



Research paper

Subclinical maternal depressive symptoms modulate right inferior frontal response to inferring affective mental states of adults but not of infants



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ABSTRACT

Background: Being a mother of young children increases the risk of depression characterised by deficits in inferring what a person is feeling, i.e., affective theory of mind (aToM). Despite the adverse consequences for mothers, children, families, and society as a whole, little is known of how the brain functions underlying aToM ability are affected by subclinical maternal depressive symptoms, and act as a risk indicator for major depressive disorders (MDD).

Methods: Thirty healthy mothers with varying levels of depressive symptoms underwent functional magnetic resonance imaging (fMRI) while performing mind-reading tasks based on the emotional expressions of adult eyes and infant faces.

Results: In the adult eyes-based mind-reading task, mothers with more severe depressive symptoms showed less activation in the right inferior frontal gyrus (IFG), a central part of the putative mirror neuron system (pMNS). This was unrelated to behavioural performance decline in the task. However, brain activation involved in the infant face-based mind-reading task was not affected by depressive symptoms.

Limitations: Although aToM ability, assessed by mind-reading tasks, can be distinguished from empathy, these can be interacting functions of the pMNS, wherein they could mutually affect each other.

Conclusion: These findings suggest that functional activation of the right IFG, which underlies aToM ability, has variable vulnerability to maternal depressive symptoms according to the type of social signal. This functional decline of the right IFG may be a risk indicator for clinical maternal depression, which is associated with impaired social functioning and communication conflicts with family members and other social supporters.

1. Introduction

Being a mother of young children increases the risk of depression (Horwitz et al., 2007; McLennan et al., 2001). Even beyond the post-partum period, mothers caring for one or more preschool children younger than 6 years old are likely to be at greater risk for maternal depression (Horwitz et al., 2007; McLennan et al., 2001; Nærde et al., 2000). Major depressive disorder (MDD) is mainly characterised by distorted interpretations of other people's mental states, which leads to impaired interpersonal and social functioning (Cusi et al., 2012; Richman and Unoka, 2015). In particular, maternal depression is one of the significant public health concerns that has adverse consequences for mothers, children, families, and society as a whole (Apter-Levy et al.,

2013; Goodman and Gotlib, 1999; Lyons-Ruth et al., 2000). Nevertheless, maternal depression often remains unrecognized and untreated by health care providers (Chabrol and Callahan, 2007; Silver et al., 2006). Since there is increasing evidence that psychiatric conditions, including depression, may be dimensional as opposed to categorical, the National Institute of Mental Health's Research Domain Criteria (RDoC) project has recently called for neuroscience research into the dimensions of psychopathology (Insel et al., 2010). In depression research, nearly all patients who develop MDD may be assumed to have progressed from a subclinical level of dimensional depression severity (Cuijpers and Smit, 2004; Schreiter et al., 2013), which can be measured by a continuous score of self-reported depressive symptoms (Besteher et al., 2017; Cuijpers et al., 2014; Laeger et al., 2012; Philipp

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et al., 2015). Subclinical depression can be defined as scoring above a cut-off threshold in a self-report depressive measure, but not fulfilling the criteria for MDD (Cuijpers et al., 2014; Cuijpers and Smit, 2004). In terms of this dimensional approach, neuroscience research with healthy mothers that show subclinical, not clinical, depression severity may provide insight into the mechanisms underlying neural vulnerability to maternal depression.

Deficits in mental state inferencing – Theory of Mind (ToM) – are thought to be one of the underlying cause of depressive features (Richman and Unoka, 2015). ToM as an important skill for maintaining interpersonal relations can be divided into cognitive and affective aspects; cognitive ToM refers to inferences about other people's intentions and beliefs, and affective ToM (aToM) refers to the ability to make inferences regarding others' emotions (Abu-Akel and Shamay-Tsoory, 2011; Poletti et al., 2012; Shamay-Tsoory et al., 2010). The "Reading the Mind in the Eyes Test (RMET)" is often considered a prototypical task for the assessment of aToM, in which the participant matches semantic definitions of mental states to pictures of the eye regions of human adult faces with emotionally valenced expressions (Baron-Cohen et al., 2001; Poletti et al., 2012). Similar to the RMET, the "Infant Facial Expressions of Emotions from Looking at Pictures (IFEEL Pictures)" is also a task for the assessment of aToM, in which the participant describes pictures of the emotional expression of human infant faces (Emde et al., 1993; Siddiqui et al., 2000; Voorthuis et al., 2014). As highlighted by a recent meta-analysis on research involving the RMET of adults clinically diagnosed with MDD, patients exhibit impaired RMET performance in contrast to their healthy counterparts (Richman and Unoka, 2015). Since a subclinical level of dimensional depression severity is a significant risk factor for MDD (Cuijpers and Smit, 2004; Schreiter et al., 2013), maternal depressive symptoms can also negatively impact the neurocognitive mechanisms underlying the aToM ability that is central to successful parental communication with infants/children as well as the communication with other adults, including family members and other social supporters, surrounding parental caregiving.

