Bidirectional relation between affective symptoms and cognitive function from middle to late adulthood: a population-based birth cohort study

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Abstract

Objectives: There is a longitudinal association between affective symptoms and cognition. However, the nature and direction of this association remains unclear. The aim of this study was to test for bidirectional relationships between affective symptoms and cognitive function from middle to late adulthood.

Method: Data were available from the MRC National Survey of Health and Development (NSHD), a prospective birth cohort of 5362 people born in 1946. Affective symptoms and cognition were measured at ages 53, 60-64, and 69. Latent scores of affective symptoms were derived at each time point and cross-lagged models were fitted for affective symptoms with verbal memory and processing speed. Models were adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test.

Results: Results revealed an inverse cross-sectional association between affective symptoms and both verbal memory ($\beta=-0.18$, SE=0.04, $p<.001$) and processing speed ($\beta=-0.13$, SE=0.06, $p=.05$) at age 53, but not at ages 60-64 or 69. Higher affective symptoms at age 53 predicted lower verbal memory at age 60-64 ($\beta=-0.58$, SE=0.27, $p=.03$), and affective symptoms at age 60-64 was associated with lower verbal memory ($\beta=-0.64$, SE=0.29, $p=.03$) and processing speed ($\beta=-1.27$, SE=0.41, $p=.002$) at age 69. Verbal memory and processing speed function did not predict subsequent level of affective symptoms.

Conclusion: Affective symptoms predict poorer verbal memory and processing speed over a period of 16 years, but the association does not operate in the opposite direction. Understanding longitudinal associations between affective symptoms and cognitive function can offer insights into maintaining better cognitive health for longer.
Key words

Longitudinal research; Affective symptoms; Ageing
Introduction

Affective disorders are common in midlife, with 19% of women and 14.9% of men between the age 55-64 reporting symptoms of depression (Stansfeld et al., 2014). Research shows that affective symptoms in older age are highly comorbid with cognitive impairment. It is estimated that around 32% of people with dementia present with high depressive symptoms, compared with only 7% of people in the general population (Lyketsos et al., 2002).

Previous research has shown that a longitudinal association may exist between affective symptoms and cognitive function over time, although the precise temporal order remains unclear. There has been some evidence that affective symptoms precede subsequent development of dementia (Da Silva, Gonçalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013; Gulpers et al., 2016; Jorm, 2001; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006), cognitive decline (John, Patel, Rusted, Richards, & Gaysina, 2018), and poorer cognitive level (John et al., 2019). However, other research has suggested that cognitive function can predict subsequent level of affective symptoms (Jajodia & Borders, 2011). A bidirectional association between affective symptoms and cognitive function is therefore possible, but evidence is inconsistent. Jajodia and Borders, (2011) reported that in 14000 adults over the age of 50, verbal memory performance predicted increases in depressive symptoms over an 8 year period, but not vice versa. Vinkers et al., (2004) studied 500 people aged 85 over a 4 year follow up. Similarly, it was concluded that poorer attention and verbal memory function at baseline were related to faster increases in depressive symptoms. No associations were observed between baseline depression and change in cognitive function. Gale, Allerhand, & Deary (2012) reported that in a sample of 8611 people over the age of 50, higher levels of depression were associated with faster cognitive decline over a follow up period of 7 years, but only in people aged 60-80 years old. However, cognitive function was
not associated with change in depressive symptoms over time. In these studies, samples were based on people over the age of 50 at baseline, and the analyses was unable to account for earlier life influences which may be pertinent within this association. Additionally, follow-up periods were relatively short (<10 years), so it is unclear how affective symptoms and cognitive function may interact with each other over a longer period of time.

The aim of the present study is to clarify and extend previous research by testing bidirectional relationships between affective symptoms and cognition function (verbal memory and information processing speed) over a period of 16 years: from middle age, through late middle age to older age.
Methods

Participants
In this study, data from the MRC National Study of Health and Development (NSHD) were used. The sample originally comprised 5362 males and females born in mainland UK in 1946. Data has been collected from participants at 24 time points, most recently when participants were aged 69. Information about data collection and participation rates in NSHD are available elsewhere (Kuh et al., 2011, 2016). 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. Written informed consent was provided by all participants and ethical approval for the current study has been received from the University of Sussex (ER/AJ316/1).

