Case Report

Orbitofrontal dysfunction in a monozygotic twin discordant for postpartum affective psychosis: a functional magnetic resonance imaging study


Background: Incomplete concordance for psychosis in monozygotic (MZ) twins has been interpreted as indicative of non-genetic cofactors in transmission of the illness. In this case study, we consider childbirth a landmark in the onset of psychotic symptoms, leading to the diagnosis of puerperal psychosis and then to bipolar/schizoaffective disorder. At the end of the third trimester, there is a sudden drop in estrogen, which exerts prominent effects on the serotonergic system in the orbitofrontal cortex (OFC).

Objectives: The purpose of the present study was to investigate OFC activation during emotional processing in MZ twins discordant for affective psychosis.

Methods: Blood-oxygen-level-dependent activation using functional magnetic resonance imaging was measured during the passive viewing of emotional film excerpts.

Results: Consistent with our hypothesis, a significant locus of activation was found in the left OFC in the normal MZ twin, but not in the psychosis MZ twin.

Conclusions: The personality changes noted in the psychosis MZ twin (postpartum psychosis) may be related to dysfunctional OFC. Ms J’s childbirth may have triggered the onset of psychotic symptoms, leading to the diagnosis of bipolar or schizoaffective disorder.

Psychiatric illness following childbirth has long been recognized, but there has been little consensus regarding the nosological status of episodes of psychotic illness in the puerperium. Opinions have varied from those who have argued that puerperal psychosis is a distinct nosological entity (1) to those who have regarded childbirth as a specific stressor, acting to trigger episodes of affective or schizophrenia psychoses (2). The DSM-IV agrees with the latter view and does not include postpartum psychosis as a distinct diagnostic category (3).

Within the first few weeks following childbirth, 1 in 1,000 women will exhibit postpartum psychosis symptoms: cognitive clouding, insomnia, mania, confusion, depersonalization, thought disorder, hallucinations and/or delusions. They are excited, over-talkative, disinhibited and intensely
overactive (4, 5). Hence, for these women, childbirth is considered a landmark in personality change and the onset of psychotic symptoms, leading to the diagnosis of bipolar or schizoaffective disorder.

The reason why nearly 0.1% of women develop psychosis during the postpartum period is not fully understood, but stress, first pregnancy, and endocrine disorders have all been implicated as causative or triggering factors (6, 7). The early postpartum period is characterized by dramatic physiological changes including a drop in the levels of estrogen, progesterone (8), melatonin, endorphins and corticotrophin-releasing hormone, all of which have been linked to puerperal disorders (9). Most notable, however, is the severe drop in the level of estrogen at term. Estrogen falls nearly 1000-fold from its peak value during the third trimester (10). Jones et al. (11) suggested that hormonal mechanisms are probably of paramount importance, of which estrogen systems have attracted the most interest to date. Other evidence in support of the estrogen hypothesis comes from the results of a treatment study of postpartum psychosis suggesting a relationship between low estradiol concentration and clinical response to estradiol (12).

Estrogen exerts prominent effects on the central serotonergic system (13, 14). It is noteworthy that its administration increases serotonin 5-HT2A receptor density in the orbitofrontal cortex (15, 16). Furthermore, changes in estrogen levels in healthy women have been closely related to orbitofrontal cortex (OFC) activation (17).

In addition, the OFC has long been implicated in personality change (18). It allows the integration of limbic and emotional information into contextually appropriate behavioral responses. In addition, various lines of evidence suggest that it plays a pivotal role in the expression and regulation of socio-emotional behavior (19). In line with this, clinical neuropsychological and neuroimaging findings indicate that patients with OFC lesions often exhibit callous disregard for their loved ones (20), impulsivity (21), liability, disinhibition, inappropriate behavior (21) personality changes and dysfunctional affectively driven instinctive behavior (e.g., motherhood) (22, 23), all of which may play a role in puerperal psychosis symptoms. Interestingly, healthy mothers exhibit bilateral OFC activation that positively correlates with pleasant mood while viewing pictures of their own children (24).

