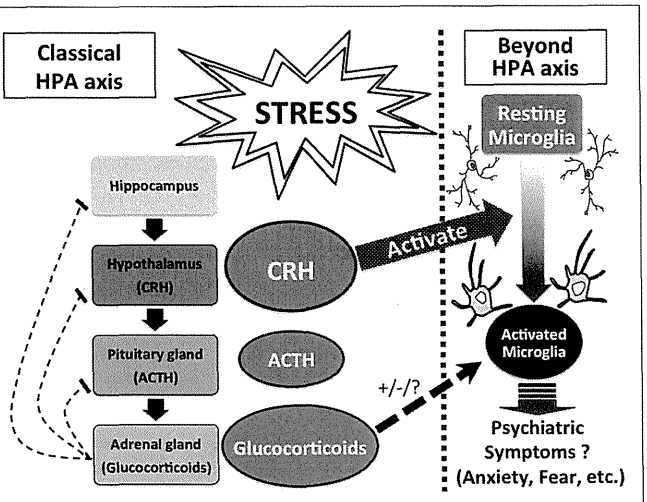

FIGURE 1 | CRH and glucocorticoids affect microglia beyond the HPA axis.

such as the adrenal gland, the mammary gland, adipose tissues, and the brain. From puberty to menopause, estrogens establish and maintain the reproductive function during the estrous cycle. In addition to these functions, estrogens have systemic functions that include for example, developing the mammary gland, regulating the immune system, protecting the cardiovascular system, and maintaining bones. At the same time, the remarkable involvement of estrogens in the brain have recently been highlighted, and the mechanism underpinning these functions such as enhancing cognitive function has gradually been clarified (Walf et al., 2011). Progesterone, one of the steroid hormones from the corpus luteum, is involved in the female reproductive system, especially developing the mammary gland and the initiation and maintenance of pregnancy (Mani and Portillo, 2010). Androgens are steroid hormones that are essential not only to the establishment and maintenance of male reproductive functions but also to muscular and bone anabolic functions (Yin et al., 2003). The most primary androgen is testosterone secreted by Leydig cells in the presence of luteinizing hormone (Mooradian et al., 1987). During reproductive age, sex hormones levels alter along with life stages of women. Estrogen and progesterone progressively increase during pregnancy, and after the delivery, both hormones abruptly decrease and a normal estrous cycle is restored. Also, both hormones gradually begin to decrease from the climacteric period toward menopause, but LH and FSH simultaneously increase during this period. In this way, sex hormones in women demonstrate cyclic alteration along with ovulation, and also the balance of sex hormones changes at the time of pregnancy or menopause, causing some women to show various psychiatric symptoms which occasionally develop into psychiatric disorders (Steiner et al., 2003).

SEX HORMONES, MENTAL CONDITIONS, AND PSYCHIATRIC DISORDERS

Women are more likely to show unipolar depression than men (Nolen-Hoeksema, 1987), and severe stresses are more likely to induce depression in women (Kendler et al., 1995). Sex hormones alter with time and subsequently establish the estrous cycle, which plays an important role in depression.

Neurosteroids such as pregnenolone, progesterone, and dehydroepiandrosterone (DHEA) have been suggested to have positive links to neuropsychiatric disorders. For example, the CSF level of pregnenolone is lower in patients with MDD than healthy controls (George et al., 1994). The saliva and serum level alterations of DHEA during depressive episodes have revealed divergent results (Eser et al., 2006), but recently Kurita et al. (2013) have reported elevated levels of serum DHEA in male and female patients with MDD. Both pregnenolone and DHEA probably have therapeutic effects for patients with MDD (Wolkowitz et al., 1999; Schmidt et al., 2005; Osuji et al., 2010). Considering the binding abilities of pregnenolone, DHEA/DHEA-sulfate (DHEA-S), progesterone, and testosterone to sigma-1 receptors, and of DHEA-S and progesterone to GABAA receptors, these receptors may be a possible link between neurosteroids and neuropsychiatric disorders (Hashimoto, 2013).

Altered mental conditions during premenstrual period

Sex hormones are widely known to influence mental conditions. Many women with existing psychiatric disorders complain of worse mental symptoms before menstruation and experience various physical and mental symptoms of premenstrual syndrome. Some women with PMS show severe symptoms and are psychiatrically diagnosed with PMDD under the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Steiner, 2000). From the latter luteal phase to the just beginning of menstruation patients with PMDD show various mental symptoms such as depressive mood, anxiety, irritability, and insomnia. The levels of estrogen and progesterone drastically alter during the same period, suggesting that the alteration of sex hormones levels may be associated with the pathology of PMDD. Administering progesterone increases the reactivity of the amygdala in women with no symptoms during the follicular phase (van Wingen et al., 2008) and causes various physical and mental symptoms in postmenopausal women (Hammarback et al., 1985; Magos et al., 1986), suggesting that progesterone induces various psychiatric symptoms in women. However, the direct association between the level of progesterone and PMS/PMDD has not been confirmed (Rubinow et al., 1988; Schmidt et al., 1991). Patients with PMS/PMDD may be vulnerable to the fluctuation of the levels of estrogen and/or progesterone. Some reports using acoustic startle response or prepulse inhibition have shown that the response to the fluctuation of sex hormones differs between healthy women and patients with PMDD (Kask et al., 2008). Animal studies have suggested that the alterations of the level of estrogen/progesterone are positively associated with aggression (Ho et al., 2001) and the depressive trend (Schneider and Popik, 2007).

Altered mental conditions during postpartum period

Both estrogen and progesterone levels increase during pregnancy, and abruptly decrease after delivery. A few days after childbirth, many women show mild depressive mood, tearfulness, anxiety, irritability, dysphoria, and insomnia; generally referred to as "maternity blues" and considered to be a transient psychological

response (Newport et al., 2002). Maternity blues is also a risk factor for depression and anxiety disorder within 3 months after delivery (Reck et al., 2009). Psychiatric disorders including depression are well known to appear frequently during the perinatal period, and estrogen and progesterone are suggested to be involved with the development of postnatal depression (Bloch et al., 2000). Freeman et al. (2002) have reported that 67% of women with bipolar disorder experience a postpartum mood episode, emphasizing the problem of the relapse and recurrence of a mood episode. Postpartum psychosis is a rare psychiatric disease characterized by hallucinations, delusions, mood swing, etc (Brockington et al., 1981). A lower blood concentration of estradiol is observed in patients of postnatal psychosis compared to normal controls, therefore the administration of estradiol could be effective to patients who are resistant to neuroleptic medications (Ahokas et al., 2000). Moreover transdermal estrogen replacement therapy has been reported to be an effective treatment of severe postnatal depression (Gregoire et al., 1996).

