

Original Article

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Executive dysfunction in depression in adolescence: the role of inflammation and higher body mass

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Abstract

Background. There is substantial evidence that many depressed individuals experience impaired executive functioning. Understanding the causes of executive dysfunction in depression is clinically important because cognitive impairment is a substantial contributor to functional impairment. This study investigated whether elevated levels of an inflammatory cytokine [interleukin-6 (IL-6)] and/or higher body mass index (BMI) concurrently and/or prospectively accounted for the relationship between depressive symptoms and impaired executive functioning in adolescents.

Methods. A diverse, community sample of adolescents ($N = 288$; mean age = 16.33; 51.4% female; 59.0% African-American) completed assessments of height and weight, IL-6, depressive symptoms, and self-report/behavioral measures of executive functioning (selective attention, switching attention) and future orientation annually over 3 years. Adolescents experiencing acute illness or medical conditions that affect inflammation were excluded from analyses. Path analysis within a structural equation modeling framework simultaneously examined the concurrent and prospective relationships between BMI, IL-6, depressive symptoms, and the measures of cognitive functioning across three timepoints.

Results. Across all timepoints, higher BMI was prospectively associated with higher levels of IL-6 and depressive symptoms, while higher levels of IL-6 were associated with worse performance on three behavioral and self-report measures of cognitive functioning. Higher depressive symptoms also were prospectively associated with elevated IL-6 and both higher depressive symptoms and a higher BMI predicted worse future executive functioning via increased IL-6.

Conclusions. More severe depressive symptoms and increased BMI may disrupt executive functioning via elevated IL-6.

Introduction

Depression is associated with the greatest disease burden among all psychological disorders (Whiteford *et al.*, 2013). The severe disease burden is largely attributable to the early onset, frequent recurrence, and substantial impairment associated with depressive disorders (Kessler *et al.*, 2003; Burcusa and Iacono, 2007). Cognitive dysfunction is a clinical feature of depression, observed in both clinical and community samples (Rock *et al.*, 2013; Snyder, 2013; Mac Giollabhui *et al.*, 2018), that contributes substantially to functional impairment in depression, both in individuals who meet criteria for a depressive episode as well as those with remitted or subclinical depressive symptoms (Gotlib *et al.*, 1995; Woo *et al.*, 2016). Thus, understanding cognitive dysfunction in depression will advance our understanding of the overall course and etiology of depression as well as providing insight on a substantial contributor of functional impairment.

Dysfunction across a broad range of cognitive functions, such as verbal memory and executive functioning, is a reliable correlate of depression in children, adolescents, and adults (Rock *et al.*, 2013; Snyder, 2013; Wagner *et al.*, 2015). However, it also has been observed prior to first onset, in unaffected first-degree relatives of depressed individuals, and when depression has remitted (Rock *et al.*, 2013; Scult *et al.*, 2017; MacKenzie *et al.*, 2018). Thus, it remains unclear whether, in addition to being a correlate of depression, cognitive dysfunction is a risk factor for depression, a consequence of depression, or whether both depression and cognitive dysfunction are caused by a common underlying process (Allott *et al.*, 2016; Mac Giollabhui *et al.*, 2018). It is likely that the inconsistent associations between cognitive dysfunction and depression observed in the literature are, in part, driven by the effect of specific clinical characteristics (e.g. persistent depression), comorbid conditions (e.g. substance use disorder), and risk factors

(e.g. chronic stress). In particular, anxiety is highly comorbid with depression and substance use disorders (Clark and Watson, 1991; Grant *et al.*, 2015; Grant *et al.*, 2016), is associated with elevated peripheral inflammatory activity (Michopoulos *et al.*, 2017), has been implicated in the up-regulation of inflammatory responses in depression (Slavich and Irwin, 2014), and could explain some of the variability in the association between depression and executive functioning (Levin *et al.*, 2007). In order to advance our understanding of who will experience cognitive dysfunction in depression and under which conditions, a more mechanistic understanding is required (Carvalho *et al.*, 2014).

Two putative mechanisms underpinning the association of depression and cognitive dysfunction are inflammation and body mass index (BMI). Sickness behaviors (e.g. anhedonia/social withdrawal) are common correlates of heightened inflammation as well as core characteristics of depression (Maes *et al.*, 1995); indeed, when an inflammatory response is experimentally induced, depressive symptoms reliably follow (Dantzer, 2001). Meta-analyses report that depressed patients – or, at least, a subsample of depressed patients – exhibit consistently elevated inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP) (Raison and Miller, 2011; Haapakoski *et al.*, 2015; Kohler *et al.*, 2017). However, the direction of the relationship between depression and inflammation also remains unclear, with some studies reporting that elevated inflammation prospectively predicts higher depressive symptoms (Stewart *et al.*, 2009; Au *et al.*, 2015; Moriarity *et al.*, *In Press*) and others the reverse (Duivis *et al.*, 2013; Zalli *et al.*, 2016). Higher BMI also is associated with increased risk of depression across the lifespan (de Wit *et al.*, 2010; Quek *et al.*, 2017); however, as is the case with inflammation, the temporal relationship between obesity and depression remains unclear, with some evidence for a bidirectional association (Preiss *et al.*, 2013).

There is considerable evidence linking both inflammation and obesity with cognitive dysfunction. Inflammatory biomarkers, particularly IL-6, IL-1 β , and TNF- α , disrupt neuronal processes (e.g. long-term potentiation, synaptic plasticity, and neurogenesis) and negatively impact learning, memory, and executive functioning (Reichenberg *et al.*, 2001; McAfoose and Baune, 2009; Carvalho *et al.*, 2014; Shields *et al.*, 2017). Similarly, obesity is reliably associated with poor cognitive performance in children, adolescents, and adults (Liang *et al.*, 2014; Prickett *et al.*, 2015). Given that adipose tissue also can secrete cytokines and contributes to levels of inflammatory cytokines in systemic circulation, the relationship between obesity and cognition is thought to be mediated, at least in part, by inflammatory processes (Spyridaki *et al.*, 2016). Although few studies have examined this longitudinally, prior research has reported that higher adiposity predicts impaired cognitive performance via elevated peripheral inflammation (Spyridaki *et al.*, 2014).