Measures

Cognitive function
The current study focuses on measures of short-term verbal memory and information processing speed measured three times, at ages 53, 60-64, and 69. Verbal memory was assessed using a word recall test with 3 administrations. At each administration participants recalled words from the list, with possible scores ranging from 0-45. A letter cancellation task was used to capture information processing speed, in which participants crossed out target letters P and W from a letter grid within a 1 minute time limit, with possible scores ranging from 0-600. These measures have been described in detail elsewhere (Davis et al., 2017; Richards, Shipley, Fuhrer, & Wadsworth, 2004).

Affective symptoms
Affective symptoms were measured at multiple time points across the life course (ages 13, 15, 36, 43, 53, 60-64, and 69). For the current study, measures of affective symptoms assessed at ages 53, 60-64, and 69 were included in main analyses. At all three of these time points, the 28 item General Health Questionnaire (GHQ-28) was used. Research has shown that the GHQ is a consistent and reliable measure in detecting psychiatric symptoms in a general population across multiple time points with long intervals between testing (Pevalin, 2000). Due to high comorbidity and overlap between symptoms of depression and anxiety, this study focussed on overall affective symptomatology, encompassing depression, anxiety, somatic and social dysfunction symptoms.

**Covariables**

The covariables selected for the analysis were sex, childhood socioeconomic position (Kaplan et al., 2001), education (Hatch, Feinstein, Link, Wadsworth, & Richards, 2007), and score on the National Adult Reading Test (NART) at age 53 (James et al., 2018). Score on the NART was included to isolate associations between affective symptoms and fluid cognitive abilities (James et al., 2018). Fathers’ occupation was used as a measure of childhood socioeconomic position. This was coded into 6 categories based on social classes I-V in the Classification of Occupations: professional; intermediate; skilled non-manual; skilled manual; partly skilled; unskilled. The highest qualification achieved by the participant at age 26 was used as a measure of education. This was coded based on the UK Burnham Scale into 9 categories: None attempted; Vocational; Sub GCE or sub Burnham C; GCE O-Level or Burnham C; GCE A-Level or Burnham B; Burnham A2; 1st degree; higher degree (Masters); higher degree (doctorate).

**Statistical Analyses**

The GHQ-28 comprises four sub-scales measuring depression, anxiety, social dysfunction, and somatic symptoms. To take account of the four factor structure within the GHQ at each
time point, second order confirmatory factor analysis (CFA) was conducted to derive latent scores of affective symptoms at each time point. Model fit was assessed and measurement invariance was tested to check that the same latent construct was captured over time.

To test bidirectional relationships between affective symptoms and cognitive function across middle to late adulthood, cross-lagged models were fitted for verbal memory and processing speed separately. This method allows directional relationships between two variables to be estimated across multiple time points. Benefits of cross-lagged methods are that lagged associations between variables can be estimated, while simultaneously allowing for cross-sectional associations and auto-correlations across repeated measures over time (Kearney, 2017). Models included affective symptoms and cognitive function at ages 53, 60-64 and 69.

Two main models were fitted, including: Model 1: Unadjusted; Model 2: Adjusted for all covariables. Model fit did not significantly improve when the analysis was stratified by sex (Supplementary Table 1), suggesting that patterns of association did not differ significantly between men and women. For this reason, sex was used as a covariable in all subsequent analyses, rather than as a stratifying variable.

As a sensitivity analysis, main models were re-run on the sample of people still alive by age 69. Main models were also re-run excluding participants using anxiolytic and antidepressant medications at ages 36, 43, 53, 60-64, and 69. Finally to maximise sample size available for the analyses, a final sensitivity analysis was run using multiple imputation with MICE in R (Buuren & Groothuis-Oudshoorn, 2011) to impute covariate data for the adjusted models. For the current analysis, eighteen imputations were conducted over 12 sweeps in NSHD data. Further information about the multiple imputation process is presented in Supplementary Materials 1.
Mplus version 8 (Muthén & Muthén, 2017) was used for analyses, and missing data were dealt with using full information maximum likelihood (FIML) methods for cognitive and GHQ data, and using multiple imputation for covariables.
Results

Available sample and missing data

The available sample included all participants with at least one measure of affective symptoms or cognitive function. Slightly different sample sizes were available for verbal memory and processing speed. Specifically, 3125 survey members had at least one measure of verbal memory or affective symptoms (58.3% of the original birth sample) and of this group, 2028 (64.9%) also had complete information for all covariables. In total, 3127 (58.3%) people had data for processing speed or affective symptoms in at least one time point of the total sample available at birth. Of this group, 2028 (64.9%) also had data for all covariables. For more information about available data, see Figure 1.

