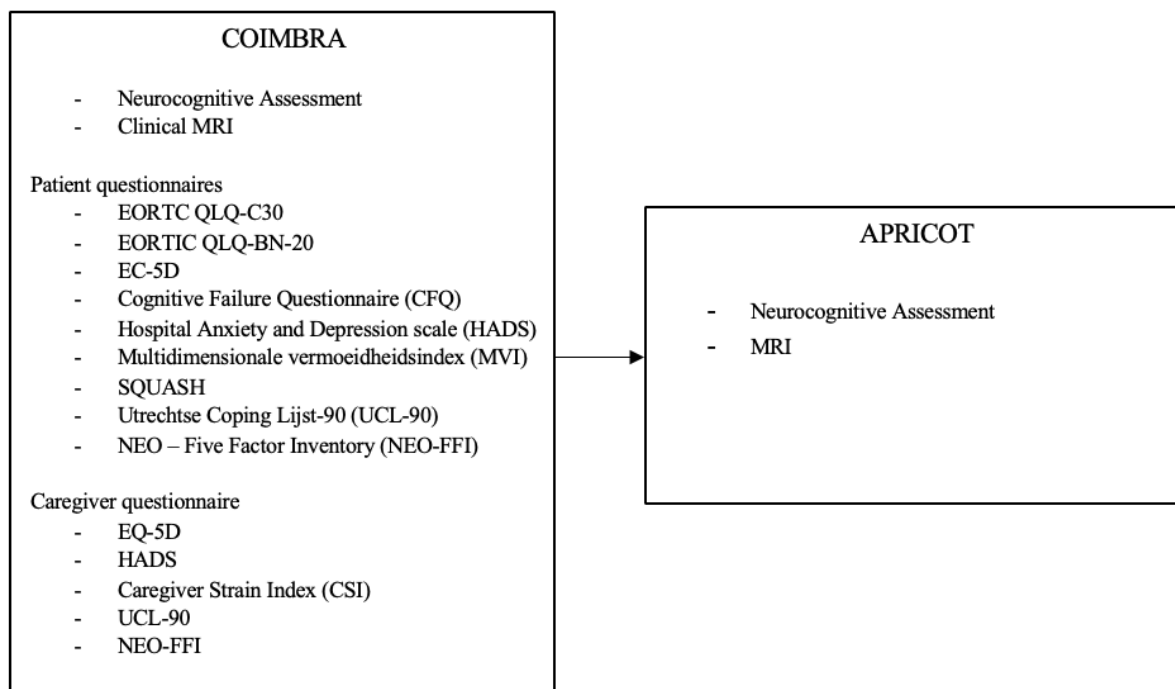
The inclusion criteria for both studies were a sufficient knowledge of the Dutch language, which allows reliable use of the standardized tests and understand the study information. In addition, for participation in APRICOT a survival rate of ≥ 5 months determined by the Graded Prognostic Assessment (GPA) score was mandatory. In addition, there were also MRI and RespirAct exclusion criteria for participation in APRICOT. Patients with pulmonary disease as diagnosed by a pulmonologist: oxygen dependence at rest or on exertion and a restrictive lung disease with a resting respiratory rate greater than 15 breaths/min were excluded. For further inclusion and exclusion criteria, see supplementary 1.

Data

The data collected from COIMBRA and APRICOT are shown in Figure 2. The questionnaires were filled out on paper or online. For the online filled-in questionnaires the Patient Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship (PROFILES) was used. This is a digital patient tracking system (Profiles Study, van de Poll-Franse 2011). The UCL-90 and NEO-FFI were only administered at baseline, but the rest of the questionnaires were also administered 1-month post-RT, 3 months after radiotherapy, and every 3 months thereafter. In addition, a neurocognitive assessment and additional MRI were administered at baseline and 3 months post-RT.

Figure 2

Data collected from COIMBRA and APRICOT

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┌─────────────────────────────────────────────────┐
│                    COIMBRA                        │
│                                                   │
│      -   Neurocognitive Assessment                │
│      -   Clinical MRI                             │
│                                                   │
│   Patient questionnaires                          │
│      -   EORTC QLQ-C30                             │
│      -   EORTIC QLQ-BN-20                          │
│      -   EC-5D                                     │
│      -   Cognitive Failure Questionnaire (CFQ)    │
│      -   Hospital Anxiety and Depression scale (HADS)
│      -   Multidimensionale vermoeidheidsindex (MVI)
│      -   SQUASH                                    │
│      -   Utrechtse Coping Lijst-90 (UCL-90)        │
│      -   NEO – Five Factor Inventory (NEO-FFI)     │
│                                                   │
│   Caregiver questionnaire                         │
│      -   EQ-5D                                     │
│      -   HADS                                      │
│      -   Caregiver Strain Index (CSI)             │
│      -   UCL-90                                    │
│      -   NEO-FFI                                   │
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                    ┌─────────────────────────────────────┐
                    │               APRICOT                │
                    │                                      │
                    │      -   Neurocognitive Assessment   │
                    │      -   MRI                         │
                    │                                      │
                    └─────────────────────────────────────┘
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Instruments

