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Full-length Article

The relationship between salivary C-reactive protein and cognitive function in children aged 11–14 years: Does psychopathology have a moderating effect?

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ABSTRACT

Elevated C-reactive protein (CRP), a non-specific biomarker of systemic bodily inflammation, has been associated with more pronounced cognitive impairments in adults with psychiatric disorders, particularly in the domains of memory and executive function. Whether this association is present in early life (i.e., the time at which the cognitive impairments that characterise these disorders become evident), and is specific to those with emerging psychiatric disorders, has yet to be investigated. To this end, we examined the association between salivary CRP and cognitive function in children aged 11–14 years and explored the moderating effect of psychopathology. The study utilised data from an established longitudinal investigation of children recruited from the community (N = 107) that had purposively over-sampled individuals experiencing psychopathology (determined using questionnaires). CRP was measured in saliva samples and participants completed assessments of cognition (memory and executive function) and psychopathology (internalising and externalising symptoms and psychotic-like experiences). Linear regression models indicated that higher salivary CRP was associated with poorer letter fluency ($\beta = -0.24$, $p = 0.006$) and scores on the inhibition ($\beta = -0.28$, $p = 0.004$) and inhibition/switching ($\beta = -0.36$, $p < 0.001$) subtests of the colour-word interference test, but not with performance on any of the memory tasks (working, visual, and verbal memory tasks). Results were largely unchanged after adjustment for psychopathology and no significant interactions between CRP and psychopathology were observed on any cognitive measure. Our findings provide preliminary evidence that elevated salivary CRP is associated with poorer cognitive function in early life, but that this association is not moderated by concurrent psychopathology. These findings have implications for early intervention strategies that attempt to ameliorate cognitive deficits associated with emerging psychiatric disorders. Further research is needed to determine whether salivary CRP levels can be used as a valid marker of peripheral inflammation among healthy adolescents.

1. Introduction

Over the past decade, there have been increased efforts to elucidate the role of inflammatory processes in both the pathogenesis and symptomology of psychiatric disorders (Haroon et al., 2012). These efforts have demonstrated that a number of psychiatric disorders, including schizophrenia, bipolar disorder, and depression,

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are characterised by elevated concentrations of C-reactive protein (CRP), a non-specific biomarker of systemic bodily inflammation (Fernandes et al., 2016a; Fernandes et al., 2016b; Howren et al., 2009). Moreover, within these populations, elevated CRP is associated with poorer cognitive function. Specifically, higher CRP has been found to correlate with greater cognitive impairments, particularly in memory and executive function domains, among individuals with schizophrenia (Bulzacka et al., 2016; Dickerson et al., 2007; Frydecka et al., 2015; Johnsen et al., 2016; Micoulaud-Franchi et al., 2015); with poorer memory and general cognitive function in those with bipolar disorder (Dickerson et al., 2013); and with attention and executive function deficits among individuals with depression (Chang et al., 2012; Krogh et al., 2014). Such findings lend support to the notion that chronic inflammation may contribute to the cognitive impairments that typically characterise these disorders; however, two major questions remain unanswered: Firstly, to what extent is the association between CRP and cognition specific to those with psychiatric disorders? Secondly, is this association present during early life? The latter is particularly pertinent given that the cognitive impairments observed among individuals with these disorders emerge during childhood, many years before disorder onset (Dickson et al., 2012; Koenen et al., 2009; Laurens et al., 2015).