Depression during the menopausal transition

Sex hormonal changes and the estrous cycle become gradually irregular during menopausal transition, consequently causing climacteric syndromes including such physical symptoms as vasomotor symptoms (hot flashes and night sweat), and vaginal dryness, and mental symptoms such as depression and irritability (Anon, 2005). A controversial issue is that the risk for depression may be high during the periods of premenopausal, perimenopausal, and/or postmenopausal. Women with a history of PMS have been reported to be susceptible to depression during the perimenopausal period (Freeman et al., 2004b). Woods and Mitchell (1996) have suggested the association between consistent depressive symptoms during the perimenopausal period and a history of postpartum depressive symptoms. Morrison et al. (2004) have reported that hormonal replacement therapy is effective for women with postpartum and premenopausal depression, but not for women with postmenopausal depression. The mechanism of the pathogenesis of psychiatric disorders during menopausal transition remains controversial possibly because of the few studies utilizing rigorous measurements such as The Structured Clinical Interview for DSM-IV (SCID). By utilizing the SCID for women without a current or past history of depression, Schmidt et al. (2004) have revealed that the risk for onset of depression is 14 times as high as for a 31-year premenopausal period of time. In the Study of Women's Health Across the Nation (SWAN), Bromberger et al. (2009) initially reported no association between the perimenopausal period and the risk for onset of depression diagnosed by SCID, but afterward, they have reported that the risk of major depression is greater for women during and immediately after the menopausal transition than for women during the premenopausal period (Bromberger et al., 2011). A higher blood concentration of testosterone is found in untreated premenopausal women with depression compared to normal controls (Baischer et al., 1995). A lower blood concentration of estradiol during the follicular phase and a shorter half-life of luteinizing hormone during both the follicular and luteal phase are found in premenopausal women with depression (Young et al., 2000). There is a significant negative correlation between the blood concentration of estradiol and Hamilton depression scores in depressed premenopausal women (Baischer et al., 1995). During transition to the menopausal period, women suffering from depressive symptoms increase, and contrastively, these symptoms decrease after menopause (Freeman et al., 2004a). Transdermal estrogen replacement therapy has been known to be effective for patients with depressive symptoms during the perimenopausal period (Soares et al., 2001). In this way, there are various arguments about perimenopausal depression. However, it's certain that sex hormones changes and also consequent stresses occur during the perimenopausal period, and this with addition of factors such as aging, the increase of physical illness, the changing role of women in society and family, and so on, the risk for depression during perimenopausal period may increase. The association between the estrous cycle and depression is probably bidirectional and interactive, making it difficult to understand the mechanism of the pathogenesis of perimenopausal. A history of major depression may be correlated with early onset of menopause due to an early diminution of ovarian function (Harlow et al., 2003). Studies in animal experiments frequently adopt an ovariectomy model, but surgically induced menopause after ovariectomy cannot be always identified with natural menopause. These facts make it difficult to research the mental condition during perimenopausal period.

Other psychiatric disorders associated with sex differences

Sex hormonal differences may also be related to some other psychiatric disorders; for example, autism including adult Autism Spectrum Disorders (ASD) is more common in men than women (Brugha et al., 2011). Schizophrenia occurs with equal rates in both sexes, but it has been widely known that schizophrenia in women occurs in older ages and female patients with schizophrenia have better prognoses than men with schizophrenia. The plasma level of testosterone in male patients with bipolar disorder has been reported to be positively correlated with the number of manic episodes and the number of suicide attempts (Sher et al., 2012). These reports suggest the importance role of sex hormones in psychiatric disorders. So far, a great number of studies have been conducted with the traditional view of sex hormones acting mainly on neurons and neurotransmitters, but a few recent studies have highlighted the association between the sex hormones and microglia.

SEX HORMONES AND MICROGLIA

The relationship between sex hormones and microglia has not been well understood. However, some studies have recently presented interesting facts about the relationship.

Estrogen

Several investigations suggest that some sex hormones have anti-neuroinflammatory and neuroprotective activities via microglia. *In vitro* studies using rat microglial cells have revealed that estradiol inhibits phagocytosis, the production of ROS (Bruce-Keller et al., 2000), and LPS-induced pro-inflammatory molecules such as inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2), and matrix metalloproteinase-9 (MMP-9) (Vegeto et al., 2001). The expression of rat microglial neuroinflammatory genes by the immunosuppressive functions of estradiol is mediated via estrogen receptor alpha (ERα) and beta (ERβ) (Sarvari et al., 2011).

It is important to investigate the response of microglia to various pro-inflammatory stimuli from the perspective of age and sex differences. Morphology and numbers of microglia alter during developmental stages. For instance, there are more microglia derived from male postnatal rats during an early stage of development than female, and the shapes of microglia derived from female postnatal rats during later developmental stages tend to be amoeboid type (Schwarz and Bilbo, 2012). The distinct microglial expression of genes of cytokines, chemokines, and receptors are attributed to age and sex differences (Schwarz and Bilbo, 2012). Similarly, expression of P2 purinergic receptors varies with age and sex in murine microglia (Crain et al., 2009). Estradiol has proved to play distinct roles depending on the situation. For instance, in female neonatal rats, microglia express more IL-1β with estradiol *in vitro*, that is to say, estradiol exerts a pro-inflammatory effect on female microglia, and on the contrary, estradiol has an anti-inflammatory effect on male microglia. Moreover, in adult rats, estradiol has pro-inflammatory effects without sex differences *ex vivo* (Loram et al., 2012). Chronic administration of estradiol *in vivo* results in the activation of microglia derived from the female hippocampus inducing IL-1β expression stimulated with LPS (Loram et al., 2012). These reports have suggested that estradiol plays different roles in modulating microglia depending on age and sex.

A remarkable function of estrogen receptor on microglia has recently been elucidated. 5-androsten-3b,17b-diol (ADIOL), converted from dehydroepiandrosterone by 17b-hydroxysteroid dehydrogenase type 14 (HSD17B14), has been proved to suppress inflammatory responses of microglia and astrocytes by the recruitment of C-terminal binding protein (CtBP) through an ERβ dependent mechanism (ADIOL/ERβ/CtBP transrepression pathway in microglia). Moreover, through this pathway, the administration of ADIOL has prevented and inhibited experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) (Saijo et al., 2011).

Progesterone/testosterone

Progesterone is widely known to play an important role in inflammation in the peripheral organs and the CNS (Stein, 2001; Brinton et al., 2008; Challis et al., 2009). Progesterone and testosterone also regulate microglial functions. Progesterone antagonizes estradiol in synaptic remodeling, which is mediated by a progesterone receptor on microglia in rats (Wong et al., 2009). Brain injury increases the expression of aromatase that metabolizes testosterone to estradiol, and the administration of testosterone reduces the number of astrocytes and microglia in the lesion (Barreto et al., 2007).