The *Hospital Anxiety and Depression Scale* (HADS) is developed to detect states of depression and anxiety in hospital medical output clinics (Zigmond & Snaith, 1983) (see Supplementary 2). It consists of 14-items divided in two scales, 7 items for depression and 7 items for anxiety. The questionnaire focuses on feelings in the past four weeks. Each question is answered on a 4-point Likert scale (0-3) with higher scores reflecting more complaints. The total score on the scales is the sum of the 7 items. HADS is a reliable instrument with a Cronbach's alpha for the anxiety subscale between 0.68 and 0.93 and a Cronbach's alpha between 0.67 and 0.90 for the depression subscale (Bjelland et al., 2002). The reliability of the HADS is also good for Dutch settings (1997). A score between 0-7 indicates no evidence of depression. A score between 8-11 indicates mild evidence of depression. Finally, a score between 11-20 indicates evidence of depression.

The *Utrechtse copinglijst* (UCL-90) (Schreurs et al., 1993) is a self-assessment scale, developed to measure the coping style. It consists of 47 questions divided into 7 subscales: 1) Actively addressing (7 items), 2) palliative response (8 items), 3) avoidance (8 items), 4) seeking social support (6 items), 5) passive response pattern (7 items), 6) expression of emotions/ anger (3 items), and 7) using reassuring and comforting thoughts (5 items). The UCL-90 is answered on a 4-points Likert scale, 1 (rarely or never) to 4 (very often). Regarding reliability, both the internal consistency and the test-retest data are reasonable. There has not yet been sufficient research into construct and congruent validity (Sanderman & Ormel., 1992). For this study,

only the maladaptive coping strategies were used. This consists of the subscales: palliative response,

avoidance, and passive response pattern.

The *NEO Five Factor Inventory* (NEO-FFI) personality questionnaire is a shortened version of the

NEO-PI-R Personality Inventory by Costa & McCrae (1992). It is a self-report personality questionnaire about

the Big Five personality dimensions: Neuroticism, Extraversion, Openness, Altruism and Conscientiousness.

The questionnaire is used to make statements about the individuals' personality. The NEO-FFI is one of the

most researched and used instruments in the world. The questionnaire contains 60 items, 12 items per

personality trait. Each question is answered on a 5-point Likert scale, 1 (totally disagree) to 5 (totally agree).

The total score per dimension is the sum of the questions in that dimension. The psychometric quality of

NEO-FFI ranges from fair to good. The reliability is an average of .78 for all the five scales (Costa & McCrae,

1992). The internal consistency of the separate five domain scales includes values from 0.64 to 0.88 (Hoekstra

et al., 1996). For the current study only the score on the neuroticism subscale was used.

A *Neurocognitive Assessment (NCA)* consists of the following tasks:

Raven's APM short form, Digit span forward and backward (WAIS-IV) (Wechsler, 2008), Hooper Visual

Organization Test, Hopkins Verbal Learning Test-R (Benedictet al., 1998), Rey Figure copy and delay

(Trembly et al., 2015), Trail Making Test A+B (Bouma et al., 2012; Drane et al., 2002), Grooved Pegboard

(Heaton et al., 1986; Klonoff & Low, 1974; Knights & Moule, 1968; Matthews & Healand, 1979), Verbal

Fluency (letter fluency), Verbal Fluency (category/semantic fluency), STROOP (D-KEFS) (Hammes, 1978;

Barnett et al., 2020), Visual Association Task (long form) (Lindeboom & Schmand, 2014) and Facial

Expressions of Emotion – Stimuli and Tests (FEEST). Certain tasks of the above test battery are classified into

three cognitive domains, figure 3 shows the subdivision. This classification was supervised by a clinical

neuropsychologist with expertise in neuropsychological testing in glioma patients (MJEvZ) (van Kessel et al.,

2017). The patients needed to have completed more than 50% of the tests within the domain. The scores will

be interpreted through standardized Z-scores, which are corrected for age, gender, and educational level. The

Z-scores were calculated as the mean of the patients score on the task in the domain. A Z-score of ≤ 1.5 was

considered to present a cognitive deficit.

Finally, the clinical *magnetic resonance imaging* (MRI) data were used to obtain information about

the location of the BM. This data was used to divide the patients into two groups: 1) cerebellar involvement

group, which consists of patients with a metastasis in the cerebellum, and 2) the non-cerebellar involvement group, which consists of patients that have no metastases in the cerebellum.

