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Cognition as predictor of current and follow-up depressive symptoms in the general population

Simons CJP, Jacobs N, Derom C, Thiery E, Jolles J, van Os J, Krabbendam L. Cognition as predictor of current and follow-up depressive symptoms in the general population.

Objective: Previous studies have reported an association between depression and poor cognitive functioning. Unknown is to what degree such associations are merely state-related or reflect an enduring depression vulnerability. This study examined whether cognitive deficits predict current and/or follow-up (sub)clinical depressive symptoms in the general population.
Method: A population-based sample of 569 female twins and 43 of their sisters completed a neuropsychological battery. Cross-sectional and prospective associations between depressive symptoms measured at the subclinical [Symptom Checklist-90 (SCL-90)] and clinical level (Structured Clinical Interview for DSM-IV disorders) and neuropsychological factors (episodic memory and information processing speed) were examined.
Results: Structured Clinical Interview for DSM-IV disorders baseline depressive symptoms were significantly associated with information processing speed but not with episodic memory. Episodic memory was significantly associated with follow-up SCL-90 depressive symptoms.
Conclusion: Being depressed is accompanied by slower information processing. Poor memory functioning may be a predictor for the onset of subclinical depressive symptoms.

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Key words: depression; cognition; memory; risk factors; follow-up studies

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Significant outcomes

- Slower information processing was associated with clinical depressive symptoms at baseline, which disappeared at follow-up 2 years later, suggesting a state effect.
- Poor episodic memory functioning predicted subclinical depressive symptoms assessed over a 2-year follow-up period, suggesting mediation.

Limitations

- The sample consisted of female participants only.
- The sample was a relatively highly educated group.
- The cognitive assessment in this study was limited to tasks involving verbal memory, attention and speed of information processing.

Introduction

Previous studies have found depression to be associated with a number of deficits across a range of domains of cognitive functioning including memory, executive functioning, attention and speed of information processing (1–5). Studies investigating cognitive functioning in depressed patients have shown that resolution of the depressive symptoms is paired with improvement in cognitive functioning, although residual impairments in cognitive functioning can be detected (6–8). These findings, therefore, suggest that poor cognitive functioning is at least in part a state effect

and that depression might also be a predictor of future cognitive impairment. It is generally believed that depression precedes the development of cognitive deficits. However, the causality may be reversed. Prospective studies investigating the impact of cognitive functioning on follow-up depressive symptoms have been rare and have generally focussed on depressed elderly patients; such studies do suggest, however, that cognitive deficits may be a risk factor for future depression (9–13). Airaksinen et al. (14) studied a general population sample of non-depressed individuals (20–64 years) and found that low episodic memory performance was a reliable predictor for depression diagnosis three years later. Colman and colleagues (15) showed that depression, measured in a birth-cohort over the life course, is associated with neurodevelopmental impairments and the relationship between neurodevelopmental impairments and depression may be mediated by cognition (15, 16).

It has been shown that depressive symptoms exist as a continuous distribution of symptoms in the general population (17–22) ranging from subclinical depressive symptoms or dysphoria to a major depressive disorder. Subclinical depression may be more sensitive to detect associations with risk factors in general population studies. The advantage of a general population design is that confounding as a result of illness characteristics such as medication effects or severe psychopathology can be avoided. In addition, in a longitudinal design temporal relationships between emergence of cognitive deficits and depressive symptoms can be assessed adjusted for their baseline presence.

Aims of the study

This study investigated whether depressive symptoms in the general population are associated with cognitive dysfunction. The existence of cross-sectional associations between cognitive deficits and depressive symptoms would imply a state effect of depressive mood on cognitive functioning. However, if poor cognitive functioning would precede the depressive state, this would imply that cognitive functioning may be causally related to the onset of depressive symptoms.

Material and methods

Subjects

The study sample consisted of 569 monozygotic and dizygotic female twin pairs and 43 of their sisters, all between 18 and 61 years of age. The sample was recruited in the context of a study on stress and depression (23, 24). Two-hundred and thirty-six pairs came from the East Flanders Prospective Twin Survey. This population-based survey has prospectively recorded all multiple births in the province of East Flanders since 1964 (25, 26). Sixty-two pairs were recruited using registers from Flemish municipalities. The project was approved by the Local Committee of Medical Ethics and all participants gave written informed consent.