Prolactin

Prolactin is a sex-related hormone. Prolactin is mainly synthesized by and secreted from the anterior lobe of pituitary gland. The secretion of prolactin is mediated by prolactin inhibiting factors, predominantly dopamine (Ben-Jonathan and Hnasko, 2001), and prolactin releasing factors such as TRH and oxytocin (Egli et al., 2010). Other factors stimulating the secretion of prolactin include suckling and various stresses (Otte et al., 2002; Lennartsson and Jonsdottir, 2011). Prolactin has multiple functions such as lactation, maintenance of gestation, mediating maternal behavior (Freeman et al., 2000), and has been suggested to have anxiolytic and anti-stress effects on the evidence of an experiment with rats (Torner et al., 2001).

Möderscheim et al. have just reported the first possible correlation between prolactin and microglia. They have shown that unilateral hypoxic ischemic injury in rats made astrocytes and reactive microglia strongly prolactin immunoreactive, and prolactin immunoreactivity was increased in the affected cortex prolactin. On the other hand, prolactin and prolactin receptors were decreased on penumbral neurons. In this report, prolactin has been proved to be proliferative for astrocytes *in vitro*, but it has been uncertain whether prolactin has any effect on microglia (Möderscheim et al., 2007).

CLINICAL IMPLICATIONS

As stated above, we are just in the early stages of digging up the relationship between sex hormones and microglia. The role of sex hormones in neuropsychiatric disorders such as MDD, PMDD, and postnatal depression is being gradually clarified. The existence of sex differences in a variety of physical diseases has also been widely known, and sex hormones play crucial roles in the pathophysiology of autoimmune diseases, such as MS, systemic lupus erythematosus, and rheumatoid arthritis which are reported to be more prevalent in women than in men (Duquette et al., 1992; Ostensen et al., 2011). In contrast to this prevalence, women with MS have better prognoses than men, and men with MS show more progressive disease course and more severe gray matter atrophy (Voskuhl and Gold, 2012). Both the incidence and activity of MS decrease during the latter half of pregnancy (Confavreux et al., 1998), and increase in the postpartum period (Alonso et al., 2005; Finkelsztejn et al., 2011). In addition, it has been reported that the experience of more pregnancies increases the rate of MS onset (Ponsonby et al., 2012). These reports imply a significant role for sex hormones in the pathogenesis of MS. It is widely know that microglia also play an important role in MS (Jack et al., 2005). Regarding the pathogenesis of some psychiatric diseases involved with sex differences, the interactive network where various psychiatric diseases interact with sex hormones, the fluctuation of sex hormones, and the vulnerability to the fluctuation may be involved. Neurons have been traditionally considered to be the main player in such interactive networks, which have been studied with an emphasis on various neurotransmitters, for example, glutamate (Batra et al., 2008), serotonin (Roca et al., 2002; Hiroi et al., 2006; Dhingra et al., 2007; Landen et al., 2007; Brown et al., 2009), and GABA (Epperson et al., 2002). We hypothesize that not only neurons but also microglia may play an important role as a connector in the network. Sex hormones such as progesterone may develop and aggravate psychiatric disorders via microglial inflammatory responses through their receptors. On the other hand, sex hormones such as estrogen and androgen suppress microglial inflammatory responses through their receptors, which may induce therapeutic effects in psychiatric disorders (**Figure 2**). In order to profoundly understand the relationship between sex hormones, psychiatric disorders, and microglia, it is necessary to investigate how sex hormones and microglia directly interact, and also the microglial behavior in the above-mentioned networks.

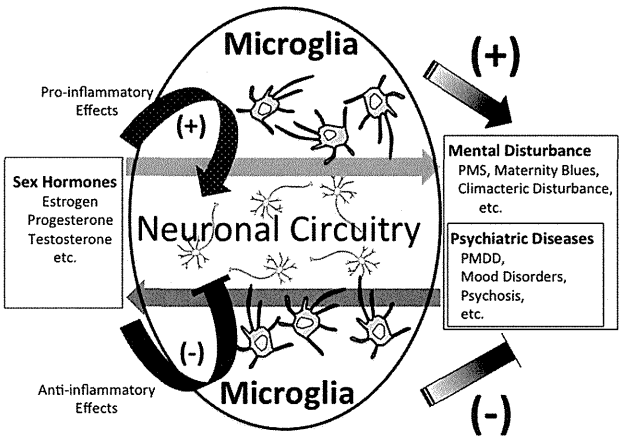

FIGURE 2 | Possible link between sex hormones and microglia.

OXYTOCIN

Oxytocin is secreted by the posterior pituitary gland and synthesized in the paraventricular and supraoptic of the hypothalamus (Moos et al., 1984). Oxytocin, which is released within the supraoptic nucleus of hypothalamus, exerts positive feedback on the production and release of oxytocin into the peripheral circulation and the CNS (Neumann et al., 1994, 1996). Oxytocin has been classically known as the hormone that is related to uterine contraction, lactation, and the regulation of atrial natriuretic peptide (ANP) release in the cardiovascular system (Jankowski et al., 1998, 2000). Besides, oxytocin is released into the CNS and facilitates maternal nurturing behavior, the bondage between a mother and child, and affiliative behavior and social cognition in both sexes (Ross and Young, 2009). Recently, the intranasal administration of oxytocin in humans proved that oxytocin is a possible prosocial hormone that increases trust (Kosfeld et al., 2005). In addition to these functions, oxytocin is associated with stress-suppression effects. In rats, the administration of a SSRI has shown to increase the plasma concentration of oxytocin (Uvnas-Moberg et al., 1999). In humans, the intranasal administration of oxytocin has been reported to exert an anxiolytic effect on healthy men, and reduce salivary concentration of cortisol in combination with social support in response to stress (Heinrichs et al., 2003). It is controversial whether the plasma concentration of oxytocin is low in patients with depression, but the negative correlation between plasma oxytocin concentration and scores of Hamilton Depression Rating Scale (HDRS) and the State-Trait Anxiety Inventory (STAI)/A-trait among depressed patients has been reported (Scantamburlo et al., 2007). A human postmortem study has revealed that the number of oxytocin neurons increases in the PVN of the hypothalamus in patients with MDD or bipolar disorder (Purba et al., 1996). These reports suggest various functions of oxytocin in human mental activities.