Table 1

Subdivision into cognitive domains with their associated tasks

Memory	Executive functioning & Attention	Processing speed
1. HVLT (Hopkins Verbal learning Test) – R – Immediate – Recall - Discrimination	Stroop III & IV*	Stroop I & II
2. Rey-Osterrieth Complex Figure – Delayed copy	Trail Making Test – B*	Grooved Pegboard – Both dominant and non-dominant hand
3. Visual Association Task – immediate	WAIS (Wechsler Adult Intelligent Scale) – R/III – Digit Span – Forward and backward	Trail Making Test – A

Note. * Ratio scores of these tests are used

Analysis

The data was analyzed using Statistical Package for the Social Sciences (version 26) (SPSS; IBM Corp., 2017). First a multiple regression analysis was used to examine whether there was a relationship between depressive symptoms and the neurocognitive domains: executive functioning and attention, verbal and visual memory, and information processing speed. The sample consisted of patients in the COIMBRA cohort with a NCA and patients in APRICOT. In addition, a multiple regression analysis was also used to examine whether there was a relationship between depressive symptoms and 1) neurotic traits, 2) maladaptive coping strategies, and 3) cerebellar involvement. The sample used for the second multiple regression analysis consisted out of patients from both COIMBRA and APRICOT. The data met the necessary assumptions: absence of outliers, absence of multicollinearity, homoscedasticity, and normally distributed residuals. A *p*-value of smaller 0.05 was retained as significant. Finally, an additional analysis was done. A one-tailed Pearson correlation was used to look at the relationship between dexamethasone use and (1) neurotic traits and (2) depressive symptoms.

Results

In total 290 patients (COIMBRA: [$n = 268$]; APRICOT: [$n = 22$]), participated in this study. However, 252 participants were excluded (Figure 3). Therefore, the sample consists of 38 patients (COIMBRA: [$n = 18$]; APRICOT: [$n = 20$]). Baseline statistics and clinical characteristics are presented in table 2. The sample consists for 60.5% out male with a mean age of 62.7 years. Patients took on average 4.08 microgram of dexamethasone on the day of the neurocognitive assessment. The most prominent primary tumor was lung cancer and melanoma.

Table 2

Demographics of the Included Patients

Descriptives	*N*	%	Mean	Range
Sex				
Male	23	60.5		
Female	15	39.5		
Age (in years)			62.7	32-81
Education level				
3	1	2.6		
4	4	10.5		
5	12	31.6		
6	9	23.7		
7	3	7.9		
Primary tumor				
Lung	17	44.7		
Melanoma	12	31.6		
Gastro - intestinal	3	7.9		
Kidney	3	7.9		
Gynecology	1	2.6		
Mamma	2	5.3		
BM Location				
Cerebellar involvement	12	36.8		
No cerebellar involvement	24	63.2		
Dexamethasone (Mg) at the day of NCA	33	86.8	4.8	0-8

Figure 3

Flowchart depicting the Excluded Patients
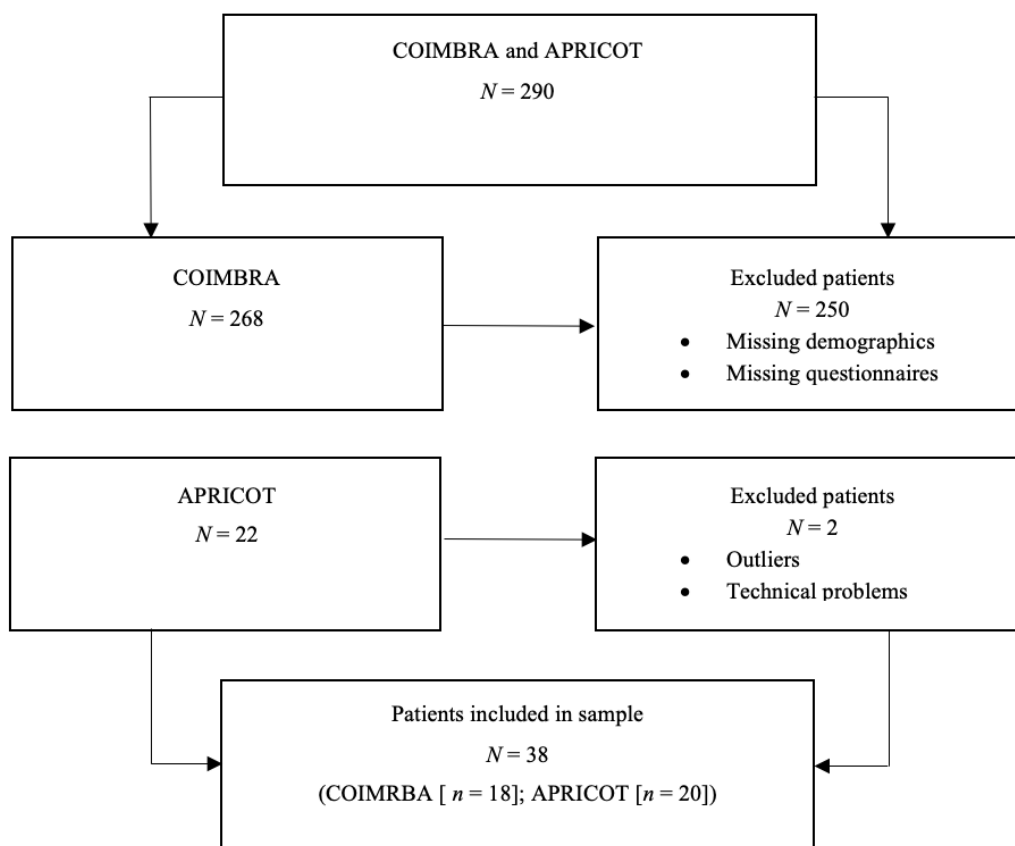
Depressive symptoms and NCF