Executive functioning refers to cognitive abilities needed to effortfully guide behavior toward a goal, especially in non-routine situations (Banich, 2009). Although consensus is lacking on a specific model of executive functioning (Friedman *et al.*, 2008; Miyake and Friedman, 2012; Diamond, 2013), there is general consensus that it involves multiple cognitive processes, including inhibition, working memory, set-shifting, and planning (Packwood *et al.*, 2011). Executive dysfunction is reliably observed during depressive episodes and when depression is in remission (Rock *et al.*, 2013; Snyder, 2013); it is also associated with increased peripheral inflammation (Chang *et al.*, 2012; Heringa *et al.*, 2014; Huang *et al.*, 2016)

and BMI (Smith *et al.*, 2011; Yang *et al.*, 2018). However, no study to date has tested whether peripheral inflammatory cytokines or BMI are predictors of worse executive function in depression, particularly in a diverse community sample of largely unmedicated adolescents, who are less likely to be afflicted by some of the confounding/moderating factors in older adults (e.g. repeated depressive episodes, pre-clinical dementia-related cognitive decline) (Misiak *et al.*, 2018).

The present study

We used a structural equation model (SEM) framework to simultaneously examine the concurrent and prospective associations between peripheral inflammatory biomarkers, BMI, depressive symptoms, and executive functioning in a diverse sample of adolescents. These measures were obtained across three timepoints, thereby assessing if inflammation and BMI are two processes that can explain the association between depression and impaired executive functioning over time. Two measures of executive functioning (selective attention, switching attention) and one self-report questionnaire assessing future orientation, a construct reliant on executive functioning (D'Argebeau *et al.*, 2010), were administered. It was hypothesized that a higher BMI would predict more severe depressive symptoms and worse cognitive functioning via elevated peripheral inflammatory activity. Although five inflammatory biomarkers were assayed (IL-6, IL-8, IL-10, TNF- α , and CRP), the main analyses primarily focus on IL-6 because it is the inflammatory cytokine most reliably associated with BMI (Amaral *et al.*, 2015), depression, and executive dysfunction in humans (Kohler *et al.*, 2017). Supplemental analyses investigated whether (i) associations observed for depressive symptoms also were present for anxiety and substance use, (ii) results differed for TNF- α , CRP, IL-8, and IL-10, (iii) results were affected by sex and race, and (iv) whether the reported results held after controlling for additional confounds.

Methods

Participants

Participants were drawn from a prospective, longitudinal study of adolescent-onset depression. A diverse community sample of 642 adolescents aged 12–13 years and their primary female caregivers were recruited from the Philadelphia area for the Adolescent Cognition and Emotion (ACE) Study. Inclusion criteria for the original study were: adolescents aged 12–13 years and their mothers were willing to participate, and that adolescents self-identified as Caucasian, African-American, or biracial (examining racial differences in depression was a goal of ACE). Exclusion criteria included if the adolescent/mother had insufficient English reading/speaking skills to complete assessments or a psychotic, developmental, or learning disorder.

From the 642 adolescents initially enrolled in the study, 307 agreed to participate in a supplementary section of the study, introduced 4 years after initial enrollment, to assess peripheral inflammation. From the 307 participants with blood assayed to date, IL-6 data were available for: 91 individuals at one assessment, 73 at two assessments, 73 at three assessments, 54 at four assessments, and 16 at five or six assessments. Following enrollment in this supplementary section of the study, the 307 participants took part in an average of 4.03 assessments (s.d. = 2.73) per person, with blood draws at 3.01 of these assessments (s.d. = 1.20),

totaling 753 blood samples. From the 753 blood samples, 151 observations were removed either because CRP values were > 10 (indicative of a possible acute infection), participants reported a pertinent medical condition (autoimmune disease, diabetes, blood-clotting disorder), were pregnant at time of blood draw, or the observation at which the blood was drawn represented an individual's fourth or fifth blood draw, leaving a total of 288 participants with 602 observations; time to first follow-up was 1.39 years (s.d. = 0.61) and to second follow-up was 1.01 years (s.d. = 0.51). Observations occurring at the fourth or subsequent blood draw were not included in analyses because of the small number of participants who had completed this number of blood collections.

Missing data analyses tested whether the analytic sample differed significantly from the complete ACE sample. The analytic sample did not differ significantly from the complete sample in the proportion of females, $\chi^2(1, 642) = 0.57, p = 0.45$. However, the racial composition of the analytic sample differed significantly from what was expected based on the complete ACE sample, $\chi^2(1, 642) = 9.16, p = 0.002$. There were fewer Caucasians present in the analytic sample (standardized residual = -1.6) and more African-Americans (standardized residual = 1.5) than expected. Similarly, a trend was observed for socioeconomic status (SES), $\chi^2(1, 642) = 3.46, p = 0.06$, with fewer participants of low SES present in the analytic sample than anticipated (standardized residual = -1) and more participants not of low SES (standardized residual = 1).

Measures

Depressive symptoms

The Children's Depression Inventory (CDI) is a valid, reliable self-report measure of current depressive symptoms in youth (Kovacs, 1992). The CDI consists of 27 items scored on a three-point scale ranging from zero to two. Items were summed, with higher scores indicating more severe depressive symptoms. The CDI was administered at every timepoint in the study and demonstrated consistent reliability; Cronbach's α over time was consistently > 0.80 .