OXYTOCIN AND AUTISM

Recent studies have suggested that oxytocin is probably relevant to psychiatric disorders, especially autism. The intravenous administration of oxytocin to autistic patients increases retention of social cognition (Hollander et al., 2007), on the other hand, the intranasal administration of oxytocin ameliorates emotional cognition. Oxytocin inhalation strengthens social interactions, induces more adaptable social behavior, and enhances feelings of trust and preference (Andari et al., 2010). However, the underlying mechanism explaining how oxytocin exerts these effects on autism has not been sufficiently clarified. The relationship between autism and a variation in the CD38 gene has been reported (Munesue et al., 2010). CD38, a multi-functional molecule, is involved in the secretion of oxytocin. Amelioration of neural processing of social stimuli by the intranasal administration of oxytocin depends on a CD38 gene variant in healthy volunteers (Sauer et al., 2012). Female CD38 knockout mice defect in maternal nurturing, and male knockout mice impair prosocial behavior (Jin et al., 2007). Observed in oxytocin receptor knockout mice, the intracerebroventricular administration of oxytocin and vasopressin (AVP) ameliorates impaired cognitive flexibility, social deficits, increased aggression, and seizure susceptibility, which is mediated by an AVP receptor (V1a) (Sala et al., 2011). These reports have suggested that oxytocin has a variety of psychotropic, prosocial, and subsequent therapeutic effects in animal models of autistic disorders, but in humans with autism, whether oxytocin has therapeutic effects have not been sufficiently validated yet so far, and needs to be further investigated.

AUTISM AND MICROGLIA

Microglia may play an important role in autism. Rett syndrome is classified as an ASD, mainly caused by *X*-linked methyl-CpG-binding protein 2 (MeCP2) gene mutations (Amir et al., 1999). MeCP2 gene is expressed predominantly in neurons in the CNS and prompts neuronal differentiation (Tsujimura et al., 2009), indicating that the etiology of Rett syndrome mainly caused by MeCP2 gene mutations is of neuronal origin (Chen et al., 2001). On the other hand, it has been recently suggested that glial cells such as astrocytes and microglia are also involved with the pathology of Rett syndrome (Maezawa et al., 2009; Maezawa and Jin, 2010). In a mouse model of Rett syndrome, transplantation of wild-type bone marrow resulted in wild-type microglial engraftment, which showed significant improvements in autistic symptoms (Derecki et al., 2012). A postmortem study on the brains of autistic patients revealed an increase of microglia in the fronto-insular cortex and visual cortex (Tetreault et al., 2012). Moreover, a spatial pattern analysis of the postmortem brains of autistic patients indicated the abnormal interaction between microglia and neurons especially in the dorsolateral prefrontal cortex (Morgan et al., 2012). These postmortem studies of child autism have suggested that the inflammatory hypotheses of psychiatric disorders are, to some extent, rooted in unique periods of vulnerability when an inflammatory assault permanently re-wires the brain for the expression of these neurodevelopmental disorders. A recent PET study has shown that excessive microglial activation in multiple brain regions has been observed in young adult subjects with ASD (Suzuki et al., 2013). These reports suggest that microglial activation during adulthood may moderate the disease symptomatology of autism, while it is unclear whether microglial activation has lasted from childhood or not.

CD38, OXYTOCIN, AND MICROGLIA

To the best of our knowledge, there are only a few studies about the relationship between CD38, oxytocin, and microglia. CD38, a multi-functional molecule involved in oxytocin secretion, has some effects on microglia. Firstly, Mayo et al. (2008) have reported that CD38 generates cyclic-adenosine diphosphate ribose (cADPR) from nicotinamide adenine dinucleotide (NAD) as a substrate. CD38, via cADPR as a second messenger, increases intracellular calcium concentration and helps to promote microglial activation and activation-induced cell death (AICD) in primary mouse microglia induced by LPS/IFN-γ treatment. Secondly, Ma et al. (2012) have reported that siRNA for CD38 gene silencing promotes caspase 3-dependent apoptosis, which decreases survival of BV2 microglia cells. Oxytocin also interacts with microglia. Karelina et al. (2011) have reported that oxytocin suppresses LPS-induced expression of MHC class II dose-dependently in primary mouse microglia.

PERSPECTIVE

Microglia and CD38 may possibly play crucial roles in the pathophysiology and treatment of autism. Oxytocin has a variety of effects on autistic patients (Hollander et al., 2007; Andari et al., 2010; Sauer et al., 2012) and stress-suppression effects as mentioned above, which implies a yet to be fully comprehended relationship between oxytocin and microglia. However, there have been so few reports about the relationship that we can only be certain of the following two points; one, that unknown factors secreted by microglia inhibit the oxytocin receptor binding in astrocytes (Mittaud et al., 2002), and two, that macrophages, close-related with microglia, express oxytocin receptors and are inhibited by oxytocin from secreting LPS-induced Interleukin-6 and decreasing NADPH-dependent superoxide activity (Szeto et al., 2008). A recently published *in vitro* study also showed pro-inflammatory effects of oxytocin on activated macrophage (Oliveira-Pelegrin et al., 2013). It is unclear and yet to be investigated whether microglia could be involved with production and release of oxytocin via direct or indirect action on the hypothalamus or the pituitary gland, and the interaction between oxytocin and microglia should be clarified in the future. In addition, to our knowledge, we are not aware whether the intranasal administration of oxytocin is physiologically comparable to hormonal levels released by microglia or not, and this aspect should be investigated in future research.

FINAL REMARKS; MISSING AND POSSIBLE LINKS BETWEEN NEUROENDOCRINE FACTORS, NEUROPSYCHIATRIC DISORDERS, AND MICROGLIA

Neuropsychiatric disorders have been mainly considered as the consequence of abnormal conditions in neural circuitry. Many neuropsychiatric disorders are widely known to be involved with endocrine diseases, however the correlation has not been well understood. Microglia have been suggested to have several important roles in neuropsychiatric disorders. We have introduced up-to-date knowledge on the interaction between neuroendocrine factors, neuropsychiatric disorders, and microglia; especially highlighting the hormones; CRH, glucocorticoids, estradiol, and oxytocin. We believe that some microglial roles may be revealed by further research efforts in line with our proposed hypothesis. Finally, we have shown some possible mechanisms and missing links to understand the interaction between neuroendocrine factors, neuropsychiatric disorders, and microglia.

POSSIBLE MECHANISM

Strong psychological stress and/or physical stress induce neuroendocrine hormones such as CRH in the brain, which may lead to microglial activation. Especially during childhood, microglial over-activation due to severe stress may formulate maladaptive neuronal networks due to a microglial impacted synaptic pruning. A recent study has shown the novel role of NO as an activity-dependent regulator of target neuron intrinsic excitability, transforming synaptic integration and information transmission (Steinert et al., 2011), and we suppose that microglia-derived NO may contribute to this phenomenon. The above highlighted maladaptive synaptic formulations themselves may induce psychiatric conditions such as autistic syndrome. On the other hand, when these maladaptations are not severe, small pathologies may be reserved as vulnerabilities for psychiatric disorders such as schizophrenia and depression in later life. Stressful life events during adolescent periods and adulthood, as a secondary hit, may also activate the above-mentioned maladaptive cascades of neuroendocrine-microglia-neuronal networks, which may induce psychiatric conditions. Based on evidence that we have introduced, we hypothesize that microglia and microglia-derived mediators such as inflammatory cytokines and free radicals may be a bridging player between our highlighted neuroendocrine factors and psychiatric disorders (Steiner et al., 2011; Maes et al., 2012) (**Figure 3**).

