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Depression, immune function, and early adrenarche in children

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ABSTRACT

Despite consistent findings of an association between depression and immunity in adult and adolescent populations, little is known about the nature of this relationship at earlier ages. Studies of children have yielded mixed results, suggesting methodological confounds and/or the presence of significant moderating factors. Timing of adrenarche, the first phase of puberty that occurs during late childhood, is a plausible moderator of the depression-immunity relationship in late childhood due to its associations with both the immune system and psychological wellbeing. We hypothesized that: (1) a depression-immunity association exists in children, (2) this association is moderated by adrenarcheal timing, and, (3) this association is also moderated by gender. Data were drawn from a nested study of 103 participants (62 females, *M*age = 9.5, age range: 8.67–10.21 years) participating in a population based cohort study of the transition from childhood to adolescence (across puberty). Participants in this nested study completed the Children's Depression Inventory 2 (CDI-2) and provided morning saliva samples to measure immune markers (i.e., C-reactive protein, CRP; and secretory immunoglobulin A, SIgA). Using hierarchical regression, inflammation measured by CRP was positively associated with the negative mood/physical symptoms (NM/PS) subscale ($\beta = 0.23$, $t = 2.33$, $p = 0.022$) of the CDI-2. A significant interaction effect of SIgA x adrenarcheal timing was found for NM/PS ($\beta = -0.39$, $t = -2.19$, $p = 0.031$) and Interpersonal Problems ($\beta = -0.47$, $t = -2.71$, $p = 0.008$). SIgA and NM/PS were positively associated for relatively late developers. SIgA and Interpersonal Problems were positively associated for late developers, and negatively associated for early developers. We suggest that both sets of findings might be partially explained by the immunosuppressive effect of the hormonal changes associated with earlier adrenarche, namely testosterone. These results also suggest that adrenarcheal timing has an effect on the association between depression and immunity, and is therefore an important measure in research with younger populations. Future research should utilize longitudinal designs to demonstrate direction of influence of variables, and use a broader range of pro- and anti-inflammatory markers.

1. Introduction

There is consistent evidence for a depression-immunity association in both adults and adolescents (Gabbay et al., 2009; Howren et al., 2009); however, this association has not yet been conclusively demonstrated at earlier ages. Three published studies on this topic have included children, but have also included adolescents and/or adults, often without adequate differentiation between the age groups (Brambilla et al., 2004; Copeland et al., 2012; Keller et al., 2010). This is problematic because puberty (the developmental process normally thought to distinguish childhood and adolescence) is a major endocrine event that has known effects on immune function (Bouman et al., 2005) and psychological wellbeing (Angold et al., 1998). Indeed, these studies have yielded varied results, which may be due in part to moderators such as puberty and gender.

Although there are known links between pubertal development and depression (e.g., Patton et al., 1996) and pubertal hormones and immune function (Bouman et al., 2005), few studies have

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conjointly considered both immune function and puberty. For example, Keller et al. (2010) controlled for pubertal status when investigation a depression-inflammation association in a child and adolescent sample (aged 7.5–12 years), but did not use hormonal markers of puberty that are more sensitive to the distinct phases of puberty. Specifically, puberty has two distinct, independently regulated phases—adrenarche and gonadarche. Adrenarche is the earlier phase, beginning around 6–8 years of age, and occurs when the adrenal cortex secretes increased levels of the androgens dehydroepiandrosterone (DHEA), its sulfated esther, (DHEA-S), and testosterone (Patton & Viner, 2007). Early adrenarcheal timing as measured by hormone levels, even within normal variation, has been shown to be associated with increased inflammatory markers (Utriainen et al., 2010) and depressive symptoms (Dorn et al., 1999). As adrenarche includes physical signs of maturation that usually manifest after hormonal changes have occurred (Dorn, 2006), the most accurate measure of the timing of this process is hormonal markers.

Keller et al. (2010) found a female specific inflammation-depression relationship, which is consistent with previous literature on sex differences in depression and immune function. Indeed, during puberty, diagnoses of depression in females nearly doubles (Angold et al., 1998), and females have been found to have a stronger immune response than males (Schuurs and Verheul, 1990). As Keller et al.'s (2010) is the only study including a child sample to have tested the moderating effect of gender, further research is also needed to establish the robustness of this finding.

Finally, Blume et al. (2011) have suggested that different facets of depression, which is symptomatically heterogeneous, may show different immune profiles. Therefore, individual features of depression should be examined separately to evaluate if some are more strongly associated with immune function.