In the case report we present here, psychotic symptoms appeared in a monozygotic (MZ) twin following childbirth. Using functional magnetic resonance imaging (fMRI), we predicted *a priori* that the normal twin will show activation of the OFC in response to the passive viewing of emotional film excerpts, based on our hypothesis that a dysfunctional OFC is involved in the personality change resulting in postpartum psychosis. Conversely, the affective psychotic twin will not show activation of the OFC. To our knowledge, this investigation constitutes the first study of its kind.

Our rationale for presenting this case is to systematically document a possible association between OFC, personality change and postpartum psychosis; hence, to increase clinician and investigator awareness of postpartum syndromes. Although the OFC has long been suspected to be responsible for personality change (22), a MEDLINE search (back to 1965, English language) did not reveal any previous systematic case reports on postpartum psychosis and orbitofrontal dysfunction.

**Case report**

Ms J and Ms D are French-Canadian 24-year-old MZ twins who are right-handed and discordant for affective psychosis. Although the zygosity of these twins could be questioned since no blood group analysis was done, zygosity was assessed using the questionnaire developed by Eisen et al. (25). In addition, several observations associated with monozygosity characterized Ms J and Ms D, including the remarkable resemblance in their childhood photographs, family members perceiving them as identical, and the fact that only the mother could differentiate between them (26). Ms J was admitted to the hospital for the first time at the age of 22 years, when she tried to commit suicide 4 months after giving birth to her first baby boy from an unknown father. Following postpartum, Ms J was unable to take care of herself or her infant and eventually the custody of her child was given to her parents. She suffered from agitation, severe insomnia, delusions, weight loss and heat intolerance, and began to experience visual and auditory hallucinations. Unusual thought content included a belief that Satan wanted to control her and possess her soul, and was against her reading the Bible. Ms J’s repeated suicidal attempts aimed to prevent satanic possession. Based on family interviews, this represented a significant change in Ms J’s personality. Since then, Ms J has been readmitted five times to psychiatric hospitals. Precipitants have been mainly suicide attempts, aggressive and violent behavior such as threatening a waiter with a gun, changes in relationships, and
medication non-compliance. During her stay in various hospitals, Ms J was aggressive and violent toward the nurses. She also showed inappropriate and uninhibited sexual behavior with male patients. Ms J escaped from hospitals several times and became involved in prostitution. She has worked as a waiter, and had multiple sexual partners, including men more than twice her age. With respect to her MZ twin, Ms D lives a normal life with her boyfriend and is currently working as a waiter. She recently had a second baby without any problem. Ms D was carefully screened by a psychiatrist (ES), psychologist and social worker following her first and second childbirths for exclusion of any psychiatric or psychotic symptoms. School records were also screened, and showed no history of depression, antisocial behavior, violence, suicidal tendencies or any other psychiatric problems.

Medical records indicate that both twins were normal newborns, and their mother – a housewife – reported normal developmental milestones. Both sisters finished high school. Interestingly, family history shows that their maternal grandmother suffered from a psychiatric illness, the nature of which is not clear, and their paternal grandmother (in her 60s) and aunt committed suicide.

Ms J was treated with a mood stabilizer (valproic acid, 500 mg twice a day) and a second-generation antipsychotic drug (olanzapine, 10 mg a day). She has been in individual and group therapies. Ms J’s past medical history includes hepatitis C. Neither sister has a history of head trauma with or without loss of consciousness. Ms J had no remarkable life events indicative of psychiatric instability.

Methods

Ms J and Ms D gave written informed consent and the study was approved by the local ethics and scientific committees.

Behavioral procedure

Blood-oxygen-level-dependent (BOLD) signal changes were measured during two experimental conditions, i.e., a ‘Sad’ and an emotionally ‘Neutral’ condition. In the ‘Sad’ condition, subjects watched a sad film excerpt for 3 min. The sad film excerpts depicted the death of a father in front of his young son and wife extracted from the film ‘The Champ’ (1979). This film has been validated by Gross and Levenson (27) and has been used in several studies (28–33). In the ‘Neutral’ condition, subjects watched an emotionally neutral film excerpt – about gardening – also for 3 min [for complete methodology, see Stip et al. (33)].