MISSING AND POSSIBLE LINK BETWEEN HPA AND HPG AXIS

Endocrine systems such as the HPA axis and the HPG axis communicates with the other, and these mutual interactions play important roles in neuropsychiatric disorders (Tsigos and Chrousos, 2002; Ochedalski et al., 2007; Pittman, 2011; Schwarz and Bilbo, 2012). Many reports have indicated that the HPA axis and HPG axis interact with each other in various ways. Concentration of

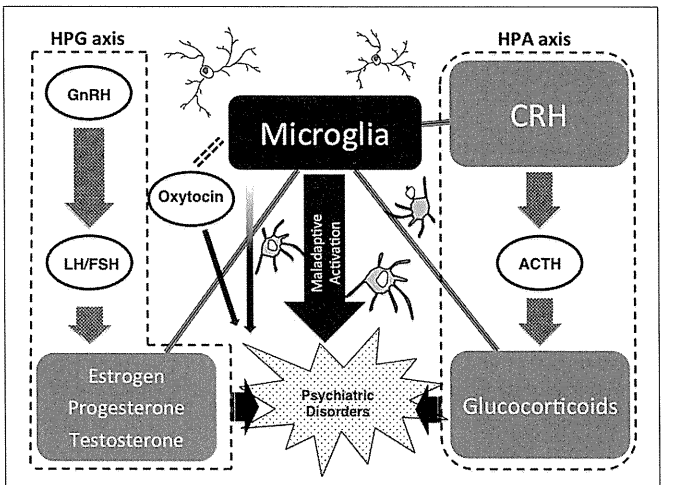

FIGURE 3 | Possible link between neuroendocrine factors, neuropsychiatric disorders, and microglia.

cortisol in plasma has been highly maintained during the third trimester of normal pregnancy (Nolten et al., 1980), probably due to high concentration of estrogen and progesterone (Bloch et al., 2003). The concentration of CRH decreases due to the negative feedback system during the third trimester of pregnancy, and the low concentration of CRH remains for a period of time and causes the hypoactivity of the HPA axis after delivery. In patients with postpartum depression, this period of HPA axis hypoactivity is maintained longer than in healthy puerperant women (Magiakou et al., 1996). Cortisol level of patients with postpartum depression does not respond to the administration of ACTH, suggesting the HPA axis dysregulation during the postpartum period (Jolley et al., 2007). Bloch et al. have reported an abnormal response to the alteration of sex hormones in patients with postpartum depression. They have shown the increased reactivity of cortisol to the administration of CRH in euthymic patients with a past history of postpartum depression (Bloch et al., 2005), and that the administration of a high dose sex hormone followed by abrupt withdrawal induce depressive symptoms (Bloch et al., 2000). Thus, the HPA axis may be involved with the pathogenesis of postpartum depression. HPA axis activation has been known to suppress the HPG axis (Petraglia et al., 1987; Polkowska and Przekop, 1997). It is necessary to investigate the yet to be clarified microglial role in the dynamic interactions between the HPA and HPG axis.

POSSIBLE EXAMPLE

It is epidemiologically well known that suicide has a higher prevalence in men, and is lower in women. This review paper has indicated that progesterone/testosterone (so-called male hormones) may induce maladaptive microglial activation, and estradiol (so-called female hormone) may suppress microglial inflammatory reactions. A significant number of studies suggest that testosterone is associated with aggression, and aggression is positively linked to suicidal behaviors (Sher, 2012). In addition, a recent postmortem study has shown the positive link between microglial activation and suicide (Steiner et al., 2006, 2008). Summing up such cellular, clinical, and epidemiological evidence, we have proposed a possible mechanism – that male hormones may easily induce suicidal acts by hormone-induced microglial activation, and estradiol may prevent suicidal behaviors by suppressing microglial activation.

LIMITATIONS AND FUTURE PERSPECTIVE

Endocrine factors such as steroid hormones may interact with microglia to produce inflammation-dependent neuropsychiatric conditions. If so, what signals allow for discrimination between schizophrenia, autism, and depression? If microglia are the common link between neuroendocrine systems and neuropsychiatric disorders, then what differentiates the role of microglia in these disorders? These research questions have yet to be clarified and should be focused on in future research. As reviewed above, each hormone affects microglia differently in different brain regions, which might be a cue to explore the dark-side mechanism. A growing body of evidence has revealed that abnormalities of specific brain regions contribute to each neuropsychiatric disorder and each psychiatric condition. We suppose that the location of the microglia-induced neuropathology may determine the specific psychiatric abnormality. On the other hand, not only microglia but also other brain cells such as brain macrophage, T cells, and astrocytes are known to release cytokines, chemokines, and free radicals. Therefore, these alternative pathways may also be important in the process.

Future investigations to clarify the correlation between neuroendocrine factors and microglia may contribute to a novel understanding of the pathophysiology of neuropsychiatric disorders and the development of effective treatment strategies.

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Neuron-glia interaction as a possible glue to translate the mind-brain gap: a novel multi-dimensional approach toward psychology and psychiatry

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Neurons and synapses have long been the dominant focus of neuroscience, thus the pathophysiology of psychiatric disorders has come to be understood within the neuronal doctrine. However, the majority of cells in the brain are not neurons but glial cells including astrocytes, oligodendrocytes, and microglia. Traditionally, neuroscientists regarded glial functions as simply providing physical support and maintenance for neurons. Thus, in this limited role glia had been long ignored. Recently, glial functions have been gradually investigated, and increasing evidence has suggested that glial cells perform important roles in various brain functions. Digging up the glial functions and further understanding of these crucial cells, and the interaction between neurons and glia may shed new light on clarifying many unknown aspects including the mind-brain gap, and conscious-unconscious relationships. We briefly review the current situation of glial research in the field, and propose a novel translational research with a multi-dimensional model, combining various experimental approaches such as animal studies, *in vitro* & *in vivo* neuron-glia studies, a variety of human brain imaging investigations, and psychometric assessments.