Measures

At baseline, a neuropsychological battery was administered. The neuropsychological assessment was directed at the following cognitive domains: episodic memory, and simple and complex information processing. The Auditory Verbal Learning Task [AVLT; (27)] was used to evaluate memory storage and retrieval of information in episodic memory. The measures used were the total number of words recalled over the three trials and number of words recalled after a 20-min delay. Tests used to measure the speed of information processing were the Stroop Color-Word Test [SCWT; (28)], the Concept Shifting Test [CST; (29)], which is a modified version of the Trail-Making Test (30) and the Letter Digit Substitution Test [LDST; (31)], which is a modified version of the Symbol Digit Modalities Test (32).

Subclinical depressive symptoms were measured with the Symptom Check List [SCL-90 (33, 34), Dutch version: (33)]. The SCL-90 is a widely used 90-item self-report questionnaire measuring general psychological distress. This study only used the depression subscale, consisting of 13 items. The SCL-90 was administered five times with an interval of 5.2 (SD = 0.6) months between two measurements. The first administration of the SCL-90 was at baseline, at the same time the neuropsychological test battery was administered. This measure of current subclinical depressive symptoms was used to test for cross-sectional association between cognition and depressive symptoms. To investigate the role of cognition as a possible predictor for future subclinical depressive symptoms, the mean number of depressive symptoms over follow-up 1–4 was used (Fig. 1). To account for partial non-response, depression scores were weighted for the valid number of items.

Clinical depressive symptoms were assessed with the Structured Clinical Interview for DSM-IV axis I Disorders (SCID). The SCID was administered at baseline and the fourth follow-up, approximately 24.3 (SD = 7.5) months after assessment of

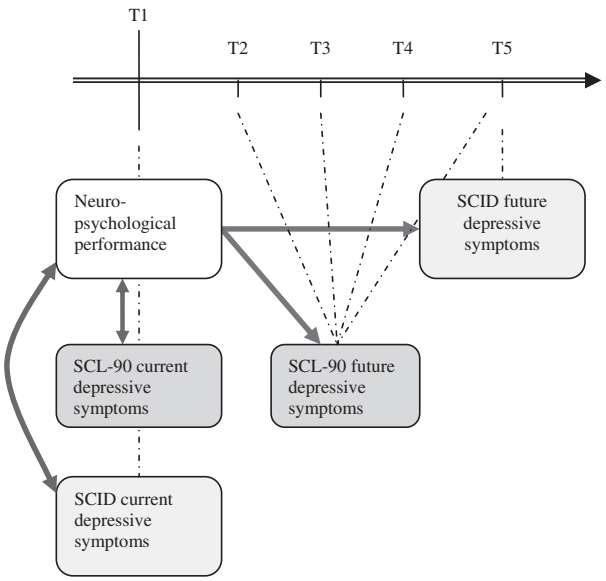

Fig. 1. Cross-sectional and prospective associations between cognition and depression. Dashed lines indicate at what time-points the tests were administered. Cross-sectional associations were tested between neuropsychological performance and depression scores gathered at T1. The blue lines indicate multilevel regression analyses to investigate these associations. The arrows are bidirectional to emphasize the cross-sectional nature of the analyses. Prospective associations were tested between neuropsychological performance at T1 and subclinical depression (mean of T2–T5) and clinical depression (measured at T5). The green lines indicate multilevel regression analyses to investigate these associations.

neuropsychological test performance. A continuous depression scale was created by taking the sum of the items, scored 0 (absent) or 1 (present), on the SCID that form the nine symptoms listed under criterion A for major depressive episode in DSM-IV. The SCID baseline score was used to test for a cross-sectional association between cognition and clinical depressive symptoms; the SCID score at follow-up 4 was used to test for a prospective association between cognition and clinical depressive symptoms (Fig. 1).

Statistical analysis

The number of neuropsychological test variables was reduced by means of a principal component factor analysis of the entire study sample followed by varimax rotation, using STATA version 9.0 (35). Guided by the scree plot, a two-factor solution was chosen, accounting for 52% of the variance. The variables of the AVLT loaded on the first factor, which was termed episodic memory (factor loadings −0.92). The variables of the Stroop, CST (factor loadings from 0.49 to 0.70) and LDST (factor loading −0.66) loaded on the second factor, which was termed information processing speed. Factor scores for this factor were multiplied by −1 so that higher scores on each factor indicated better performance.