Executive attention

Four subtests of the Test of Everyday Attention for Children (TEACh) and the Test of Everyday Attention (TEA) were administered assessing switching, sustained, divided, and selective attention (Robertson *et al.*, 1994; Manly *et al.*, 2001). However, given the inadequate reliability of sustained and divided attention when transitioning from TEACh to the TEA and the focus of this study on executive functioning, only behavioral measures of selective and switching attention were used (Mac Giollabhui *et al.*, 2018). Scaled scores, where a score of 10 is indicative of performance in the 50th percentile (s.d. = 3), are reported for each domain of attention, with higher scores indicating superior performance. The 'Sky Search' subtest is a non-linguistic measure of selective attention that controls for motor speed (in the TEACh), in which participants were asked to identify cases in which identical stimuli are paired together on a page. Different stimuli were used for the TEA and TEACh to improve the ecological validity for their respective age groups. Both speed and accuracy are encouraged and the outcome is based both on the participant's ability to correctly identify targets and the speed with which they complete the task. Attentional switching is assessed in the TEACh using the 'Creature Counting' subtest and in the

TEA using the 'Elevator Counting' subtest. Both tests measure the temporary slowing that is associated with switching from one task or mental set to another. Separate scores are computed for the speed and accuracy with which participants complete all test items. Both the TEA and TEACh are ecologically valid measures of attentional functioning that are extensively used in both research and clinical settings with demonstrable validity and reliability (Robertson *et al.*, 1994, 1996; Manly *et al.*, 2001).

Future orientation

The Future Orientation Scale (FOS) is a reliable and valid measure of the degree to which adolescents tend to perceive, anticipate, and plan for the future (Steinberg *et al.*, 2009). Participants are presented with a series of contrasting statements with the word 'BUT' between them (i.e. 'Some people like to think about all the possible good and bad things that can happen before making a decision' BUT 'Other people don't think it's necessary to think about every little possibility before making a decision') and are asked to select the statement that best describes them. They then are asked to indicate whether the selected descriptor was really true or sort of true. Responses for each pair of statements then were coded on a four-point Likert scale, ranging from really true for one descriptor to really true for the contrasting descriptor. The internal consistency of this measure in the current sample was adequate with Cronbach's α ranging from 0.71 to 0.82 across assessments.

Inflammation

Blood (10 mL) was obtained primarily in the late afternoon to control for diurnal variation and collected via antecubital venipuncture by a certified phlebotomist. The blood was centrifuged to separate the plasma fraction (BD Hemogard with K2 EDTA) and stored at -80°C until the day of assay. Medication use, medical disorder status, time of last meal, time of day, and participant's BMI were recorded at each blood draw. Cytokines were quantified by multi-cytokine array (IL-6, IL-8, IL-10, and TNF- α) and high-sensitivity CRP (hsCRP) determined via singleplex assay using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for analyte detection (Meso Scale Discovery, Gaithersburg, MD, USA). The analytes were run in duplicate, with intra-assay coefficients varying from 1.94% to 4.38%. Values were referenced to a standard curve generated from seven calibrators with known concentrations. The lower limit of detection for cytokines was 0.1 pg/mL, with a dynamic range up to 2000 pg/mL. However, hsCRP is present in sera at higher concentrations, and thus, plasma was diluted to correspond to the standard curve. Values were converted to mg/L units and were quantified down to 0.1 mg/L (Breen *et al.*, 2011).

Body mass index

BMI was quantified as weight (kg), determined with an electronic scale, divided by height.

Demographics

Age, sex, race, and SES were assessed via self-report. Mothers indicated whether their child received federally-subsidized school lunch, with receipt of free lunch assumed to indicate low SES.

Procedure

Participants completed two types of assessments. The first type was a comprehensive assessment scheduled to occur annually. During comprehensive assessments, participants completed the