Keywords: translational research, neuron-glia interaction, mind-brain gap, unconscious, neuropsychoanalysis

INTRODUCTION

Neurons and synapses have long been the dominant focus of neuroscience, thus the pathophysiology of psychiatric disorders has come to be understood within the neuronal doctrine. However, the majority of cells in the brain are not neurons but glial cells including astrocytes, oligodendrocytes, and microglia. Traditionally, neuroscientists regarded glial functions as simply providing physical support and maintenance for neurons. Thus, in this limited role glia had been long ignored (1). Recently, glial functions have been gradually investigated, and increasing evidence has suggested that glial cells perform important roles in various brain functions. Digging up the glial functions and further understanding of these crucial cells, and the interaction between neurons and glia may shed new light on clarifying many unknown aspects including the mind-brain gap, and conscious-unconscious relationships. In addition, glial pathophysiology may explain the possible implications for the pathogenesis of major psychiatric disorders. The complexity of these aspects has yet to be well investigated. To explore these physiological and pathological aspects, novel translational methods should be applied with a multi-dimensional approach. Herein, we will briefly review the current situation of glial research in the field, and propose a novel translational research with a multi-dimensional model, combining various experimental approaches such as animal studies, *in vitro* & *in vivo* neuron-glia studies, a variety of human brain imaging investigations, and psychological/psychiatric assessments.

GLIAL ROLES AND PATHOLOGY IN PSYCHIATRIC DISORDERS

Recent biological studies have been revealing the important roles of glial cells in the process of neuropsychiatric disorders.

ASTROCYTES

Astrocytes are the most prevalent cell type in human brain and contribute to the homeostasis of the brain by regulation of neuronal metabolism, modulation of CNS inflammation, and direct/indirect synaptic transmission such as MNDA receptors (2, 3). Astrocyte dysfunction has been critical for various neurological disorders (4). Recent studies have shown abnormal expression of glial fibrillary acid protein (GFAP) – a prototypical marker of astrocyte – in postmortem brain of patients with schizophrenia and major affective disorders (5–7). In addition, recent rodent studies have suggested that astrocytes modulate anxious and depressive behaviors (8, 9). On the other hand, direct modulating effects of antidepressants have also been revealed (10–13). Thus, astrocytes have been supposed to be a novel therapeutic target against various psychiatric disorders such as major affective disorders and bipolar disorders (14, 15).

OLIGODENDROCYTES

Oligodendrocytes contribute to brain development and homeostasis in the brain by formulating myelin around axons, supporting neuronal networks in the brain. Recently, novel oligodendrocyte functions have been revealed such as monitoring neuronal

activities via myelin-forming oligodendrocytes (16) and modulating the conduction velocity of action potentials along axons in the rat hippocampus (17). Dysfunctions of oligodendrocytes have been indicated in psychiatric disorders, especially schizophrenia and major affective disorders, from a series of genetic studies (18, 19), postmortem studies (20–22), and diffusion tensor imaging (DTI) studies (23–27). A novel animal model of schizophrenia has been developed by treating a copper chelator, which induces oligodendrocyte dysfunction and white matter abnormality as demyelination and schizophrenia-related behaviors (28, 29). Cuprizone caused marked behavioral changes (working memory deficit) indicated by the results of Y-maze task, which showed an increase in the number of arm entries and a decrease in alternation behavior. These cuprizone-induced behavioral changes were effectively prevented by chronic administration of quetiapine, an atypical antipsychotic, which also diminished demyelination (28). On the other hand, recent rodent studies have revealed the interaction between oligodendrocyte dysfunction and social behaviors. Makinodan et al. reported that oligodendrocyte dysfunction is formed by early-period social isolation and this maladaptive environment induces working memory deficit associated with prefrontal cortex (PFC) function in later life (30). Liu et al. reported that protracted social isolation of adult mice induces behavioral, transcriptional, and ultrastructural changes in oligodendrocytes of the PFC and impairs adult myelination (31).

MICROGLIA

Microglia are unique glial cells of mesodermal origin in the brain that act as "brain macrophage"; immunological/inflammatory players by moving around and releasing cytokines and free radicals (32, 33). Thus, microglia have proved to play important roles in various brain pathologies such as neurodegenerative diseases and neuropathic pain via inducing inflammation and oxidative stress (34–36). Recently, microglia have been revealed to have direct contact with synapses and have proved to play crucial roles in neuronal development through synaptic pruning (37–39). Postmortem studies have shown microglial activation in the brain of patients with schizophrenia and major affective disorders, especially suicide victims (40–42). In addition, positron emission tomography (PET) imaging studies using the peripheral benzodiazepine receptor bindings has shown that microglia are activated in patients with schizophrenia (43–45) and autism (46). On the other hand, minocycline, an antibiotic with inhibitory effects on microglial cells, has been reported to have therapeutic effects on schizophrenia and unipolar psychotic depression (47–49). In addition, rodent *in vitro* studies have proved the novel effect of psychotropic drugs (atypical antipsychotics such as risperidone and aripiprazole, and antidepressants such as paroxetine and sertraline, both selective serotonin reuptake inhibitors) directly on microglia by suppressing release of inflammatory cytokines and free radicals (50–54). Thus, microglia are suggested to play key roles in psychiatric disorders (53, 55, 56).

In the brain, neurons, astrocytes, oligodendrocytes, and microglia are mutually communicating with each other, by direct-contacting or via neurotransmitters and other various small molecules (57), and dysfunction of neuron-glia communication may induce pathological conditions not only in neurodegenerative diseases (58) but also in psychiatric conditions such as psychosis, depression, and anxiety. The above-mentioned recent findings strongly suggest that glial cells contribute to psychiatric disorders, while the underlying mechanisms have not been clarified.

POSSIBLE GLIAL ROLES IN HUMAN MENTAL FUNCTIONS

Until recently, the actual roles of glia in mental activities, especially for healthy humans, have not been investigated. As the first step to clarify this unexplored field, we have started to conduct a series of social decision-making experiments with healthy human subjects using minocycline, a microglial inhibitor (59–61). Healthy Japanese adult males made a monetary decision about whether or not to trust an anonymous partner after a 4-day oral administration of minocycline. Our first trial revealed that the minocycline group showed a positive correlation between their monetary score in trust game and their evaluation scores of others' trustworthiness in a questionnaire (Yamagishi's General Trust Scale), but surprisingly the placebo group did not (60). It would be rational to consider the monetary and questionnaire score to be positively correlated because both scores measure the other's trustworthiness, but there was no positive correlation with the placebo group. The questionnaire is measuring only conscious-level decision-making, on the other hand the monetary score is measuring the final decision-making affected by not only the conscious but also the unconscious; suggesting that some unconscious noisy factors seem to be affecting the placebo group. Treatment with minocycline, a microglial inhibitor, has shown the positive correlation. Therefore, this first trial has indicated that microglial activation may cause "unconscious noises" against appropriate social decision-making, and inhibiting microglial activity may reduce such noise (60). In a next trial with larger samples, we additionally measured the effects of anxiety and personality as candidates for "noise" factors, by using Temperament and Character Inventory (TCI) and State-Trait Anxiety Inventory (STAI) (59). The monetary score in trust game was significantly lower in the minocycline group. Interestingly, participants' ways of decision-making were significantly shifted; certain personality traits (cooperativeness, reward dependence, and self-directedness) proved to be the main modulating factors of decision-making in the placebo group, on the other hand the minocycline group was mainly modulated by state anxiety and trustworthiness. Our results of the second trial suggest that minocycline led to more situation-oriented decision-making, possibly by suppressing the effects of personality traits, and furthermore that personality and social behaviors might be modulated by microglia. Interestingly, cooperativeness has proved to be the most influential factor in the process of decision-making in the placebo group of Japanese participants (59). It is widely known that cooperativeness and cooperative behaviors have been highly respected and emphasized aspects in Japanese society. Thus, of course, these aspects are ingrained during childhood by various sociocultural experiences within family relationships, schools, and other areas of society in Japan. Early-life events may activate human microglia, establish a certain neurosynaptic connection, and this formation may determine personality and personality-oriented social behaviors in later life (59, 62). If these experiments are conducted in other countries with different sociocultural backgrounds, other personality traits may be identified.