Studies examining the relationship between CRP and cognition among those without psychiatric disorders have typically focused on distinct sub-populations characterised by cognitive impairments. Much research has focused on healthy older adults ($\geq$50 years); both cross-sectional and longitudinal studies indicate that elevated CRP is associated with poorer cognitive function in this population (Jenny et al., 2012; Marioni et al., 2009; Noble et al., 2010; Schram et al., 2007; Teunissen et al., 2003), though the association is rendered non-significant after adjustment for sociodemographic factors in some studies (Alley et al., 2008; Dik et al., 2005; Kao et al., 2011). Whilst a small number of these studies assessed depression symptoms, none examined the effect of these symptoms on the relationship between CRP and cognition; thus, the extent to which this relationship might be explained by psychiatric morbidity is unknown. Other studies have focused on populations with specific medical conditions. In cross-sectional investigations, CRP has been associated with poorer cognitive ability (again, particularly in the domains of memory and executive function) in preterm infants (O'Shea et al., 2013; Rose et al., 2016), infants with congenital heart problems (Li et al., 2014), children with obstructive sleep apnoea (Huang et al., 2016), and in adults experiencing mild traumatic brain injury (Su et al., 2014) or chronic obstructive pulmonary disease (Crisan et al., 2014). Inconsistent findings characterise studies examining populations that are neither exclusively older in age nor characterised by physical health conditions. A study of adults aged 18–82 years reported that CRP was not associated with executive function abilities (Schuur et al., 2010), whilst another large study of 28–91 year olds observed negative correlations between CRP and slower processing speed (but not executive function or memory performance) among African American (but not European American) participants (Windham et al., 2014). Only two studies, both longitudinal, have focused on young individuals from the general population; CRP did not predict memory or executive function in a two-year follow-up of adolescents (Jonker et al., 2014) or global cognition in a 13-year follow-up of young adults (Cohen-Manheim et al., 2015).

Thus, whilst elevated CRP has been associated with greater cognitive impairment in some non-psychiatric samples, the association appears to be restricted to populations in which cognitive impairment is also prevalent (e.g., older adults and those with physical health conditions). In contrast, a lack of evidence exists to suggest that CRP predicts later cognitive function in adolescents and young adults in the general population, which may reflect follow-up periods exceeding two years that were employed in these studies. However, the only previous study of adolescents did not investigate whether the relationship was present among those experiencing psychopathology (e.g., depression or subclinical psychotic symptoms). This is important, as opportunities for intervening to improve cognitive deficits associated with psychiatric disorders (either by psychological or biological means) are likely to be maximised in early life.

In light of these issues, the current study sought to investigate associations between inflammation, cognitive impairments, and emerging psychopathology in childhood, utilising salivary CRP as a marker of inflammation. Salivary CRP offers a less-invasive alternative to blood-based CRP measurement, particularly in child/adolescent populations in which there is often reluctance to provide blood samples. With the exception of a single study of healthy adults that failed to find an association between salivary and serum CRP (Dillon et al., 2010), most previous studies have demonstrated moderate-to-high correspondence between CRP levels in serum/plasma and saliva (Byrne et al., 2013; Iyengar et al., 2014; Ouellet-Morin et al., 2011; Out et al., 2012). The linear relationship observed between CRP in blood and saliva in these studies implies that the latter is a valid marker of peripheral inflammation. Nonetheless, the origin of salivary CRP is currently unclear. It has been proposed that CRP derived from saliva samples may reflect systemic CRP (predominately produced by the liver) that has leaked into gingival crevicular fluid via gingival tissues, though salivary CRP might also be produced by gingival tissues in response to periodontal infections (Salimetrics, 2011). By utilising salivary CRP as a marker of inflammation, the current study provides an opportunity to determine whether associations observed between blood-derived CRP and cognition extend to salivary CRP.

Capitalizing on a well-established longitudinal study of children recruited from the community (Laurens and Cullen, 2016), we examined the effect of salivary CRP on measures of memory and executive function in a sample of children aged 11–14 years that was enriched for children presenting with psychopathology (as determined using screening questionnaires). We first examined the predictive effect of salivary CRP on memory and executive function after adjusting for various methodological and participant factors that might confound the association. We then explored interactions between salivary CRP and psychopathology domains (internalising and externalising symptoms and psychotic-like experiences) to determine whether any associations between CRP and cognitive performance differed among children with and without psychopathology. We predicted that, in this sample of adolescents enriched for psychopathology, higher salivary CRP would be associated with poorer memory and executive function. We also anticipated that concurrent psychopathology would moderate the association between CRP and these cognitive functions.

2. Materials and methods

2.1. Participants and procedure

The current study uses data from an established longitudinal investigation of children initially recruited from the general population of South London at age 9–12 years (Laurens and Cullen, 2016; Laurens et al., 2007; Laurens et al., 2011). From the community sample of 1343 children and caregivers completing screening, a subset of these participants were selected (N = 123) to participate in laboratory-based assessments conducted at the Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK. This intensely-studied sample was enriched with children presenting with psychopathology [developmental delays

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