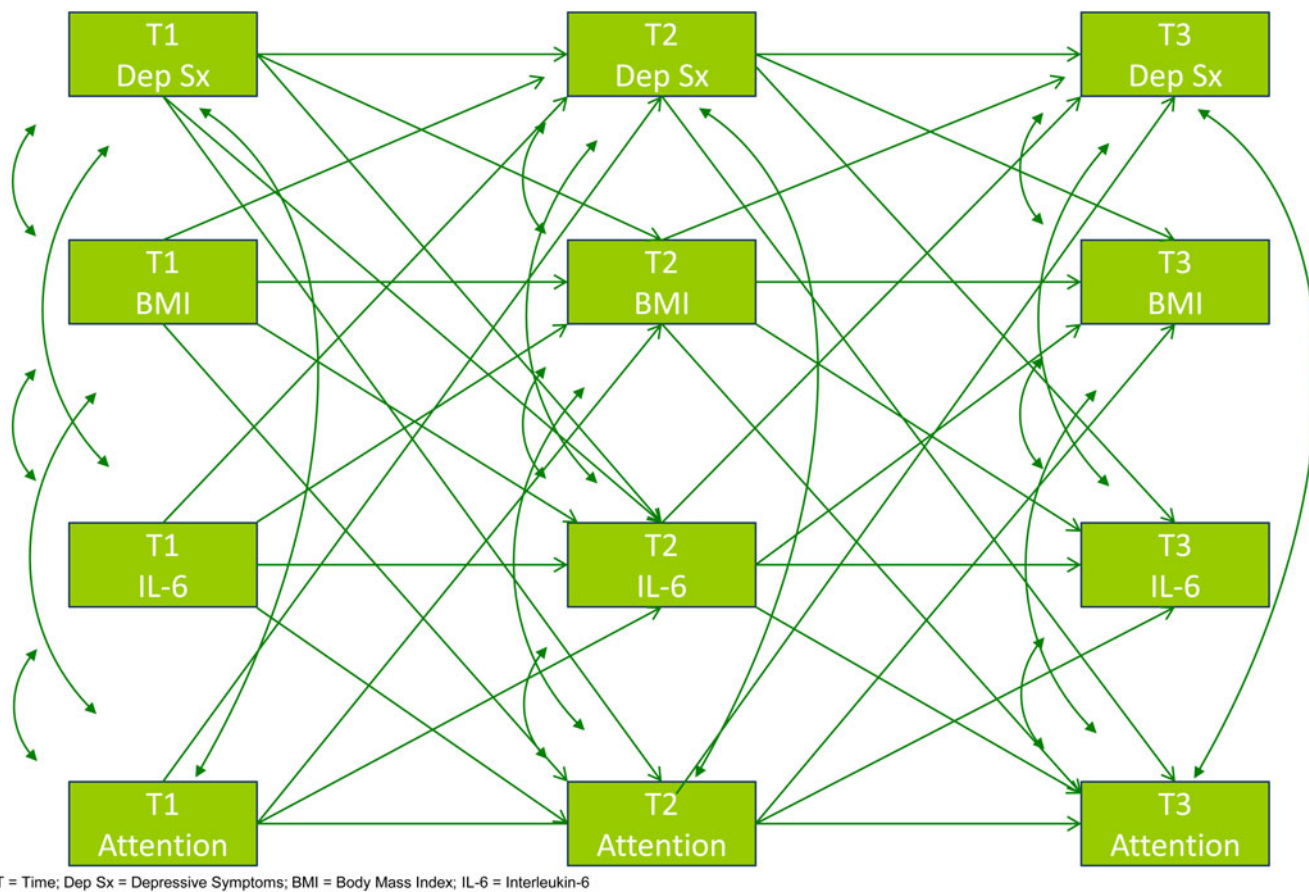


Fig. 1. Path Analysis Model Examining Associations of Depressive Symptoms, Cognitive Functioning, Inflammation and BMI over three years.

CDI, FOS, and interviewers conducted a behavioral assessment of attentional functioning (TEAch/TEA). Shorter 6-month assessments also were scheduled in which participants completed measures of negative life events and the CDI assessing depressive symptoms. Blood draws could occur at either annual or 6-month assessments.

Data analysis

Analyses were conducted in Mplus (Version 7.4) and missing data were handled using Full Information Maximum Likelihood. Path analysis within a SEM framework simultaneously examined concurrent and prospective relationships between IL-6, BMI, depressive symptoms, and four measures of executive/cognitive functioning. All pathways are graphically presented in Fig. 1, which consists of all concurrent, prospective, and auto-regressive pathways among the four variables in each model. Models assumed that the relationship between variables across all timepoints were equivalent (i.e. the relationship between Time 1 depression and Time 2 inflammation was the same as Time 2 depression and Time 3 inflammation) and, therefore, equality constraints were applied to associations between the same variables across different timepoints. Although sex and race were variables of theoretical interest given their association with BMI, inflammation, and depression, they were not included in analyses to limit the number of parameters being simultaneously estimated by the model. Model fit was estimated using: χ^2 estimate of goodness of fit, comparative fit index (CFI), and root-mean-square

error of approximation (RMSEA). The χ^2 test of model fit was reported according to convention, but not interpreted given its limited utility in large samples (Cheung and Rensvold, 2002; Chen, 2007). For the CFI, 'good' fit is indicated by a value > 0.90 and 'excellent' fit by a value > 0.95. A RMSEA statistic between 0.05 and 0.10 is indicative of 'good' fit and a value ≤ 0.05 is indicative of 'excellent' fit (Schermele-Engel *et al.*, 2003). Finally, indirect pathways were tested, based on 5000 bootstrapped samples, where significant associations between variables of interest were observed. Supplemental analyses also investigated whether (i) findings from the model predicting depressive symptoms also were evident when predicting anxiety symptoms and substance use, (ii) the model would differ if different biomarkers were considered as predictors (i.e. TNF- α , CRP, IL-8, and IL-10), (iii) the results were different if sex and race were considered, and finally (iv) if the significance of the model was affected by considering several factors known to influence the predictor and outcome variables – complete details are provided as online Supplementary material.

Results

Bivariate correlations for the main study variables are presented in Table 1 for the 288 participants aged 16.34 (s.d. = 1.44) who were present at first blood draw. Four SEM-based path analyses were conducted for each of the following four cognitive variables sequentially considered as outcomes: selective attention, switching attention (timing), switching attention (accuracy), and future orientation.

Table 1. Descriptive statistics and bivariate correlations of study variables for 288 participants at Time 1

Measure	2	3	4	5	6	7	8	9	10	11
1: T1 Age	−0.01	−0.10	−0.02	−0.08	−0.10	−0.09	−0.07	−0.01	−0.23**	0.10
2: Female	–	−0.03	−0.01	0.10	0.14*	0.25***	−0.08	0.09	0.04	0.02
3: Race		–	0.40***	0.07	0.01	0.11	0.02	−0.04	−0.05	−0.22***
4: Low SES			–	0.02	0.13*	0.06	0.11	−0.11	−0.17*	−0.21**
5: T1 BMI				–	0.09	0.33***	−0.02	−0.07	−0.06	−0.10
6: T1 CDI					–	−0.01	−0.01	−0.04	−0.09	0.06
7: T1 IL6						–	−0.15*	−0.06	0.12	−0.18*
8: T1 FOS							–	−0.02	−0.05	0.13
9: T1 ATT								–	0.15*	0.17*
10: T1 CCT									–	0.21**
11: T1 CCA										–
Mean	0.51	0.59	0.46	23.77	7.23	0.55	2.89	10.59	9.25	10.00
(s.d.)	0.50	0.50	0.50	5.87	5.86	0.33	0.47	3.54	3.56	2.96

T1 Age, age at baseline; SES, socioeconomic status; Race: 1, African-American; BMI, body mass index; CDI, Children's Depression Inventory; FOS, Future Orientation Scale; T1: Time 1; ATT, TEA or TEACh Selective Attention; CCT, TEA or TEACh Switching Attention Timing; CCA, TEA or TEACh Switching Attention Accuracy
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Model fit

Model fit statistics are provided for each of the four models in Table 2. The χ^2 test of model fit was statistically significant, indicating that the observed data differed significantly from the expected for this model. For each of the models, both the CFI (>0.90) and the RMSEA (≥ 0.05 and ≤ 0.10) indicated adequate model fit.

Concurrent and prospective associations between depressive symptoms, cognitive

Functioning, IL-6, and BMI

All of the pathways tested in the four models are presented in Fig. 1. The pathways presented in the models can be divided into three conceptual components: concurrent, prospective, and auto-regressive associations.

