Chapter 2

Neural biomarkers of suicidal behavior: from cognition and circuits to cells (and back)

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More than 800,000 individuals die from suicide each year in the World. All countries around the globe are affected by this public health issue. Although the number of publications on suicidal behavior has exploded over the last 50 years (Astraud, Bridge, & Jollant, 2020), identified clinical and sociodemographic risk factors remain poorly predictive (Franklin et al., 2017). Mental disorders—including bipolar disorders—are a major risk factor of suicidal acts, with approximately 10% of patients who ultimately die from suicide and half of them attempting suicide in their lifetime. However, the occurrence of a severe mental disorder is not sufficient to explain who among patients is most at-risk of a suicidal act.

Neuroscience aims at shedding new light on suicidal behavior by investigating individual's brain structure and functioning. In the present chapter, we will discuss both neurocognitive and cellular approaches. These two approaches obviously require different methods but yield complementary information. Neurocognitive studies investigate individuals with histories of suicidal behavior in vivo. Current neuroimaging techniques allow the investigation of the whole brain with a *millimetric* resolution. Brain cellular approaches are conducted *postmortem* in individuals having died from suicide. Investigations are limited to one or a few brain regions, often in one hemisphere only, but with a *microscopic* resolution and a detailed exploration of cellular morphology and composition. Regarding the high number of articles published, literature report in this chapter will not be exhaustive.

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2.1 Neurocognitive studies of suicidal behavior

2.1.1 Risky decision-making

One of the most replicated neuropsychological finding is risky decision-making in suicide attempters. It was first demonstrated in 2005 by Jollant et al. (2005) with the Iowa Gambling Task (IGT). In 2020 a *meta*-analysis (Perrain, Dardennes, & Jollant, 2020) of 17 studies using the IGT confirmed significantly lower performance in suicide attempters than patient controls. Interestingly, there was no significant difference between nonattempter patients and healthy controls suggesting a certain level of suicide-related specificity among patients. Studies using the Cambridge Gamble Task, another decision-making task with no learning dimension, also reported more risky choices in suicide attempters (Perrain et al., 2020). Another *meta*-analysis showed that risky decision-making is more related to suicidal acts than suicidal ideas, suggesting a specific role in the transition from ideas to acts (Saffer & Klonsky, 2018) more than in the emergence of suicidal ideas. Finally, there was no clear effect of comorbid unipolar and bipolar disorders on the contrast between suicide attempters and nonattempters (Perrain et al., 2020).

A series of studies shed light on the mechanisms associated with risky decision-making in suicide attempters. First, risky decision-making in suicide attempters was not related to deficits in attention, executive functions (such as inhibition or planning) or working memory (Richard-Devantoy et al., 2013). Recent studies have supported the hypothesis of a particular deficit in processing of reward, punishment, and risk valuation (Jollant, Lawrence, Olie, Guillaume, & Courtet, 2011). For instance, when completing the IGT, euthymic suicide attempters displayed altered activation in left lateral orbitofrontal and dorsolateral prefrontal cortices during risky versus safe choices in comparison to patient and healthy controls (Jollant et al., 2010; Olié et al., 2015). Using a probabilistic learning task, Dombrovski, Szanto, Clark, Reynolds, and Siegle (2013) reported an association between a history of suicidal act and reduced signal for expected reward in ventromedial prefrontal cortex in elderly depressed patients (depression was associated with unpredicted reward in different brain regions). At a delay discounting task, low-lethality attempters showed a preference for immediate rewards (Dombrovski et al., 2011). Functional magnetic resonance imaging (MRI) showed deactivation of the left dorsolateral prefrontal cortex with increasing value difference favoring immediate reward (Vanyukov et al., 2016) and structural MRI found a negative correlation between voxel counts in putamen and preference for immediate reward (Dombrovski et al., 2012). A recent study in schizophrenia found reduced medial prefrontal activation during reward in those with a history of suicide attempt (Potvin, Tikàsz, Richard-Devantoy, Lungu, & Dumais, 2018). Interestingly, one study showed that, while acquiring an explicit understanding of the IGT usually leads to better performance in patient and healthy controls, this was not the

case in suicide attempters suggesting deficient use of implicit processes (Jollant, Guillaume, Jaussent, Bechara, & Courtet, 2013). The application of neuroeconomic methods to the study of suicidal behavior is just beginning and is a promising avenue.