Although the present sample consisted of twin pairs, the data analysis did not focus on specific techniques commonly associated with twin analyses, such as structural equation modelling. Rather, the analyses focussed on the longitudinal aspect of the study. Thus, within-twin linear regression analyses were conducted to examine, within subjects, the association between each cognitive factor and depression. Regression analyses were adjusted for age and education, unless stated otherwise. Regression analysis examining the association between follow-up depressive symptoms and cognition were corrected for depressive symptoms at baseline. Correction for depressive symptoms at baseline is necessary to disentangle potential prospective associations between cognition and depression from potential state effects of depressive symptoms on cognitive performance. Effect sizes were expressed as the standardized regression coefficient (β) from the multilevel models. Multilevel random regression models were constructed, using the XTREG procedure in STATA (35), given the fact that members of a twin pair cannot be considered statistically independent.

Results

Sample

Five hundred and sixty-nine female twin pairs and 43 sisters of these twins participated. Mean age of the sample was 28 years (SD = 7.9 years, range 18–61 years). A majority of 62% had a college or university degree, 38% completed secondary education and 1% had primary education. The majority was currently employed (61% employed, 35% student, 3% unemployed and 1% homemaker).

At baseline, 642 subjects completed the neuropsychological test battery. Of these subjects, 612 completed the SCL-90 at baseline. Follow-up SCL-90 scores were available for 553 subjects and for 548 of these subjects, baseline depressive symptom scores on the SCL-90 were also available. For 637 of the 642 subjects, SCID baseline depressive symptoms were available. At follow-up, 445 subjects had SCID depressive symptoms scores, for 444 of these subject, SCID baseline depression scores were also available (Fig. 2). Education ($\beta = 0.28$, $P = 0.02$) and SCL-90 subclinical ($\beta = -0.50$, $P = 0.01$), as well as SCID clinical depression scores ($\beta = 0.59$, $P < 0.001$) were significant predictors for missing scores on the SCL-90

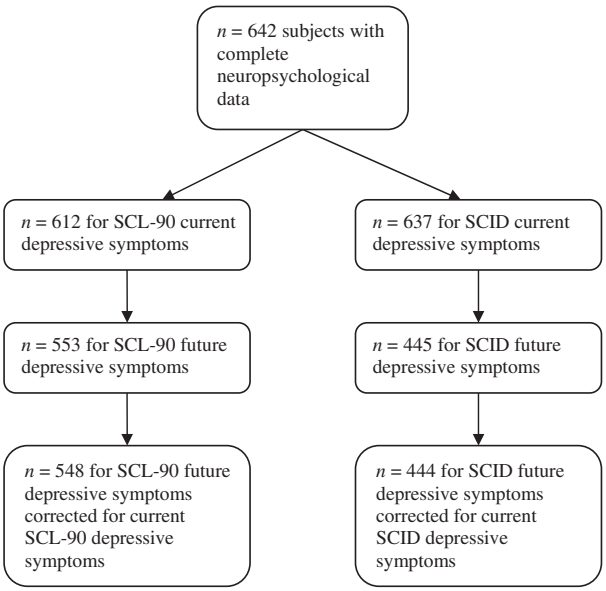

Fig. 2. Flow chart of subjects for Symptom Checklist-90 (SCL-90) and Structured Clinical Interview for DSM-IV disorders (SCID) measures of current and future depressive symptoms.

follow-up depression variable. Cognition, age, education, nor depressive symptoms on SCID and SCL-90 predicted missing values on the SCID at follow-up.

Mean score on the SCL-90 depressive dimension was 1.45 (SD = 0.52) for baseline and the mean aggregated follow-up score was 1.48 (SD = 0.48). Based on the SCID, 4.7% of the subjects could be characterized as having a current depressive episode at baseline. All depression variables were skewed to the right, indicating that a majority of the subjects scored relatively low on the depression scales and a minority had higher depression scores.

Mean scores on the neuropsychological tests are summarized in Table 1. Distributions of all neuropsychological measures were skewed, indicating that the majority of the subjects showed normal to good test performance, with the exception of the distributions of the LDST. Given the skewed distributions of the depression and cognition variables, the Huber-White estimator of variance was used in the regression analyses which is robust against distributional assumptions (36).

Current depressive symptoms

Regression analysis showed a significant association between current depressive symptoms measured with the SCID (i.e. depression measured at baseline) and information processing speed ($\beta = -0.11$, $P = 0.02$), after controlling for age. However, for the SCL-90 the effect fell just short of statistical significance ($\beta = -0.09$, $P = 0.06$). After additional adjustment for education, the association was reduced for the SCL-90 ($\beta = -0.05$, $P = 0.31$) but less so for the SCID ($\beta = -0.09$, $P = 0.05$.) No large or significant associations were found between episodic memory and current depressive symptoms measured either with the SCL-90 ($\beta = 0.05$, $P = 0.22$) or with the SCID ($\beta = -0.02$, $P = 0.60$) after adjustment for age and education.