In addition, we have recently reported a possible outcome that minocycline, a microglial inhibitor, also reduces the risk of the "honey trap" during economic exchanges between males × females (61). Males tend to cooperate with physically attractive females without careful evaluation of their trustworthiness. In our experiment, young healthy male participants made risky choices (whether or not to trust female partners, identified only by photograph, who had decided in advance to exploit the male participants). The results show that trusting behavior in male participants significantly increased in relation to the perceived attractiveness of the female partner, but attractiveness did not impact trusting behavior in the minocycline group (61). These novel effects of minocycline may highlight the unknown roles microglia play in deeper human mental activities; microglia may modulate our unconscious drives in various social settings. The above-mentioned findings shed new light on the dark side of microglial social/mental functions in humans, especially highlighting the role of microglia for the unconscious. In the same way that Sigmund Freud, the founder of psychoanalysis, proposed that our behaviors must be controlled by the unconscious world, microglia may unconsciously control our behaviors. How do microglia act as fundamental mediators between the conscious and the unconscious world? What do neurobiological mechanisms justify their eventual role in bridging the gap between neuroscience and psychoanalysis? Answers to the above questions are not yet clear, but we have recently proposed a hypothesis creating a link between Freud's unconscious drives such as the death drive and microglial activation (62). For example, microglial maladaptive over-activation in a certain brain region may activate human aggressive behaviors as a result of destructive drives [For the details, please see our recent article; Ref. (62)]. In the brain, not only microglia but also other glia such as astrocytes and oligodendrocytes exist, thus complicated neuron-glia interactions may modulate our mental activities including the unconscious (**Figure 1**). Further research should be applied to clarify these unresolved questions.

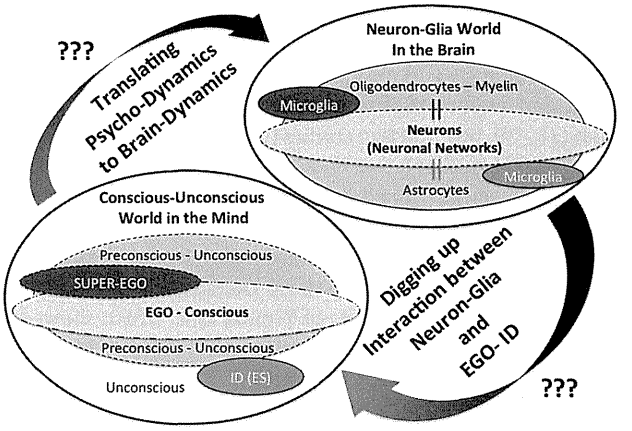

FIGURE 1 | The mind-brain gap from a novel glial neuropsychoanalytic perspective. The interaction between the mind and the brain has not been well understood. Freud, the founder of psychoanalysis, proposed the conception of mind structure models consisting of the following three components: *the ID* (unconscious/instinctual drives), *the EGO* (the exclusive apparatus of the conscious mind), and *the SUPER-EGO* (which represses *the id* in order to avoid any disruptions of rational thought). The existence and the significances of these mental components may be explained by future understandings of the neuron-glia interactions. The hypothetical interaction between the ID (unconscious drives) and microglia has already been proposed in our recent theoretical paper (62).

After Freud's theory of unconscious roles in behaviors which was initially identified in the 1980s (63), Pribram and his colleagues have developed this theory in terms of a better articulated model of neural computation (64, 65). In addition, recent neuropsychoanalytic movements have been updating Freud's theory with modern sophisticated methods of cognitive neuroscience (66–72). Thus, these recent approaches have been revealing the underlying mechanisms of implicit processing in a variety of information-processes including the social processes using rodent experiments. At present, the link underlying mechanisms between neuron-glia interactions and the conscious-unconscious relationship is largely unsolved, and few experimental methods have been developed to test these unknown brain mechanisms at either the microscopic or macroscopic level. Unconscious processing needs to be given a greater focus in terms of brain mechanisms. One possible solution is the novel ontogenetic approach; called "optogenetics" (73–76). Optogenetics is a revolutionary technique involving taking a light-activated gene (called a channel rhodopsin) targeted into a single neuron type. This technique enables to clarify direct interaction between activation of specific neuron in specific region by light and the resulting outcomes such as behaviors and emotional reactions at rodent level. A recent study has interestingly shown that activation of specific neurons in hippocampus produce a false memory in mice (77). Further technological developments in modulating glial cells by light and in activating both neurons and glial cells at the same time, by multiple fluorescent lights, may shed new light on resolving unknown roles of glia and neuron-glia interaction in behaviors and the conscious-unconscious. Functional roles and pathological contributions of astrocyte, oligodendrocyte, and/or microglia in conscious or unconscious processes have not been well understood, and we hypothesize that each cell may differently contribute to these physical and/or pathological processes in different brain regions such at the brainstem, limbic, or thalamocortical region, respectively. Future developments in optogenetics may clarify these unknown aspects.