All pathways are reported in Table 3; a number of statistically significant patterns were evident in the results. Concurrent associations represent the partial correlation of any two variables constrained to be equal across all timepoints. Across all timepoints, higher levels of IL-6 were associated with worse selective attention, switching attention (accuracy), and future orientation. Higher depressive symptoms and higher BMI both were concurrently associated with worse switching attention (timing and accuracy, respectively). Across all models, higher BMI was concurrently associated with higher IL-6. Similarly, a number of significant findings were evident in the prospective associations of depressive symptoms, cognitive functioning, IL-6, and BMI. First, higher BMI prospectively predicted worse selective attention and switching attention (accuracy). Second, across all models, higher BMI predicted both more depressive symptoms and a higher level of IL-6. Finally, higher depressive symptoms prospectively predicted higher IL-6.

Indirect effects: BMI on executive functioning via IL-6

Given the prospective associations observed between BMI and cognition, additional analyses were conducted using 5000

bootstrapped samples to test whether higher BMI predicted worse cognition indirectly via increased IL-6 levels in circulation, thereby determining whether baseline BMI predicted levels of circulating IL-6 in the future, which, in turn, predicted concurrent executive functioning. Indirect pathways via IL-6 were found when predicting to future orientation ($b = -0.02$; 95% CI -0.001 to -0.05) and selective attention ($b = -0.21$; 95% CI -0.07 to -0.41). No indirect pathway was observed for switching attention timing ($b = -0.01$; 95% CI -0.15 to 0.15) or accuracy ($b = -0.14$; 95% CI -0.31 to 0.001).

Given the prospective association of depression and IL-6, an indirect pathway also was tested to determine the influence of depression on cognitive functioning via inflammatory activity. Significant indirect effects were evident, including the effect of depressive symptoms on selective attention ($b = -0.06$; 95% CI -0.02 to -0.17), switching attention (accuracy) ($b = -0.04$; 95% CI -0.002 to -0.13), and future orientation ($b = -0.01$; 95% CI -0.0001 to -0.02) via IL-6, but not for switching attention (timing) ($b = -0.01$; 95% CI -0.05 to 0.05). No indirect effects of BMI on prospective depressive symptoms via IL-6 were obtained.

Supplemental analyses

Complete details on a series of additional analyses can be found in online Supplementary material. This statistical testing indicated that the effects reported above were specific to depressive symptomatology, and do not generalize to the future experience of anxiety symptoms nor to the initiations of substance use (see online Supplementary Tables S1–S2). The effects observed for IL-6 were not observed consistently in models examining TNF- α , CRP, IL-8, and IL-10, however similar associations were observed inconsistently; for example, higher levels of TNF- α were significantly associated with worse future orientation but not executive functioning (see online Supplementary Tables S3–S6). Finally, the conclusions did not change substantially when participant sex or ethnicity was considered, and the

Table 2. Model fit for each of the four SEM models

Model fit indices	Selective attention	Switching attention (timing)	Switching attention (accuracy)	Future orientation
χ^2 test of model fit	110.43***	122.07***	112.39***	116.88***
Comparative fit index	0.93	0.92	0.92	0.92
Root-mean-square error of approximation (95% CI)	0.07(0.05–0.09)	0.07(0.06–0.09)	0.07(0.05–0.09)	0.07(0.06–0.09)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 3. Concurrent and prospective associations for each of the four SEM models

	Selective attention	Switching attention (timing)	Switching attention (accuracy)	Future orientation
Concurrent associations				
IL6 w/COG	−0.15*	0.00	−0.13*	−0.13*
BMI w/COG	−0.07	−0.10	−0.11*	−0.05
CDI w/COG	−0.03	−0.13*	0.02	−0.03
BMI w/CDI	0.10 Ψ	0.08 Ψ	0.08	0.08 Ψ
IL6 w/CDI	0.01	0.00	0.01	0.00
IL6 w/BMI	0.15***	0.15***	0.15***	0.16***
Prospective associations				
IL6 predicting to COG	0.10	−0.05	0.02	0.01
BMI predicting to COG	−0.17**	−0.08	−0.20**	−0.03
CDI predicting to COG	−0.01	−0.12 Ψ	0.02	−0.08
BMI predicting to CDI	0.10*	0.09 Ψ	0.11*	0.10*
IL6 predicting to CDI	0.02	0.01	0.02	0.01
COG predicting to CDI	0.05	−0.06	0.06	−0.02
BMI predicting to IL6	0.33***	0.33***	0.33***	0.33***
CDI predicting to IL6	0.10*	0.10*	0.11*	0.10*
CDI predicting to BMI	−0.05	−0.02	−0.02	−0.02

IL6, interleukin-6; COG, cognitive variable of interest; BMI, body mass index; CDI, Children's Depression Inventory. Bolded coefficients represent statistically significant results.

$\Psi p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

results held when additional control variables were added to the model (see online Supplementary Tables S7–S10).

Discussion

In a diverse community sample of urban adolescents assessed annually over 3 years, we found that a higher BMI predicted increased future depressive symptoms as well as worse executive functioning/future orientation via higher levels of IL-6 in systemic circulation. Depressive symptoms also predicted an increase in peripheral IL-6. Significantly, all observed associations were unique to depressive symptoms and were not observed in models of anxious symptoms or substance use. Thus, these results suggest that higher depressive symptoms and greater BMI lead to worse cognition via a shared pathway of increased IL-6.

More severe depressive symptoms were concurrently and prospectively (trend-level) associated with worse switching attention and, moreover, prospectively predicted worse selective attention, switching attention (accuracy), and future orientation via elevated peripheral IL-6. The direct concurrent and prospective associations between depression and switching attention have been

observed in analyses examining the entire ACE sample (Mac Giollabhui *et al.*, 2018) and are consistent with previous papers reporting that depression is concurrently and prospectively associated with worse executive functioning (Rock *et al.*, 2013; Snyder, 2013). A number of previous studies have shown that inflammation is associated with concurrent and prospective impairment across a number of different cognitive functions (Chang *et al.*, 2012; Goldsmith *et al.*, 2016). Studies that included control groups found that increased inflammation predicted worse cognition irrespective of diagnostic status (Krogh *et al.*, 2014). Thus, depressed individuals experiencing chronic inflammatory activity may be more likely to experience disrupted cognitive functioning (Raison and Miller, 2011). Should inflammation be linked with cognitive dysfunction in a subset of depressed individuals, this may further explain the considerable heterogeneity in cognitive dysfunction observed in depression (Snyder, 2013).