An a priori search strategy was used, and a small volume correction was performed in the brain region of interest (ROI) defined a priori. The search volume corresponding to the ROI was defined a priori by tracing the neuroanatomic boundaries of this region on the MR reference image [Montreal Neurological Institute (MNI) template], using small volume correction (SVC) and box volume function in SPM99. For this a priori search, a probability threshold for multiple comparison of a corrected p < 0.05 was used. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis. In the ‘Sad’ condition, the a priori search strategy encompassed the left and right OFC [Brodmann area (BA) 47; box center situated at 30,28,16 mm bilaterally; box volume = 44,25,16].

Results

Self-report data

The viewing of the sad film excerpts induced a transient state of sadness in both subjects. As expected, the mean level of reported sadness was significantly higher in the ‘Sad’ condition for Ms D (Ms J reported 2 and Ms D 6 on the rating scale). The viewing of the neutral condition did not induce any emotion (both subjects reported 0 on the rating scale).

fMRI data

When the brain activity associated with the viewing of the neutral film excerpt was subtracted from that associated with the viewing of the sad film excerpt, a significant locus of activation was found in the left OFC (Brodmann area 47) in Ms D [Talairach coordinates (34) x = −53, y = 29, z = −4] (corrected p < 0.01; z = 3.01; t = 3.07; 16 clusters; cluster level correction <0.02). No OFC activation was noted in Ms J (Fig. 1).

Discussion

Lack of complete concordance for psychosis in MZ twins has been interpreted as indicative of non-genetic cofactors in transmission of the illness. This suggests that, in addition to a genetic predisposition, there must be a neurodevelopmental and/or environmental trigger for psychosis to develop (26). In the present case, we consider Ms J’s
pregnancy and the birth of her child as the environmental triggers of her personality change leading to psychotic symptoms. If so, one would have expected that the co-twin (Ms D) would also experience postpartum psychosis after giving birth. Indeed, family studies of puerperal psychosis consistently demonstrate familial aggregation of psychiatric (predominantly affective) disorder, with morbidity risks for first-degree relatives in the range of 10–50% (35, 36). In the current case study, the normal MZ twin recently gave birth, but she did not develop puerperal psychosis. Another concern that could be raised is the assumption that a lack of OFC activation actually played a role in her personality change. In support of this assumption, several functional neuroimaging studies carried out in healthy subjects have reported activation of the OFC during a transient state of sadness (19, 31). Consistent with this, significant activation of the left OFC was noted in Ms D during the viewing of the sad film excerpt. In agreement with our a priori hypothesis, the absence of OFC activation in Ms J, during the viewing of the sad film excerpt, suggests an abnormal functioning of this brain region. The OFC receives highly processed information about the individual’s experience of an environmental stimulus, and the anticipated consequences of various social and emotional behavioral responses to this stimulus. The prominent involvement of the OFC in regulating affectively driven instinctive behavior, personality changes, impulsivity, lack of social restraints, mediating empathic behavior, and taking part in object–affect associations made it reasonable to think that Ms J’s onset of postpartum psychosis may be associated with a dysfunctional OFC.

As for mechanisms involved, this abnormal OFC functioning could result from a dysfunctional serotonergic system considering the estrogen hypothesis. As previously mentioned, the sudden drop in estrogen levels at term is nearly 1000-fold from its peak value during the third trimester (10). Estrogen exerts prominent effects on the central serotonergic receptor system (13, 14) in the orbitofrontal cortex (15, 16). Thus, it is not unreasonable to propose that Ms J’s childbirth triggered her personality change and the onset of psychotic symptoms, leading to the first diagnosis of affective psychosis (bipolar mania type) and then schizoaffective disorder.

Our study must be interpreted in the light of an important limitation, sample size, common to all investigations using single subject design. The possible effects of current and previous medications should be considered. In addition, no objective measures were performed to characterize the subjects’ emotional state. Instead, self-report ratings were used. Other studies are awaited to further elucidate the relationship between the OFC, personality change, postpartum psychosis, and affective psychosis. This case report has several research and clinical implications. If replicated, this finding may improve our understanding of the etiological basis of puerperal psychosis. Discovering the neurophysiological mechanisms involved in the onset of puerperal psychosis could lead to major benefits in the treatment and prevention of puerperal psychosis and may inform research on a range of other disorders, including menstrual psychosis, premenstrual syndrome, steroid psychosis, bipolar psychosis and non-puerperal affective disorders.

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References

Puerperal affective psychosis: an fMRI study