The sample consisted of 33 patients. No evidence of depression was found in this sample. However, 2 patients scored between 8-10 on the HADS, which is a mild indication of depression. In addition, only 1 patient had a Z-score smaller than 1.5 on executive functioning and attention, 6 patients had a Z-score smaller than 1.5 on memory, and 1 patient had a Z-score smaller than 1.5 on information processing speed (Table 3). Which indicates that majority of the sample performed well at the cognitive domains.

A multiple regression analysis was used to examine the relationship between depressive symptoms and the cognitive domains: executive functioning and attention, memory, and information. These factors did not significantly predict depressive symptoms, $F_{(3,22)} = .758$, $p = .930$, $R^2 = 0.094$. Executive functioning and attention ($B = 1.74$, $t = 1.45$, $p = 0.162$), memory ($B = -.73$, $t = -1.12$, $p = 0.589$), and information processing speed ($B = -.46$, $t = -.67$, $p = 0.825$) were not related to depressive symptoms before radiotherapy in patients with BM (Figure 4).

Table 3

Mean (M) and Minimum and Maximum (range) and standard Deviation (SD) for Depressive symptoms and Z-score per cognitive domain.

Variables	*M* (range)	*SD*
Depressive symptoms	2.33 (0 – 10)	2.37
Neurocognitive Functioning		
Memory	-.55 (-3.29 – .64)	.98
Executive Functioning and Attention	-.63 (-2.31 – .51	.55
Information Processing speed	.29 (1.85 – 1.39)	.75

Figure 4

Relationship between Depressive Symptoms and the Neurocognitive Domains

Z-scores
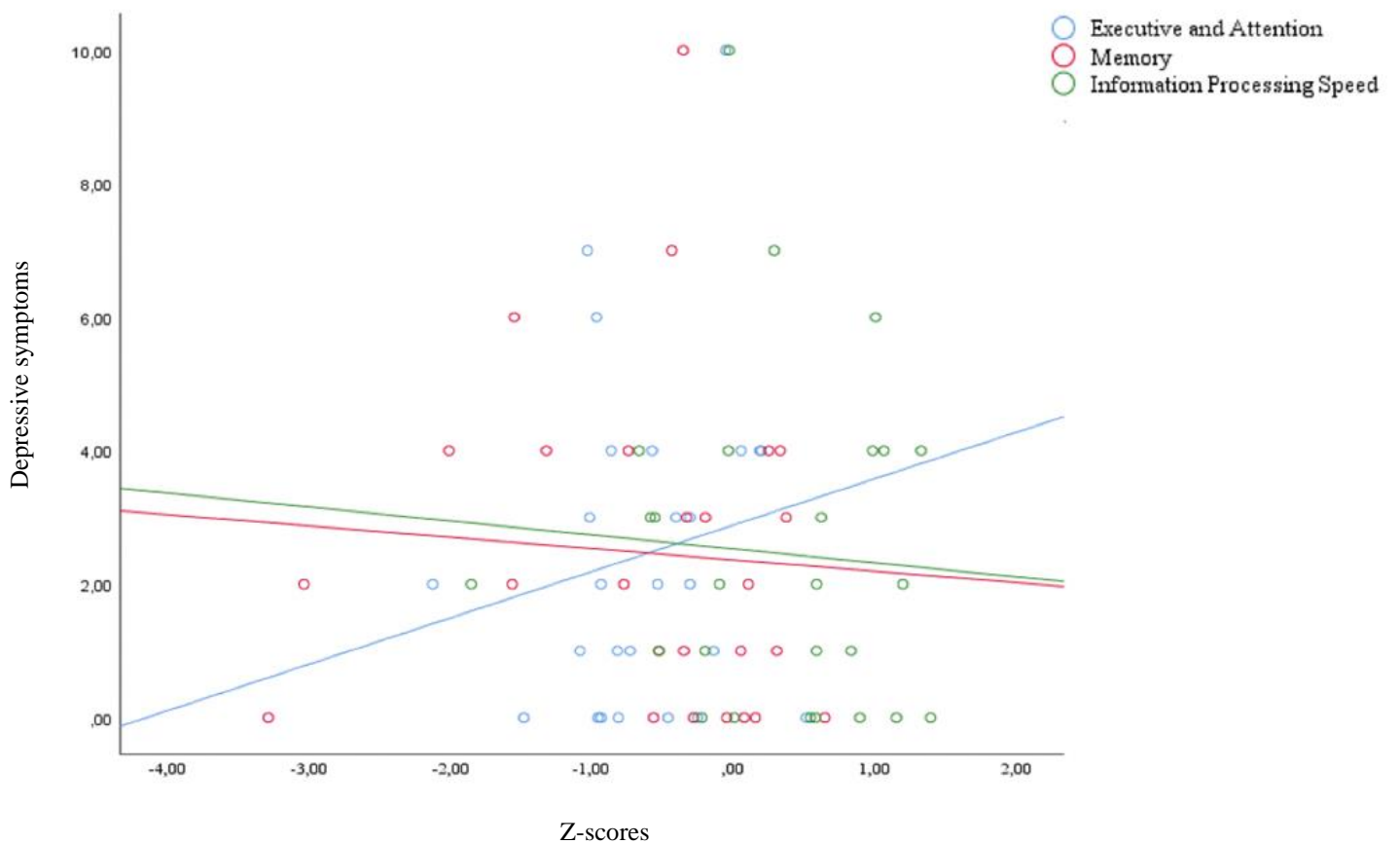
Depressive symptoms and coping strategy, neurotic traits, and cerebellar involvement