We aimed to improve on methodologies used in previous studies of depression and immunity in children by directly testing whether puberty and gender have potentially moderating roles in the relation between depression and inflammation. Given that in children, adrenarcheal processes are forefront, we focused on adrenarcheal timing (i.e., stage compared to peers), as indicated by hormone levels.

Accordingly, the purpose of this study was to examine: (1) the association between biomarkers of immune function and depressive symptoms in late childhood, (2) the extent to which adrenarcheal timing moderates observed associations, and (3) potential gender differences in observed associations. It was hypothesized that children with higher levels of depressive symptoms would have increased inflammation (CRP) and lower levels of immune competence (SIgA). Further, adrenarcheal timing was hypothesized to moderate the association between depression and immune function, with associations stronger for children with early adrenarche (i.e., higher levels of the adrenarcheal hormones DHEA and testosterone compared to peers). Finally, we predicted that sex would moderate the association between depression and immune function, with associations being stronger for girls compared to boys. We also explored subscales of self-reported depression symptoms to assess if some features of depression were more associated with immune function than others.

2. Material and methods

This study uses data collected from the Imaging Brain Development in the Childhood to Adolescence Transition Study (iCATS), conducted by The University of Melbourne and Murdoch Childrens Research Institute (MCRI). Aims, method of recruitment and protocol for iCATS have been described elsewhere (Simmons et al., 2014).

2.1. Recruitment and screening of participants

Recruitment for iCATS occurred within the larger Childhood to Adolescence Transition Study (CATS) cohort. Two groups of participants ("Hormone Group") stratified by adrenarcheal timing, within normal, non-clinical variation, were selected from the original, larger CATS cohort based on hormonal data (DHEA and testosterone). In the CATS cohort, early adrenarcheal development ("High" levels of hormones) was defined as participants scoring in the top tertile for both DHEA and testosterone, whereas late adrenarcheal development ("Low" levels of hormones) was defined as scoring in the bottom tertile for both DHEA and testosterone. In previous work from our lab, this selection strategy has shown significant associations between adrenarcheal timing and affect-related brain activity (Whittle et al., 2015). The early and late developing groups (e.g., top and bottom thirds only, based on DHEA and testosterone) from CATS comprised the iCATS sample. In the final recruited sample for iCATS, the mean level of DHEA for the "high" group was 65.75 pg/ml (range 29–244), and 1.04 pg/ml (range 0–15) for the "low" group. The mean level of testosterone was 30.17 pg/ml (range 18–55) for the "high" group and 10.81 pg/ml (range 0–15) for the "low" group.

One-hundred and twenty-eight children were recruited for iCATS. In total, 25 participants were excluded from analysis due to: (1) the use of medications that would affect immunological function on the day before saliva sample collection ($n = 11$), (2) not being willing to complete saliva samples or being unable to produce enough saliva required to assay levels of CRP and SIgA ($n = 12$), and (3) levels of CRP were too high for the assay to detect ($n = 2$). Therefore, a sample size of 103 was used for analysis (Mage = 9.5, age range: 8.67–10.21 years), with 53 "High" children (31 female) and 50 "Low" children (28 female).

Participants and their parents/guardians provided informed consent. Parents/guardians were reimbursed $55, and children with a $30 shopping voucher, for participation. Ethics approval was granted by the Royal Children's Hospital Human Research Ethics Committee (HREC REF No. 32171A).

2.2. Measures

2.2.1. The Children's Depression Inventory 2 (CDI-2)

The CDI-2 is a brief self-report assessment of cognitive, affective, and behavioral signs of depression in children and adolescents, from 7 to 17 years (Kovacs, 2004). The CDI-2 measures two core features of depression (i.e., mood and self-esteem) and associated features such as functional problems. In line with this, the CDI-2 has two scales, each with two subscales: (1) emotional problems (subscales: negative mood/physical symptoms (NM/PS) and negative self-esteem) and, (2) functional problems (subscales: interpersonal problems and ineffectiveness). The CDI-2 has demonstrated good reliability, and discriminant and convergent validity (Figueras Masip et al., 2010; Hodges, 1990). Participants completed the CDI-2 on the day of the second saliva sample, with the assistance of a researcher. CDI-2 scores were converted to T-scores based on gender.

2.2.2. Biological samples: saliva

Hormonal (DHEA and testosterone) data was collected from saliva as part of the CATS study (described in Mundy et al., 2013), and immunological data was collected from saliva as part of iCATS. Compared to blood, saliva samples are a quick, simple and non-invasive collection method (Granger et al., 2007). In addition, saliva samples have been found to be valid for systemic or major sources of CRP (e.g., Byrne et al., 2013; Out et al., 2012), SIgA (Crawford