Figure 1 here

The sample with at least one measure of affective symptoms or cognition available at any time point (Verbal memory: N=3125; Processing speed: N=3127) was compared on key childhood and adulthood variables with the sample with missing data on all assessments of cognition and affective symptoms (Verbal memory: N=2237; Processing speed: N=2235). The sample with key data available did not differ from the sample with missing data on anxiolytic medication use ($p=.08$). However, the sample with missing data had significantly more males and fewer females than the sample with complete data available ($p<.001$). The sample with missing data also had significantly lower socioeconomic position at age 15 ($p=.02$), lower cognitive scores at age 15 ($p<.001$), lower educational level ($p<.001$), higher affective symptom scores at age 36 ($p=.01$), higher affective symptom scores at age 43
(p=.03), and lower antidepressant usage in adulthood (p<.001). Due to differences between the sample with complete covariate data and the sample with missing data, a sensitivity analysis was conducted using a multiple imputation approach to impute all covariate data. Further information about the multiple imputation process is available in Supplementary Materials 1. Table 1 shows demographic information for the samples included in the analysis.

Table 1 here

Longitudinal measurement model for affective symptoms

A second order confirmatory factor analysis of the GHQ measurements over time was fitted to ensure this was an appropriate fit to the data for subsequent analysis. The second order CFA fit the data well ($\chi^2(3387)=17138.88, p<.001; \text{CFI}=9.15; \text{TLI}=0.912; \text{RMSEA}=0.036$).

Indicators all loaded significantly onto the factors ($p<.001$). Measurement invariance of the first order factors was assessed by constraining factor loadings to be equal across time over the first order. There was not a significant deterioration in model fit after constraining according to a chi square difference test (Supplementary Table 2). Next, factor loadings were constrained to be equal over the first and second order factors. Again, model fit did not significantly deteriorate (Supplementary Table 2). Therefore, it was concluded that the GHQ captured the same latent construct over the three waves for both the first and second order factors.

Cross-lagged models

Verbal memory
The cross-lagged verbal memory model showed excellent fit to the data ($\chi^2(2)=5.39$, $p=.07$; CFI=1.00, TLI=1.00; RMSEA=0.02). The unadjusted model showed that all autoregressive pathways were significant, demonstrating stability in constructs over time for both verbal memory and affective symptoms. There were significant cross-sectional associations between verbal memory and affective symptoms at all ages (Age 43: $\beta=-0.09$, SE=0.05, $p=.05$; Age 60-64: $\beta=-0.04$, SE=0.02, $p=.03$; Age 69: $\beta=-0.03$, SE=0.01, $p=.04$). Poorer verbal memory function at age 53 significantly predicted higher affective symptoms at age 60-64 ($\beta=-0.002$, SE=0.001, $p=.004$). Additionally, higher affective symptoms at age 60-64 was significantly associated with poorer verbal memory function at age 69 ($\beta=-0.60$, SE=0.25, $p=.02$).

The fully adjusted model also fit the data very well ($\chi^2(2)=7.03$, $p=.03$; CFI=1.00, TLI=0.99; RMSEA=0.03). The fully adjusted model showed that all autoregressive pathways were significant. Results also revealed that there was a significant association between verbal memory and affective symptoms at age 53 ($\beta=-0.18$, SE=0.04, $p<.001$), but this cross-sectional effect no longer persisted over time at ages 60-64 ($\beta=-0.03$, SE=0.02, $p=.20$) and age 69 ($\beta=-0.03$, SE=0.02, $p=.06$). Additionally, higher affective symptoms at age 53 significantly predicted lower verbal memory performance at age 60-64 ($\beta=-0.58$, SE=0.27, $p=.03$), and higher affective symptoms at age 60-64 were significantly associated with poorer verbal memory at age 69 ($\beta=-0.64$, SE=0.29, $p=.03$). There were no significant longitudinal associations between verbal memory scores and subsequent level of affective symptoms (Figure 2).

Figure 2 here
Processing Speed

The cross-lagged processing speed model was also an excellent fit to the data ($\chi^2(2)=0.81$, $p=67$; CFI=1.00, TLI=1.00; RMSEA=0.00). The unadjusted model revealed that as with the verbal memory model, all autoregressive pathways were statistically significant, showing stability in constructs over time. In this unadjusted model, there were no cross-sectional or longitudinal associations between affective symptoms and processing speed.