Inflammation is both concurrently and prospectively associated with impaired cognition in medical and community samples (Reichenberg *et al.*, 2001; Baune *et al.*, 2008; Jenny *et al.*, 2012; Li *et al.*, 2014; Singh-Manoux *et al.*, 2014; Huang *et al.*, 2016), although there is considerable heterogeneity in the

cognitive domains affected as well as the cytokines implicated. This study also found that IL-6 activity was associated with worse executive functioning/future orientation in a healthy adolescent sample. Supplementary analyses suggest that the association between cognitive functioning and inflammation is largely specific to IL-6 (of the cytokines assayed). It is unclear whether this finding will be replicated; however, animal research also has reported that the inflammatory effect on executive functioning is specific to IL-6 (Sparkman *et al.*, 2006). It also should be kept in mind that IL-6 is pleiotropic with multiple origins, particularly adipocytes, and thus, peripheral assessment of IL-6 is not solely a measure of immune system activation. There was no evidence of a direct prospective association between inflammation and executive functioning; this may be due to the concurrent modeling of BMI alongside inflammation in all models. Instead, this study suggested that higher BMI prospectively predicts worse cognitive functioning via increased peripheral IL-6. Higher BMI has been consistently associated with a generalized pattern of cognitive dysfunction, including executive dysfunction, across the lifespan (Laitala *et al.*, 2011; Liang *et al.*, 2014; Prickett *et al.*, 2015; Yang *et al.*, 2018) and these findings support previous research hypothesizing that inflammation may be the mechanism underpinning an association between high BMI and cognitive dysfunction (Spyridaki *et al.*, 2014; Spyridaki *et al.*, 2016). There is considerable interest in understanding how BMI and poor cognitive functioning are related, with physical activity and poor diet quality identified as two putative mechanisms (Pistell *et al.*, 2010; Esteban-Cornejo *et al.*, 2015). Further research is needed to identify the mechanisms by which BMI leads to worse cognitive functioning in humans.

A concurrent association between inflammation and depression was not observed; however, higher depressive symptoms prospectively predicted higher IL-6 (supplementary analyses also observed that higher baseline TNF- α predicted increased future depressive symptoms). There is a relatively established body of research linking acute inflammation with depression (Maes *et al.*, 1995; Dantzer, 2001) as well as evidence of a bi-directional association between inflammation and depression (Messay *et al.*, 2012). However, it is likely that elevated inflammation only characterizes a sub-group of depressed individuals, and further, the majority of studies have been conducted in adult clinical samples, rather than an adolescent community sample where significantly lower levels of depression are observed (Kohler *et al.*, 2017). Additionally, once control variables were introduced, this prospective association disappeared, which may point to a confounding factor (e.g. gender) that is underpinning the increases in both inflammation and depressive symptoms. Thus, it may be that the current sample is not sufficiently powered to observe an effect that is only present in a sub-sample of individuals with depression, or that a concurrent association between depression and inflammation is only present in individuals meeting criteria for MDD (Raison and Miller, 2011; Kohler *et al.*, 2017).

These results should be interpreted in light of the limitations of this study. Inflammation was based on a single sera assessment and variability in food intake, medication status, and diurnal variation may decrease the precision of our estimates, although significant confounds (e.g. infection) were addressed. Although established measures of attentional functioning, the TEA/TEAch are not normed on large US adolescent samples. Thus, it is possible that the normed scores used in this study do not accurately capture age- and gender-normed performance. Moreover, it is unclear whether these results generalize to a clinical sample of

depressed individuals, given that assessment relied on self-report questionnaires. Although the ACE sample is notable for its racial, gender, and socioeconomic diversity, the analytic sample was less likely to include Caucasian participants and participants of low SES compared with the entire ACE sample, which could potentially influence the generalizability of these findings. It should be noted that the SEM models presented in this paper were complex, and required estimation of a large number of parameters, which, even for a sizeable sample, increased the risk that the parameters estimated were biased. These limitations are mitigated by direct and repeated measurement of peripheral inflammatory markers in a large, diverse cohort where cognitive functioning was assessed using reliable instruments across multiple modalities.

Conclusions

This study provides strong evidence that higher BMI leads to both depression and cognitive dysfunction in adolescence. It also highlights that an inflammatory cytokine, IL-6, may play a mechanistic role linking higher BMI with impaired cognitive functioning. Moreover, it may point to a sub-type of depression that is characterized by both metabolic dysregulation and cognitive dysfunction. Importantly, these relationships were found to be largely specific to depression, rather than anxiety, and the significance of the statistical modeling held even when considering several potential confounding factors. Future research should investigate systematically whether BMI and IL-6 are associated with executive functioning impairment alone using established theoretically-based models of executive functioning.

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Ethical standards. 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.

References

- Allott K, Fisher CA, Amminger GP, Goodall J and Hetrick S (2016) Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain and Behavior* **6**, e00527.
- Amaral WZ, Krueger RF, Ryff CD and Coe CL (2015) Genetic and environmental determinants of population variation in interleukin-6, its soluble receptor and C-reactive protein: insights from identical and fraternal twins. *Brain, Behavior, and Immunity* **49**, 171–181.
- Au B, Smith KJ, Garipey G and Schmitz N (2015) The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA). *International Journal of Geriatric Psychiatry* **30**, 976–984.
- Banich MT (2009) Executive function. The search for an integrated account. *Current Directions in Psychological Science* **18**, 89–94.