To date, insufficient information exists regarding how brain activation patterns during aToM processing (e.g. RMET, IFEEL Pictures) are altered in depression, including the clinical and subclinical levels of depressive symptoms (Cusi et al., 2012). A recent meta-analysis of functional neuroimaging studies in healthy participants (Schurz et al., 2014) indicated that the RMET engages a widely distributed neural network in the brain, including the inferior frontal gyrus (IFG), posterior parts of superior/middle temporal cortices, temporo-parietal junction (TPJ), and pre-supplementary motor area (pre-SMA). Similarly, a functional magnetic resonance imaging (fMRI) study using the IFEEL Pictures has shown the widely activated brain regions, such as the IFG, superior/middle temporal cortices, and pre-SMA, when judging the emotion of the infant faces (Voorthuis et al., 2014). While the regions essential to this ability are still heavily debated, brain lesion evidence has shown an association between impaired RMET performance and lesions in the left IFG, suggesting that the left IFG may support RMET performance (Dal Monte et al., 2014). In particular, the IFG is strongly implicated in the putative mirror neuron system (pmNS) (Rizzolatti and Craighero, 2004), which is not simply associated with imitation and action recognition, but also with empathizing (mirroring) with others through the inner imitation of their actions (e.g. facial expression) of others (Iacoboni and Dapretto, 2006). According to an influential model of aToM (Keysers and Gazzola, 2007), this ability is proposed to derive from an integration of the mirroring (mainly based on the pmNS) and mentalising systems. In line with this model of aToM ability, the IFG and adjacent ventral premotor cortex, as commonly associated with the pmNS, were consistently activated for the execution and observation of expressions of emotion, as revealed in a recent meta-analysis of relevant neuroimaging studies (Molenberghs et al., 2012). The idea that the pmNS may function abnormally in depression has been suggested, but not yet tested experimentally (Cusi et al., 2012;

Schreiter et al., 2013).

In this fMRI study, we examined how individual differences in maternal depressive symptoms are associated with brain activation while performing the mind-reading tasks based on the emotional expressions of adult eyes and infant faces. Given that clinical depression (MDD) has been strongly associated with impaired aToM ability (Richman and Unoka, 2015), we hypothesized that subclinical maternal depressive symptoms, as a significant risk indicator for MDD, would negatively impact the neurocognitive mechanisms underlying aToM ability. In order to investigate this hypothesis, we used the mind-reading tasks based on the emotional expressions of adult eyes (RMET) and infant faces (IFEEL) for the assessment of aToM ability (Poletti et al., 2012; Voorthuis et al., 2014). Specifically, the perception and interpretation of the immature faces of infants and children (so-called "baby schema" or "infant/child schema") can commonly contribute to the facilitation of protective, caregiving, and rearing behaviours in parents (Kringelbach et al., 2016). Such immature (vulnerable) face-based mind-reading is likely to be an important skill of parents during the period following postpartum as well as the postpartum period. Moreover, based on the constructs of the systems for the social processes domain of the RDoC framework, "Perception and Understanding of Others" assessed experimentally by the RMET and IFEEL can be different from "Social Communication" assessed by emotional expression tests (Kupferberg et al., 2016). For the latter construct, neuroimaging studies have consistently reported hyperactivation of the amygdala and hypoactivation of the dorsolateral prefrontal cortex (DLPFC) in response to negative (e.g. sad/fearful) emotional stimuli in subclinical (Laeger et al., 2012) and clinical depression (Groenewold et al., 2013). In this fMRI study of the psychological construct for "Perception and Understanding of Others", there would not be altered task-related activation in the amygdala and DLPFC in subclinical maternal depression. Our main experimental prediction was that higher levels of maternal depressive symptoms would be associated with reduced activation in brain regions included in the widely distributed neural network (e.g. the IFG, superior/middle temporal cortices, and pre-SMA), as previously suggested by Schurz et al. (2014), while completing the mind-reading tasks based on the emotional expressions of adult eyes (RMET) and infant faces (IFEEL).

2. Methods

2.1. Participants

Thirty healthy mothers (age range = 27–43 years; mean age = 35.3 years; standard deviation (SD) = 4.3 years) participated in this study after providing written informed consent. They were targeted as female caregivers who were caring for young children during 2015–2016. The study protocol was approved by the Ethics Committee of the University of Fukui, Japan (Assurance # FU-20150109), and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Ministry of Health, Labour, and Welfare of Japan. All mothers were caring for one or more preschool non-adopted children. Nine of the 30 mothers were primiparous, and 21 mothers were multiparous. All mothers had completed at least 12 years of education (non-compulsory secondary level, or post-school university level education), which is categorised as high level education (Pearson et al., 2013). They all were living above the relative poverty line, which is set at 50% of the median household income in the country (Organization for Economic Cooperation and Development, 2016). All had normal vision or corrected-to-normal vision. Based on self-report questionnaires, they reported no history of brain injury, neurological or psychiatric illness, or current use of psychoactive medications. Participants had never been diagnosed with or treated for depression. All mothers further met the safety requirements for participation in an fMRI study (exclusion of ferromagnetic implants, claustrophobia, pregnancy, and others).

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