This sample consisted out of 25 patients (cerebellar involvement: n = [7]; non-cerebellar involvement n = [18]); (maladaptive coping strategy n = [7]; adaptive coping strategy n = [18]). Only one patient had a score between 11 – 21 on the HADS, which indicates evidence of depression. In addition, one patient scored between 8 – 10, suggesting a mild indication of depression. No patient scored high on the maladaptive coping strategies or neuroticism (table 4).

A multiple regression analysis was used to examine the relationship between depressive symptoms and cerebellar involvement, neurotic traits, and maladaptive coping strategies. A significant regression equation as found, F (3,19) = 3.137, p = .050, R^2 = 0.331. Suggesting that 33.1% of the variance is predicted by the factors. However, only neurotic traits were significantly related to depressive symptoms before radiotherapy (B = 0.29, t = 2.73, p = 0.013). Cerebellar involvement (B = - 68, t = - .11, p = 0.573) and maladaptive coping strategies (B = 2.68, t =2.03 p = 0.057) were not related to depressive symptoms (Figure 4)

Table 4

Mean (M) and Minimum and Maximum (range) and standard Deviation (SD) for Depressive Symptoms, Neurotic traits, and Maladaptive Coping Strategy

Variables	*M* (range)	*SD*
Depressive symptoms	2.72 (0 – 11)	2.72
Neuroticism	26.8 (15 – 26)	5.87
Maladaptive coping strategy	13.87 (9 – 18)	2.06

Figure 5

Relationship between Depressive Symptoms and Neurotic Traits, Maladaptive Coping Strategies and Cerebellar Involvement
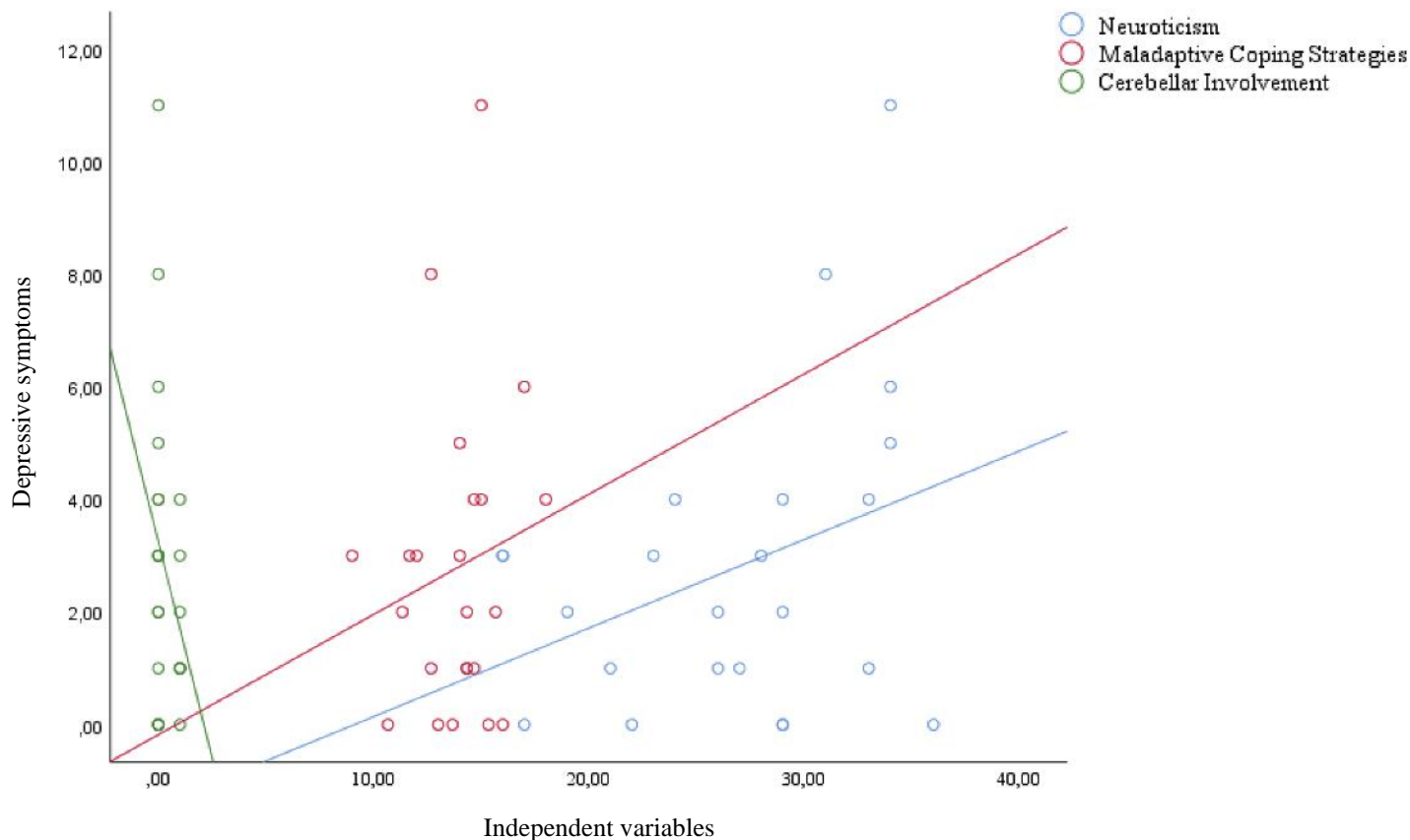
Additional analysis: dexamethasone and 1) neurotic traits, and (2) depressive symptoms.