- Baune B, Ponath G, Golledge J and Varga G (2008) Association between IL-8 cytokine and cognitive performance in an elderly general population – the MEMO-Study. *Neurobiology of Aging* **29**, 937–944.
- Breen EC, Reynolds SM, Cox C, Jacobson LP, Magpantay L, Mulder CB, Dibben O, Margolick JB, Bream JH, Sambrano E, Martinez-Maza O, Sinclair E, Borrow P, Landay AL, Rinaldo CR and Norris PJ (2011) Multisite comparison of high-sensitivity multiplex cytokine assays. *Clinical and Vaccine Immunology* **18**, 1229–1242.
- Burcusa SL and Iacono WG (2007) Risk for recurrence in depression. *Clinical Psychology Review* **27**, 959–985.
- Carvalho AF, Miskowiak KK, Hyphantis TN, Kohler CA, Alves GS, Bortolato B, PM GS, Machado-Vieira R, Berk M and McIntyre RS (2014) Cognitive dysfunction in depression – pathophysiology and novel targets. *CNS & Neurological Disorders Drug Targets* **13**, 1819–1835.
- Chang HH, Lee IH, Gean PW, Lee SY, Chi MH, Yang YK, Lu RB and Chen PS (2012) Treatment response and cognitive impairment in major depression: association with C-reactive protein. *Brain Behavior and Immunity* **26**, 90–95.
- Chen FF (2007) Sensitivity of goodness of fit indexes to lack of measurement invariance. *Structural Equation Modeling: A Multidisciplinary Journal* **14**, 464–504.
- Cheung GW and Rensvold RB (2002) Evaluating goodness-of-fit indexes for testing measurement invariance. *Structural Equation Modeling: A Multidisciplinary Journal* **9**, 233–255.
- Clark LA and Watson D (1991) Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology* **100** and 316.
- D'Argembeau A, Ortoleva C, Jumentier S and Van der Linden M (2010) Component processes underlying future thinking. *Memory & Cognition* **38**, 809–819.
- Dantzer R (2001) Cytokine-induced sickness behavior: where do we stand? *Brain Behavior and Immunity* **15**, 7–24.
- de Wit L, Luppino F, van Straten A, Penninx B, Zitman F and Cuijpers P (2010) Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Research* **178**, 230–235.
- Diamond A (2013) Executive functions. *Annual Review of Psychology* **64**, 135–168.
- Duivis HE, Vogelzangs N, Kupper N, de Jonge P and Penninx BW (2013) Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology* **38**, 1573–1585.
- Esteban-Cornejo I, Tejero-Gonzalez CM, Sallis JF and Veiga OL (2015) Physical activity and cognition in adolescents: a systematic review. *Journal of Science and Medicine in Sport* **18**, 534–539.
- Friedman NP, Miyake A, Young SE, DeFries JC, Corley RP and Hewitt JK (2008) Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology: General* **137**, 201.
- Goldsmith DR, Haroon E, Woolwine BJ, Jung MY, Wommack EC, Harvey PD, Treadway MT, Felger JC and Miller AH (2016) Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. *Brain Behavior and Immunity* **56**, 281–288.
- Gotlib IH, Lewinsohn PM and Seeley JR (1995) Symptoms versus a diagnosis of depression: differences in psychosocial functioning. *Journal of Consulting and Clinical Psychology* **63**, 90.
- Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B and Hasin DS (2015) Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry* **72**, 757–766.
- Grant BF, Saha TD, Ruan WJ, Goldstein RB, Chou SP, Jung J, Zhang H, Smith SM, Pickering RP, Huang B and Hasin DS (2016) Epidemiology of DSM-5 drug use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry* **73**, 39–47.
- Haapakoski R, Mathieu J, Ebmeier KP, Alenius H and Kivimäki M (2015) Cumulative meta-analysis of interleukins 6 and 1 β , tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behavior and Immunity* **49**, 206–215.
- Heringa S, Van den Berg E, Reijmer Y, Nijpels G, Stehouwer C, Schalkwijk C, Teerlink T, Scheffer P, van den Hurk K and Kappelle L (2014) Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population – the Hoorn study. *Psychoneuroendocrinology* **40**, 108–118.
- Huang YS, Guillemainault C, Hwang FM, Cheng C, Lin CH, Li HY and Lee LA (2016) Inflammatory cytokines in pediatric obstructive sleep apnea. *Medicine* **95**, e4944.
- Jenny NS, French B, Arnold AM, Strotmeyer ES, Cushman M, Chaves PH, Ding J, Fried LP, Kritchevsky SB, Rifkin DE, Sarnak MJ and Newman AB (2012) Long-term assessment of inflammation and healthy aging in late life: the Cardiovascular Health Study All Stars. *The Journals of Gerontology: Series A* **67**, 970–976.
- Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE and Wang PS (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* **289**, 3095–3105.
- Kohler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctot KL and Carvalho AF (2017) Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatrica Scandinavica* **135**, 373–387.
- Kovacs M (1992) *The Children's Depression Inventory*. North Tonawanda, NY: Multi-Health Systems, Inc.
- Krogh J, Benros ME, Jørgensen MB, Vesterager L, Elfving B and Nordentoft M (2014) The association between depressive symptoms, cognitive function, and inflammation in major depression. *Brain Behavior and Immunity* **35**, 70–76.
- Laitala VS, Kaprio J, Koskenvuo M, Raiha I, Rinne JO and Silventoinen K (2011) Association and causal relationship of midlife obesity and related metabolic disorders with old age cognition. *Current Alzheimer Research* **8**, 699–706.
- Levin RL, Heller W, Mohanty A, Herrington JD and Miller GA (2007) Cognitive deficits in depression and functional specificity of regional brain activity. *Cognitive Therapy and Research* **31**, 211–233.
- Li X, Robertson CM, Yu X, Cheyesh A, Dinu IA and Li J (2014) Early postoperative systemic inflammatory response is an important determinant for adverse 2-year neurodevelopment-associated outcomes after the Norwood procedure. *The Journal of Thoracic and Cardiovascular Surgery* **148**, 202–206.
- Liang J, Matheson BE, Kaye WH and Boutelle KN (2014) Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. *International Journal of Obesity* **38**, 494–506.
- Mac Giollabhui N, Olinio TM, Nielsen J, Abramson LY and Alloy LB (2018) Is worse attention a risk factor for or a consequence of depression, or are worse attention and depression better accounted for by stress? A prospective test of three hypotheses. *Clinical Psychological Science* **7**, 93–109.
- MacKenzie LE, Uher R and Pavlova B (2018) Cognitive performance in first-degree relatives of individuals with vs without major depressive disorder: a meta-analysis. *JAMA Psychiatry* **76**, 297–305.
- Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R and Desnyder R (1995) Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *Journal of Affective Disorders* **34**, 301–309.
- Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P and Robertson IH (2001) The differential assessment of children's attention: The Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *Journal of Child Psychology and Psychiatry* **42**, 1065–1081.
- McAfoose J and Baune BT (2009) Evidence for a cytokine model of cognitive function. *Neuroscience and Biobehavioral Reviews* **33**, 355–366.
- Messay B, Lim A and Marsland AL (2012) Current understanding of the bi-directional relationship of major depression with inflammation. *Biology of Mood & Anxiety Disorders* **2**, 4.
- Michopoulos V, Powers A, Gillespie CF, Ressler KJ and Jovanovic T (2017) Inflammation in fear-and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacology* **42**, 254.