The fully adjusted model was also a good fit to the data ($\chi^2(2)=1.76$, $p=.41$; CFI=1.00, TLI=1.00; RMSEA=0.00). In the fully adjusted model, all of the autoregressive pathways remained significant. There was a significant association between affective symptoms and processing speed present at age 53 ($\beta=-0.13$, SE=0.06, $p=.05$), but not at ages 60-64 ($\beta=-0.02$, SE=0.03, $p=.52$) or 69 ($\beta=-0.02$, SE=0.02, $p=.31$). Additionally, results from the fully adjusted model showed that higher level of affective symptoms at age 60-64 significantly predicted worse processing speed performance at age 69 ($\beta=-1.27$, SE=0.41, $p=.002$). No other cross-lagged pathways were statistically significant (Figure 3).

Sensitivity analysis

As a sensitivity analysis, the main models were re-run after excluding participants who died by age 69 from the analysis, to ensure results were not influenced by mortality. These models
fit the data well (Verbal memory: $\chi^2(2) = 6.86, p = .03; \text{CFI}=1.00; \text{TLI}=0.99; \text{RMSEA}=0.04$). Processing speed: $\chi^2(2) = 1.76, p = .42; \text{CFI}=1.00; \text{TLI}=1.00; \text{RMSEA}=0.00$). Results from verbal memory models including the sample alive by age 69 remained consistent. The fully adjusted model showed a significant cross-sectional association between affective symptoms and verbal memory at age 53 ($\beta=-0.16, \text{SE}=0.05, p=.001$), and significant lagged pathways between affective symptoms at age 53 and verbal memory at age 60-64 ($\beta=-0.65, \text{SE}=0.28, p=.02$) and between affective symptoms at age 60-64 and verbal memory at age 69 ($\beta=-0.64, \text{SE}=0.29, p=.03$). No other pathways reached statistical significance. Results from processing speed models excluding people who died by age 69 were also similar to those from the main models. Specifically, affective symptoms at age 60-64 significantly predicted poorer processing speed at age 69 ($\beta=-1.27, \text{SE}=0.41, p=.002$). Again, no other pathways were statistically significant.

Main models were re-run excluding people taking anxiolytic or antidepressant medication. Results from this analysis were similar to main models. The models fit the data well (Verbal memory: $\chi^2(2) = 4.82, p = .09; \text{CFI}=1.00; \text{TLI}=0.99; \text{RMSEA}=0.03$). Processing speed: $\chi^2(2) = 1.22, p = .54; \text{CFI}=1.00; \text{TLI}=1.00; \text{RMSEA}=0.00$). Results from verbal memory models showed that there was a cross-sectional association between affective symptoms and verbal memory function at age 53 ($\beta=-0.14, \text{SE}=0.05, p=.002$), and a longitudinal association between affective symptoms at age 53 and verbal memory function at age 60-64 ($\beta=-0.63, \text{SE}=0.31, p=.04$). No other cross-sectional or lagged pathways reached statistical significance. Results from processing speed models showed no significant cross-sectional associations between affective symptoms and processing speed function. However, affective symptoms at age 60-64 significantly predicted lower processing speed scores at age 69 ($\beta=-1.38, \text{SE}=0.46, p=.003$). No other longitudinal pathways were significant.
Finally, a sensitivity analysis was run, using multiple imputation to impute missing covariate data. Again models fit the data very well (Verbal memory: $\chi^2(2)=2.88, p=.24; CFI=1.00$; TLI=1.00; RMSEA=0.01. Processing speed: $\chi^2(2)=1.29, p=.53; CFI=1.00; TLI=1.00$; RMSEA=0.00) and results were consistent with main models. The fully adjusted verbal memory model showed significant cross sectional associations between affective symptoms and verbal memory function at age 53 ($\beta=-0.15, SE=0.04, p < .001$) and age 60-64 ($\beta=-0.04, SE=0.02, p=.03$), but not at age 69 ($\beta=-0.02, SE=0.01, p=.10$). Affective symptoms at age 60-64 also significantly predicted poorer verbal memory at age 69 ($\beta=-0.73, SE=0.25, p=.004$). No other longitudinal pathways were significant. The fully adjusted processing speed model revealed a significant cross-sectional association between affective symptoms and processing speed at age 53 ($\beta=-0.16, SE=0.05, p=.003$) but not at ages 60-64 ($\beta=-0.01, SE=0.02, p=.68$) or age 69 ($\beta=-0.03, SE=0.02, p=.12$). Affective symptoms at age 60-64 significantly predicted poorer processing speed at age 69 ($\beta=-0.73, SE=0.36, p=.04$), but no other pathways reached statistical significance.
Discussion