Table 1. Summary of performance on neuropsychological tasks

Neuropsychological measure	Mean (SD)
Episodic memory	
AVLT†	
Immediate recall	32.7 (5.0)
Delayed recall	11.5 (2.5)
Information processing speed	
SCWT (s)‡	
Names	14.0 (3.5)
Colors	19.5 (3.3)
Interference	33.8 (6.9)
CST (s)‡	
Numbers	16.2 (3.5)
Letters	19.1 (5.1)
Number/letter	25.3 (7.8)
LDST†	61.0 (8.2)

AVLT, Auditory Verbal Learning Task; SCWT, Stroop Color-Word Test; CST, Concept Shifting Test; LDST, Letter Digit Substitution Test.
†Higher scores indicating better performance.
‡Higher scores indicating poorer performance.

Follow-up depressive symptoms

Regression analysis of mean aggregated follow-up SCL-90 depression score, after adjustment for age and education but without adjustment for baseline SCL-90 depression score, showed no significant association between follow-up SCL-90 depression score and episodic memory ($\beta = -0.04$, $P = 0.35$). Baseline SCL-90 depression score significantly predicted follow-up SCL-90 depression score ($\beta = 0.65$; $P < 0.001$) and accounted for the most variance in future subclinical depressive symptoms. With adjustment for baseline SCL-90 depression score, the association between follow-up SCL-90 depression score and episodic memory became larger and statistically significant ($\beta = -0.07$; $P = 0.03$). The association between follow-up SCL-90 depression score and information processing speed was significant ($\beta = -0.12$; $P = 0.02$), but the significance was strongly reduced and non-significant after controlling for baseline SCL-90 depression score ($\beta = -0.05$, $P = 0.17$).

Structured Clinical Interview for DSM-IV axis I Disorders follow-up depressive symptoms were associated with neither information processing

speed ($\beta = -0.06$, $P = 0.31$) nor episodic memory ($\beta = 0.05$, $P = 0.35$). SCID baseline depressive symptoms significantly predicted SCID follow-up depressive symptoms ($\beta = 0.22$; $P = 0.001$) and accounted for the most variance in future clinical depressive symptoms. After adjustment for SCID baseline depressive symptoms, information processing speed ($\beta = -0.04$, $P = 0.43$) and episodic memory ($\beta = 0.06$, $P = 0.25$) still showed no significant associations.

Discussion

Depression and episodic memory

Episodic memory functioning was not associated with depressive symptoms measured at baseline. In contrast, a significant association was found between episodic memory functioning and SCL-90 follow-up depressive symptoms, controlling for depressive symptoms at baseline. However, episodic memory functioning was not significantly associated with SCID follow-up depressive symptoms. The SCID is an interview that measures clinical symptoms, whereas the SCL-90 is a self-report questionnaire that measures psychological distress. The difference in results for the SCL-90 and the SCID may be explained by the fact that the present research sample was a general population sample and not a clinical sample. The SCL-90 may be a more sensitive instrument for the present population than the SCID. A similar differential sensitivity of subclinical vs. clinical instruments was noted by Colman and colleagues (15) in relation to associations with low birth weight. Furthermore, SCID follow-up depressive symptoms scores were available for fewer subjects than SCL-90 follow-up scores. In addition, SCID follow-up depressive symptoms were assessed at one time-point (follow-up 4), examining symptoms during the past month. In contrast, for the SCL-90 the mean of four follow-ups was used, thus reflecting a much longer time span. Therefore, the SCL-90 arguably constituted a much more sensitive measure.