LIMITATION AND FUTURE PERSPECTIVES OF NEURO-GLIA RESEARCH ON PSYCHOLOGY AND PSYCHIATRY

To explore the above-mentioned hypothesis, further translational research is needed. Several limitations should be made note of at the present stage. At first, rodent studies focusing on the unconscious are limiting. Even if the unconscious exists in rodents, it seems to be impossible to measure the unconscious in rodents devoid of human language capabilities. Therefore, to uncover the unconscious mechanisms, we have no alternative method except examining actual human subjects. We have no specific drugs to modulate glial cells utilized in human, and minocycline is reported to have other brain functions in addition to microglial inhibition (78, 79). On the other hand, some brain imaging techniques enable us to explore the unknown roles of glial cells such as DTI technique and PET imaging using the peripheral benzodiazepine receptor bindings, while the specificities of these imaging methods are not

at satisfactory levels (80). On the other hand, we can reconsider previous findings of brain imaging experiments. Functional MRI (fMRI) is a brain imaging procedure measuring brain activity by detecting associated changes in blood flow (81, 82). Outcomes of fMRI have long been believed to monitor solely neuronal activities, because cerebral blood flow and neuronal activation have been thought to be almost equivalent. However, not only neuronal activities but also glial activities, especially astrocyte activities, rely on cerebral blood flow. Therefore, at least to some extent, brain activities expressed by fMRI may be showing a part of glial activation. In addition, MR spectroscopy (MRS) is one of the novel imaging approaches to measure dynamic brain functions focusing on metabolomics including glia-related molecules. For example, myo-inositol, which can be measured by MRS, is regarded as a marker of astrocyte activity (83). These imaging methods and combination of these imaging techniques may shed new light on clarifying unknown roles of glia in psychiatric disorders (84, 85). For example, activated microglia-derived myelin damage has been indicated in the pathophysiology of schizophrenia by rodent experimental models (28, 29, 86, 87), while it is not confirmed in human subjects. Combination of human DTI and PET may clarify the mutual interaction between microglial activation and myelin damage in schizophrenia patients. On the other hand, connectivity of each brain region has been important in the understanding of the roles of brain functions from the era of Hughlings Jackson. fMRI studies have revealed the importance of these aspects (88, 89), and the recent development of DTI is showing us the significance of more complicated brain networks focusing on not only neurons but also glial cells such as oligodendrocytes (90, 91).

Finally, we propose the multi-dimensional approach to clarify the underlying brain mechanisms of mental functions including the unconscious (**Figure 2**). Based on our discussion, we believe that not only neurons but also glial cells have a vital role in the process of mental activities, a novel approach focusing on neuron-glia interactions should be applied. Combination of brain imaging techniques focusing on both neurons and glial cells should be applied (24, 26, 27, 43–46, 92–94). The most significant limitation in human brain research is that we cannot obtain living brain cells, including glial cells, from living human subjects from an ethical perspective. Presently, we can apply an alternative method; human brain cells such as neuronal cells can be established from somatic cells (not from the brain) such as skin fibroblasts by utilizing the gene-modification technique of induced pluripotent stem (iPS) cells. In addition, recently, neuronal cells are more easily established from directly conversion of human skin fibroblasts, called induced neuronal (iN) cells (95–99). Novel methods of establishing glial cells are strongly warranted based on iPS or direct conversion techniques in the near future. Multi-dimensional aspects of same human subjects, from genes, blood, brain imaging, psychometrics, social function, unconscious functions, psychodynamic assessments to molecular functions of somatic tissue-derived neuronal and glial cells, should be investigated and analyzed together (**Figure 2**). This approach may explore the novel roles of glial cells in various human mental activities including the unconscious. The application of this method for psychiatric patients should also be encouraged in the establishment of novel diagnostic methods and novel therapies.

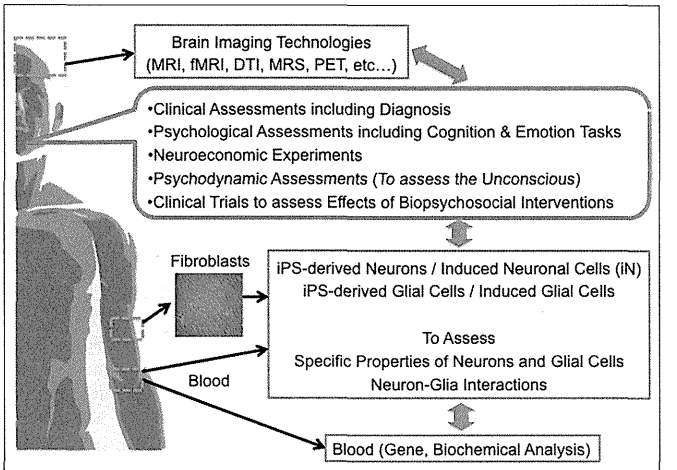

FIGURE 2 | A novel multi-dimensional approach toward psychology & psychiatry.

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特集　精神疾患の病理機構

ミクログリアと精神疾患

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1950年代にハロペリドール・クロルプロマジンに抗精神病作用が発見され，これらの薬剤が神経ドーパミンD2受容体拮抗作用を有するというエビデンスから，神経伝達の異常こそが精神疾患における病態基盤であるという説がドグマとなり，本仮説に基づく生物学的精神医学研究が進められてきたが，いまだ，その病理機構は十分には解明されていない。脳内には神経伝達の主役ニューロン(神経細胞)以外にも，アストロサイト・オリゴデンドロサイト・ミクログリアといったグリア細胞が生息しており，実際にはニューロンよりもグリアのほうが圧倒的に多く存在している。従来，脇役とみなされていたグリア細胞が精神疾患の病態に関与するという可能性が近年注目されており，筆者らはミクログリアに着目した精神薬理学的研究を進めてきた。興味深いことに，ミクログリア活性化抑制作用を有する抗生物質ミノサイクリンによる向精神作用が国内外で報告されており，ミクログリアが精神疾患研究の新たなターゲットになりつつある。本稿では精神疾患におけるミクログリア仮説を国内外の最新の研究知見と共に紹介する。

ミクログリアとは？

ミクログリアはグリア細胞の一種で，脳全体に分布し，脳内細胞全体の10%程度を占めている。中枢神経系では数少ない中胚葉由来の細胞であり，胎生期早期に卵黄嚢から脳へ直接的に移動した未成熟なマクロファージがその起源とされる。胎生期から発達期には，神経の分化誘導やシナプスの刈り込みにおいて不可欠な存在であり[1]，次第に樹状に突起を伸展したramified(分岐した)様の形態へと変化し，静止型として脳内の微細な環境変化を監視し続けている。最近では定常的にシナプス間の監視役を果たすことも明らかになっている[2]。

脳内の環境変化に敏速に反応し活性状態になると，遊走能を有するアメーバ様状の形態へと変化しマクロファージと類似した性質を呈し，標的部位まで移動し，脳内炎症免疫機構の主役として，貪食能を発揮し，炎症性サイトカインやフリーラジカルといった神経障害因子および神経栄養因子を産生する。このようにして，ミクログリアは中枢神経系における神経免疫応答・酸化ストレス反応に重要な役割を担い，脳内の恒常性維持，あるいは過剰な活性化による神経細胞傷害やオリゴデンドロサイト傷害を介してアルツハイマー病などの神経変性疾患や神経因性疼痛の病態に深く関与している。

統合失調症とミクログリア

脳画像研究の進展により，神経変性疾患だけでなく統合失調症でも，脳の特定部位の萎縮が薬物治療開始前から存在することや，病態の進行に伴

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