A Pearson correlation was computed to assess the linear relationship between dexamethasone use and neurotic traits. No correlation was found between the two variables, r (8) = -.35, p = .160. In addition, a Pearson correlation was computed to assess the linear relationship between dexamethasone use and depressive symptoms. There was no correlation between the two variables, r (32) = .26, p = .08.

Discussion

Since depressive symptoms are present in patients with BM and may be exacerbated by radiotherapy, identifying predictive factors for these depressive symptoms could lead to early stabilization or even prevent the development of depressive symptoms. Furthermore, depressive symptoms are known to play a role as a mediator between radiotherapy and NCF. By keeping baseline depressive symptoms as low as possible, worsening of NCF can minimized. The results indicate that neurotic traits were the only predictive factor for depressive symptoms in patients with BM. Pre-radiotherapy NCF, cerebellar involvement, and maladaptive coping strategies were not found to be predictive factors in this patient population.

Several studies in different patient groups have shown that depressive symptoms are associated with poor NCF (Janelsins et al., 2018; Tibbs et al., 2020). In contrast to this, this current study finds no relationship between NCF and depressive symptoms; executive functioning and attention, information processing speed, and verbal and visual memory were not related to depressive symptoms in patients with BM. A reason for this difference in study findings could be due to differences in the sample being investigated. Tibbs' sample consisted of patients diagnosed with clinical depression or anxiety, while the current study did not select participants based on this inclusion criteria. Even though patients with brain tumors and BM are known to be at risk of developing depressive symptoms, the majority of our study's sample had no indication of depression. Only 2 patients had indications for possible depression. On top of that, associations between NCF and depressive symptoms are mostly found when the sample consists of many patients with a wide range of depressive severity. In addition, different studies investigating the relationship between NCF and depression often used different depression rating scales. Therefore, there is little to no consistency in the different associations found between NCF and depressive symptoms. This explains the contradicting findings regarding this topic.

Despite our hypothesis, patients with cerebellar involvement did not have more depressive symptoms. Functional MRI (fMRI) data has shown different neural circuits originating from different cerebellar subregions. The cerebellar area VII has been shown to be important in affective and emotion processes and is, unlike the other cerebellar areas, not connected to the somatomotor region (Depping et al., 2018). It could be the case that only BM in this cerebellar subregion is linked to depressive symptoms. Involvement of the cerebellum in emotion regulation has been linked to the functional connections of the cerebellum with the limbic system. Moreover, the patients in our study that were included in the cerebellar involvement group, also had BM elsewhere in the brain. These locations can also influence the limbic system and therefore emotion processing. In addition, the hippocampus is known to be involved in mood disorders. Research has shown that the hippocampus is almost certainly not solely responsible for depressive symptoms (Campbell & MacQueen, 2004). Since this study did not control for different cerebellar areas and other brain locations, this may be why no effect was found.