The results of the SCL-90 thus suggest that poor episodic memory may be a risk factor for the development of depressive symptoms, in contrast with the more commonly voiced notion that cognitive deficits represent a secondary consequence of the depressive disorder or depressive mood. However, several studies investigating cognitive performance in depressive patients have shown that the cognitive deficits do not always resolve with the remission of the depressive symptoms (8, 10, 11, 37, 38). The present findings are in accordance with the study of Airaksinen et al. (14), who found that low episodic memory performance (the sum of free and cued recall) predicted depression diagnoses 3 years later. This suggests that cognitive deficits may be more than just an epiphenomenon of a depressed mood. A recent study by Colman and colleagues (15) add further credence to this suggestion. In a large birth-cohort, they found depressive symptoms to be associated with neurodevelopmental markers and suggested that prenatal maternal stressors may play a crucial role by altering the development of the hypothalamic–pituitary–adrenal axis in the foetus, leading to a permanently altered stress response. Repeated stress may lead to loss of hippocampal volume as a consequence of the neurotoxic effects of excessive glucocorticoid levels (39, 40) and the effect of stress may be modulated by genetic variants (41). As the hippocampus is involved in episodic memory (42) and there is evidence that depression correlates with lower hippocampal volume (43, 44), it is attractive to speculate that decreased hippocampal functioning plays a crucial role in the mechanism underlying the association between episodic memory functioning and depressive symptoms observed in this study. Alternatively, depression has been associated with subcortical white matter lesions (45) and episodic memory functioning has been associated with white matter lesions in periventricular areas of the brain (46). Although explanations in terms of underlying biology are speculative, this may suggest that decreased connectivity throughout the brain could lead to depressive symptoms and poor episodic memory functioning. Alternatively, depression could be a reaction to cognitive problems, although this explanation cannot account for the specificity of the association for episodic memory. It can also be speculated that episodic memory deficits may give rise to stressful events, which in turn may fuel depressive symptoms. As this study controlled for depressive symptoms at the time of neuropsychological testing, and still found a significant association with depressive symptoms measured at later moments in time, it can be argued that motivational factors are not involved in the longitudinal association between episodic memory and depressive symptoms.

The findings of this study that poor episodic memory functioning predicts future depressive symptoms, is not compatible with a general recommendation of screening for deficits in episodic memory functioning, because this would lack sensitivity and specificity. Rather, as Colman and co-workers (15) already suggested, general population screening of cognition and longitudinal

depressive symptoms may be important in finding factors involved in the aetiology of depression.

Depression and information processing speed

Depressive symptoms measured at baseline showed a significant association with information processing speed. This association was seen regardless of whether depressive symptoms were measured with the SCL-90 or with the SCID. However, the association disappeared for the SCL-90 when controlling for educational level, whereas it still remained significant for the SCID. Higher educational level was associated with significantly lower level of current depressive symptoms, even though the present sample was a relatively highly educated group with more than 60% of the subjects having a college or university degree. Therefore, it is possible that in a sample with a lower educational level, associations between present state depression and cognition could be observed, that nonetheless may be confounded.

There was a significant association between SCL-90 follow-up depressive symptoms and information processing speed when the association was not adjusted for baseline depressive symptoms. This is to be expected in the presence of state effects of current depressive symptoms on information processing speed, because current depressive symptoms are predictive of future depressive symptoms and therefore can confound the relation between cognition and future depressive symptoms. After adjustment for baseline depressive symptoms, the association between information processing speed and future depressive symptoms did indeed disappear. These findings indicate that the association between clinical depressive symptoms and information processing speed is a state effect. This is in accordance with studies reporting state effects in clinical populations (47–49). Although the cross-sectional association between depressive symptoms and cognitive deficits is usually interpreted as depressive states impacting negatively on information processing speed, the cross-sectional nature of the association between clinical depressive symptoms and information processing speed, makes it is impossible to assess causality. Furthermore, it can not be excluded that both poor episodic memory functioning and depressive symptoms are not causally related but are caused by a shared vulnerability factor.

Limitations

The findings of this study must be interpreted in the light of several sample and methodological issues. First, the sample consisted of female participants only. A consistent finding in epidemiological research is that women are at least twice as likely as men to suffer from a unipolar depression (50, 51) and in non-clinical samples, women tend to score higher on depression scales (52, 53). Therefore, the range of depressive symptoms in a general population female sample may be wider than the range of depressive symptoms in a male sample. Thus, it is possible that any association with cognitive functioning is more easily detected in a female sample.

The cognitive assessment in this study was limited to tasks involving verbal memory, attention and speed of information processing. Other cognitive domains and their associations with depression should be the subject of further study.

The continuous outcome measure of depressive symptoms is different from clinical diagnosis according to DSM criteria. However, several arguments can be brought to bear to demonstrate that this would not have biased or otherwise negatively impacted on the results. First, there is good evidence that constructs such as major depressive episode defined by DSM or ICD criteria may be arbitrary diagnostic conventions imposed on a continuum of depressive symptoms (17, 19, 54–57). Second, it would be difficult to conceive how any phenotype would depend on a categorical rather than a dimensional expression for associations with cognition to be valid or significant.

To conclude, the results indicate that slow processing of information may be the result of being in a depressed state, whereas poor episodic memory functioning may a predictor of depressive symptom.

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