- Misiak B, Beszlej JA, Kotowicz K, Szewczuk-Boguslawska M, Samochowiec J, Kucharska-Mazur J and Frydecka D (2018) Cytokine alterations and cognitive impairment in major depressive disorder: from putative mechanisms to novel treatment targets. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **80**, 177–188.
- Miyake A and Friedman NP (2012) The nature and organization of individual differences in executive functions: four general conclusions. *Current Directions in Psychological Science* **21**, 8–14.
- Moriarty DP, Mac Giollabhui N, Ellman LM, Klugman J, Coe C, Abramson LY and Alloy LB (In Press) Inflammatory biomarkers differentially predict change in depressive symptoms over time in male and female adolescents. *Clinical Psychological Science*.
- Packwood S, Hodgetts HM and Tremblay S (2011) A multiperspective approach to the conceptualization of executive functions. *Journal of Clinical and Experimental Neuropsychology* **33**, 456–470.
- Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK and Bruce-Keller AJ (2010) Cognitive impairment following high fat diet consumption is associated with brain inflammation. *Journal of Neuroimmunology* **219**, 25–32.
- Preiss K, Brennan L and Clarke D (2013) A systematic review of variables associated with the relationship between obesity and depression. *Obesity Reviews* **14**, 906–918.
- Prickett C, Brennan L and Stolwyk R (2015) Examining the relationship between obesity and cognitive function: a systematic literature review. *Obesity Research & Clinical Practice* **9**, 93–113.
- Quek YH, Tam WWS, Zhang MWB and Ho RCM (2017) Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. *Obesity Reviews* **18**, 742–754.
- Raison CL and Miller AH (2011) Is depression an inflammatory disorder? *Current Psychiatry Reports* **13**, 467–475.
- Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A and Pollmacher T (2001) Cytokine-associated emotional and cognitive disturbances in humans. *Archives of General Psychiatry* **58**, 445–452.
- Robertson IH, Ward T, Ridgeway V and Nimmo-Smith I (1994) *The Test of Everyday Attention: TEA*. Bury St. Edmunds, UK: Thames Valley Test Company.
- Robertson IH, Ward T, Ridgeway V and Nimmo-Smith I (1996) The structure of normal human attention: The Test of Everyday Attention. *Journal of the International Neuropsychological Society* **2**, 525–534.
- Rock PL, Roiser JP, Riedel WJ and Blackwell AD (2013) Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine* **44**, 1–12.
- Schermelleh-Engel K, Moosbrugger H and Müller H (2003) Evaluating the fit of structural equation models: tests of significance and descriptive goodness-of-fit measures. *Methods of Psychological Research Online* **8**, 23–74.
- Sculth MA, Paulli AR, Mazure ES, Moffitt TE, Hariri AR and Strauman TJ (2017) The association between cognitive function and subsequent depression: a systematic review and meta-analysis. *Psychological Medicine* **47**, 1–17.
- Shields GS, Moons WG and Slavich GM (2017) Inflammation, self-regulation, and health: an immunologic model of self-regulatory failure. *Perspectives on Psychological Science* **12**, 588–612.
- Singh-Manoux A, Dugravot A, Brunner E, Kumari M, Shipley M, Elbaz A and Kivimaki M (2014) Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife. *Neurology* **83**, 486–493.
- Slavich GM and Irwin MR (2014) From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin* **140**, 774–815.
- Smith E, Hay P, Campbell L and Trollor J (2011) A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obesity Reviews* **12**, 740–755.
- Snyder HR (2013) Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological Bulletin* **139**, 81–132.
- Sparkman NL, Buchanan JB, Heyen JR, Chen J, Beverly JL and Johnson RW (2006) Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. *Journal of Neuroscience* **26**, 10709–10716.
- Spyridaki EC, Simos P, Avgoustinaki PD, Dermitzaki E, Venihaki M, Bardos AN and Margioris AN (2014) The association between obesity and fluid intelligence impairment is mediated by chronic low-grade inflammation. *British Journal of Nutrition* **112**, 1724–1734.
- Spyridaki EC, Avgoustinaki PD and Margioris AN (2016) Obesity, inflammation and cognition. *Current Opinion in Behavioral Sciences* **9**, 169–175.
- Steinberg L, Graham S, O'Brien L, Woolard J, Cauffman E and Banich M (2009) Age differences in future orientation and delay discounting. *Child Development* **80**, 28–44.
- Stewart JC, Rand KL, Muldoon MF and Kamarck TW (2009) A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain, Behavior, and Immunity* **23**, 936–944.
- Wagner S, Müller C, Helmreich I, Huss M and Tadić A (2015) A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *European Child & Adolescent Psychiatry* **24**, 5–19.
- Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJL and Vos T (2013) Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* **382**, 1575–1586.
- Woo YS, Rosenblat JD, Kakar R, Bahk WM and McIntyre RS (2016) Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clinical Psychopharmacology and Neuroscience* **14**, 1–16.
- Yang Y, Shields GS, Guo C and Liu Y (2018) Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neuroscience & Biobehavioral Reviews* **84**, 225–244.
- Zalli A, Jovanova O, Hoogendijk WJ, Tiemeier H and Carvalho LA (2016) Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology* **233**, 1669–1678.