Despite the evidence that maladaptive coping strategies are related to depressive symptoms, no relationship was found in our study. The result found was marginally not significant. This may be due to an

underpowered sample size. Goebel et al. (2018) concluded that patients with brain tumors most often used an optimistic adaptive coping strategy, which is efficient to achieve better psychological well-being. An example of these adaptive coping strategies could be actively addressing or using reassuring and comforting thoughts. Moreover, studies suggest that older adults deal with the highs and lows associated with the cancer diagnosis more effectively due to their coping strategy (Liang et al., 2020). This effect was also seen in our sample. Most patients (72%) reported using an adaptive coping strategy. Maladaptive coping strategies were thus underrepresented. This may have resulted in a bias.

Personality traits are the most investigated psychological factor in patients with depression (Banjongrewadee et al., 2020; Macia et al., 2020). Conformingly, in this current study, patients with high levels of neurotic traits reported significantly more depressive symptoms. Thus, neurotic traits could be considered risk predictors for developing depressive symptoms, in patients with BM. These personality traits can lead to poor psychological and mental health as they cause one to experiencing life events as threatening and distressing (Perry et al., 2018). A person characterized by high neurotic traits, may experience the diagnosis of cancer as more threatening or severe. Therefore, these patients will experience more fear and emotional distress, leading to the development of depressive symptoms (Macia et al., 2020).

An additional analysis was performed on dexamethasone use. It has been concluded that dexamethasone use induces mood disorders such as depression and psychosis. This can be due to elevated levels of corticosterone which in turn damages the hippocampus (Haynes et al., 2001). Despite this evidence, dexamethasone use was not found to be related to depressive symptoms or neurotic traits in our sample. Since research has shown that the effects of dexamethasone on mood is dose dependent this may explain why no effect was found. In this current study patients took an average of 4.08 mg dexamethasone a day with a maximum of 8 mg. Ozdel et al. (2006) suggest that dexamethasone use up to 10 mg a day does not lead to any mood problems.

Some limitations of the current study have to be mentioned. Even though COIMBRA and APRICOT collect longitudinal data, this study chose only to look at the baseline characteristics of the patients. Therefore, no causality between neurotic traits and depressive symptoms can be inferred. Future research should use a bigger sample size with longitudinal data to examine causality between predictive factors and the severity of depressive symptoms. Subsequently, the distribution of the cerebellar involvement group and the non-

cerebellar involvement group was not proportional. Most patients had no cerebellar metastases. In addition, patients with cerebellar metastases also had metastases elsewhere in the brain. Therefore, it was not possible to examine the relationship between metastases solely in the cerebellum and depressive symptoms. Since the cerebellum is becoming an important topic in emotion regulation, follow up research is needed to investigate the cerebellar involvement in patients with BM further. For example, follow-up research could focus on the different cerebellar regions. Examining the relationship between depressive symptoms and BM in area VII, could provide some more evidence for the already existing literature. Finally, since the APRICOT study includes patients of the COIMBRA with a GPA score of ≥ 5 it can be suggested that these patients do better cognitively and emotionally than most patients with BM. Our sample consisted of most patients from APRICOT. Therefore, most patients appeared to have good intact NCF and reported few depressive symptoms before radiotherapy. This could ultimately have created a bias.

Besides these limitations, the current study also had its strengths. This study provided insight into vulnerabilities for developing depressive symptoms in patients with BM. Research on this topic is very limited but highly requested. Moreover, the dataset used is broad. In addition, the data also consists of patients with multiple types of primary tumors. Therefore, it is generalizable to the BM population. Lastly, the data of this study is relevant since it consisted of recently collected data, unlike many older studies.

In conclusion, this study reveals that neurotic traits can be considered risk predictors for developing depressive symptoms in individuals with BM before undergoing radiotherapy. Early identification of patients with neurotic traits allows for early identification of patients that are at risk for developing depressive symptoms. From previous research it is known that radiotherapy can elevate depressive symptoms, which in turn has negative effects on NCF. Therefore, it is important for health care professionals to consider personality traits from the first consultation onward. This will allow patients with a high score on this personality trait to be better informed about possible effects radiotherapy on the onset or worsening of depressive symptoms and in turn its effects on NCF. In addition, this offers the possibility for early psychological intervention in patients with high levels of neurotic traits, which may modulate the risk of depression. This study has contributed to the knowledge about which factors are associated with depressive symptoms in an extremely vulnerable population at the point that they start radiotherapy.

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Supplementary 1

Inclusion and exclusion criteria for participation in the COIMBRA and APRICOT study

COIMBRA

Inclusion criteria

- Age ≥ 18 years;
- Radiographic and/or histologic proof of metastatic brain disease, or eligible for prophylactic cranial irradiation;
- Referred to the Department of Radiotherapy for cranial irradiation.

Exclusion criteria

- Mental disorder or cognitive dysfunction that hinder the patient's ability to understand the informed consent procedure and/or details;
- Patients with severe psychiatric disorders;
- Inability to understand the Dutch language.