There was a cross-sectional inverse association between affective symptoms and both verbal memory and processing speed at age 53, but not at ages 60-64 or 69. Higher affective symptoms at age 53 significantly predicted lower verbal memory scores at age 60-64, and affective symptoms at age 60-64 also predicted lower verbal memory at age 69. However, verbal memory function did not predict subsequent affective symptoms at any time-point. Results for processing speed models were similar; higher affective symptoms at age 60-64 significantly predicted poorer processing speed at age 69. Processing speed did not predict later affective symptoms at any time-point assessed. Overall, these results are consistent with previous research showing that affective symptoms can predict subsequent cognitive function (James et al., 2018; John et al., 2019, 2018). These findings extend previous evidence by demonstrating that this relationship does not operate in the opposite direction over the period of 16 years.

There are four primary hypotheses that can explain associations between affective symptoms and cognitive function over time. First, affective symptoms may be a risk factor for poorer cognitive outcomes (Bennett & Thomas, 2014; Butters et al., 2008). Second, affective symptoms may be a prodromal symptom of cognitive impairment (Bennett & Thomas, 2014; Butters et al., 2008; Byers & Yaffe, 2011). Third, there may be some common cause factor which increases risk for both affective disorders and poorer cognitive function (Bennett & Thomas, 2014; Djernes, 2006). Finally, affective symptoms may emerge as a response to awareness of verbal memory impairment (Vinkers et al., 2004). The temporal sequencing over an extended time frame which emerges in this study does not support the fourth possibility that affective symptoms reflect a subjective response to cognitive impairments. Instead, these results indicate that affective symptoms may precede cognitive impairments by several years and that increased affective symptoms predict later cognitive function.
The finding that affective symptoms predicted subsequent processing speed at the later time-point only suggests that the effects of affective symptoms on processing speed, may not be observed until later in the life course. This is consistent with previous research showing that adult affective symptoms can predict poorer mid-life verbal memory function at age 50, but no effects were observed on information processing speed at this age (John et al., 2019). This finding is inconsistent with work that suggests processing speed may be an important component in verbal memory processing (Salthouse, 1996). This can potentially be explained by the digit checking task containing a motor component, compared to the verbal component within the verbal memory task.

Future research should focus on identifying biological and socio-behavioural mechanisms of the longitudinal association between affective disorders and cognitive function. Future research should also investigate whether effective treatment of affective symptoms can reduce risk of poorer cognitive outcomes later in life.

**Strengths and limitations**

The key strength of the study is a large, nationally representative, and prospective sample, with 16 years follow up. An additional strength of the study is the use of consistent measures of affective symptoms and cognitive function. However, sample attrition is a problem in all long-running cohort studies. In the present study, missing data was addressed using FIML methods and an additional supplementary analysis was conducted using multiple imputation. Another limitation of the study is that single cognitive tests were used to measure verbal memory and processing speed, rather than more comprehensive cognitive batteries.

Results from the present study show that affective symptoms can predict poorer cognitive outcomes over a 16-year period. Understanding longitudinal associations between affective symptoms and cognitive function offer insights into maintaining better cognitive health for longer.
References


Tables and Figures

**Figure 1:** Flow chart showing available sample size.

**Table 1:** Demographic information for analysed sample.

**Figure 2:** Cross lagged model of affective symptoms and verbal memory from age 53 to 69. Fully adjusted model.

**Figure 3:** Cross lagged model of affective symptoms and processing speed from age 53 to 69. Fully adjusted model.
Table 1: Demographic information for analysed sample.

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Childhood socioeconomic position

| N (%)                   | 1149 (36.8)            | 1151 (36.8)               |
|                        | 1670 (53.4)            | 1670 (53.4)               |
|                        | 306 (9.8)              | 306 (9.8)                 |

Educational attainment

| N (%)                   | 17.2 (9.8)             | 17.2 (9.8)                |

National Adult Reading Test score

| NART Score              | 2833 (90.7)            | 2834 (90.6)               |
|                        | 292 (9.3)              | 293 (9.4)                 |

Antidepressant medication use

| N (%)                   | 2968 (95.0)            | 2970 (95.0)               |
|                        | 157 (5.0)              | 157 (5.0)                 |

Anxiolytic medication use

| N (%)                   | 23.93 (6.30)           | 281.07 (76.09)            |
| Age 53                  | 24.26 (6.11)           | 266.71 (71.74)            |
| Age 69                  | 22.20 (6.02)           | 262.30 (74.15)            |