APRICOT

Inclusion criteria

- Age ≥ 18 years;
- Expected survival ≥ 5 months, as determined by the Graded Prognostic Assessment (GPA) score;
- Either radiographic and/or histologic proof of metastatic brain disease eligible for cranial irradiation;
- Eligible for brain irradiation for prophylaxis or treatment;
- Signed informed consent;
- Sufficient knowledge of the Dutch language to allow reliable use of the standardized tests and understand the study information;
- Participation in the COIMBRA cohort, with given consent for filling in QoL questionnaires.

Exclusion criteria

- Unwilling or unable to cooperate with breathing manoeuvres or keeping still;
- Medical contraindications to limited hypercapnia (known metabolic acidosis or alkalosis);
- Standard contraindications for 3T MRI scanning;
- Standard contraindications for using the RespirAct RA-MRTM MRI UNIT (see D2 IMDD 2.5 contraindications);
- Noncompliance with prescribed anti-seizure medication;

- Severe current neurological or psychiatric diseases (including pre-existent dementia or other cognitive disorders as diagnosed by a neurologist, psychiatrist or gerontologist), not related to the primary malignancy or cerebral metastases;

- History of cerebrovascular disease (ischaemic stroke or intracranial haemorrhage);

- Non-prophylactic use of > 4 mg dexamethasone on the day of CST;

- Cardiovascular disease: congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, and myocardial infarction within past 6 months as diagnosed by a cardiologist;

- Pulmonary disease as diagnosed by a pulmonologist: oxygen dependency at rest or with exercise, restrictive lung disease with resting respiratory rate over 15 breaths/min;

- Concurrent severe or uncontrolled medical disease (e.g., active systemic infection);

- History of bleomycin treatment;

- Body weight <30 kg, >100 kg;

- Pregnancy.

Supplementary 2

Hospital Anxiety and Depression Scale (HADS)

Naam: Leeftijd:
Geslacht: Datum:

Het is bekend dat emoties bij de meeste ziektes een belangrijke rol kunnen spelen.
Deze vragenlijst dient als hulpmiddel om te weten te komen hoe u zich voelt. Lees iedere vraagen
<u>onderstreep</u> het antwoord dat het beste weergeeft hoe u zich **gedurende de laatste week** gevoeld heeft.

Denk niet te lang na over uw antwoord. Uw eerste reactie op elke vraag is waarschijnlijk
betrouwbaarder dan een lang doordacht antwoord.

1. **Ik voel me gespannen**:

   Meestal
   Vaak
   Af en toe, soms
   Helemaal niet

2. **Ik geniet nog steeds van de dingen waar ik vroeger van genoot**:Zeker

    zo veel

       Niet zo veel als vroeger
       Weinig
       Haast helemaal niet

3. **Ik krijg een soort angstgevoel alsof er elk moment iets vreselijks zal gebeuren**:Heel

       zeker en vrij erg
       Ja, maar niet zo erg
       Een beetje, maar ik maak me er geen zorgen over
       Helemaal niet

4. **Ik kan lachen en de dingen van de vrolijke kant zien**:Net

       zoveel als vroeger
       Niet zo goed als vroeger
       Beslist niet zoveel als vroeger
       Helemaal niet

5. **Ik maak me vaak ongerust**:

       Heel erg vaak
       Vaak
       Af en toe maar niet te vaak
       Alleen soms

6. **Ik voel me opgewekt**:

      Helemaal niet
      Niet vaak
      Soms Meestal

7. **Ik kan rustig zitten en me ontspannen**:

    Zeker

      Meestal
      Niet vaak
      Helemaal niet

8. **Ik voel me alsof alles moeizamer gaat**:

      Bijna altijd
      Heel vaak
      Soms
      Helemaal niet

9. **Ik krijg een soort benauwd, gespannen gevoel in mijn maag**:

      Helemaal niet
      Soms
      Vrij vaak
      Heel vaak

10. **Ik heb geen interesse meer in mijn uiterlijk**:

    Zeker

      Niet meer zoveel als ik zou moeten
      Waarschijnlijk niet zoveel
      Evenveel interesse als vroeger

11. **Ik voel me rusteloos en voel dat ik iets te doen moet hebben**:Heel erg

      Tamelijk veel
      Niet erg veel
      Helemaal niet

12. **Ik verheug me van tevoren al op dingen**:Net

      zoveel als vroeger
      Een beetje minder dan vroeger
      Zeker minder dan vroeger
      Bijna nooit

13. Ik krijg plotseling gevoelens van panische angst:

Zeer vaak
Tamelijk vaak
Niet erg vaak
Helemaal niet

14.   Ik kan van een goed boek genieten, of van een radio- of televisieprogramma:Vaak

Soms
Niet vaak
Heel zelden

Wilt u controleren of u alle vragen beantwoord heeft?

BEDANKT