Second, patients who used a violent suicidal means seemed to be more impaired (Jollant et al., 2005; Perrain et al., 2020). This subgroup of suicide attempters are at higher risk of future suicide death (Bergen et al., 2012) and showed more biological alterations, notably serotonergic deficits (Asberg, Traskman, & Thoren, 1976). Serotonin may actually be in play in the biochemical mechanisms underlying risky-decision in suicide attempters as suggested by one genetic study (Jollant et al., 2007). More biochemical studies are definitely necessary. Furthermore, a recent structural MRI study (Jollant et al., 2018) revealed that individuals who used a violent means in comparison to those who used overdose showed increased bilateral caudate and left putamen volumes. A previous study also showed a negative correlation between the volume of nucleus accumbens and lethality of suicidal act (Gifuni et al., 2016), in agreement with the known role of this subcortical structure in the modulation of actions. Risky decision-making may therefore contribute, not only to the choice of suicide in the face of stressful and painful events, but also to the choice of more lethal means partly in relation to a prefrontal−subcortical network.

Third, findings suggest that risky decision-making may be a persisting and heritable trait, being found in euthymic suicide attempters (Jollant et al., 2005) but also in first-degree biological relatives of suicide victims (Hoehne, Richard-Devantoy, Ding, Turecki, & Jollant, 2015) and in offsprings of suicide attempters (Keilp et al., in prep). Risky decision-making may therefore respond to the definition of an endophenotype. Again, these findings indirectly point toward the role of serotonergic deficits in suicidal behavior (Mann et al., 2006), a biological system with a high stability (Higley et al., 1996) and associated with personality traits such as impulsivity and aggression (Coccaro, Kavoussi, Sheline, Lish, & Csernansky, 1996). Risky decision-making in relatives of suicide victims was associated with altered processing of risk in left ventromedial and right dorsolateral prefrontal cortices (Ding et al., 2017). Of note, childhood abuse may also contribute to risky decision-making in suicide attempters (Guillaume et al., 2013).

2.1.2 Deficient social cognition

Suicidal acts often occur in a stressful social context, whether interpersonal conflicts, unemployment or loss of a beloved one (Foster, 2011). The way individuals perceive themselves, perceive others (as reasons for discontent, or as a potential help), interact with others and respond to stressful social situations is obviously relevant for understanding suicidal behavior.

Using pictures of faces expressing various emotions, one study (Jollant et al., 2008) showed increased activation of the right lateral orbitofrontal and decreased response of the dorsomedial prefrontral cortex in response to angry versus neutral faces in euthymic suicide attempters in comparison to patient controls with major depressive disorder (MDD). A replication attempt in euthymic unipolar and bipolar patients showed increased response of the same region on the left side in suicide attempters (Olié et al., 2015) whereas a study in adolescents reported increased activity in anterior cingulate cortex to angry faces (at 50% intensity) in attempters relative to nonattempters (Pan et al., 2013). Results have been interpreted as a particular sensitivity and attention to signals of social threat and disapproval. In adolescents and young adults with bipolar disorder, decreased functional connectivity between the amygdala and the left ventral and right rostral prefrontal cortices during happy, neutral, and fearful faces were also reported in attempters versus nonattempters (Johnston et al., 2017). A study in older adult(s) did not observe group difference (Vanyukov et al., 2015).

Second, one study assessed the neural response to social exclusion using the Cyberball game in euthymic adult women (Olié et al., 2017). When comparing activation during the exclusion versus inclusion periods of the test, suicide attempters in comparison to patient controls and healthy controls showed altered contrasts in left posterior insula and supramarginal gyrus. These regions have been implicated in pain and interoceptive information processing (Cauda et al., 2012) as well as in social cognition and self-other representation (Lawrence et al., 2006).

Third, not surprisingly, social abilities and decision-making maintain close links. One study in suicide attempters showed a significant correlation between IGT performance and the number of problems in affective relationships over the last 12 months (Jollant et al., 2007). Another study using the ultimatum game in elderly showed that high-lethality suicide attempters tend to refuse all unfair offers whatever the level of unfairness (Szanto et al., 2014), a result recently replicated (Carbajal et al., 2017). Higher sensitivity to unfairness has been associated with serotonin depletion (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008).

Fourth, several studies reported deficient social problem solving in suicide attempters (Jollant et al., 2011), a deficit associated with overgeneral autobiographical memory (Arie, Apter, Orbach, Yefet, & Zalzman, 2008). Authors have found that difficulties in generating efficient solutions in social situations are mainly state deficits influenced by depression (Speckens & Hawton, 2005), ruminations (Sharaf, Lachine, & Thompson, 2018), and negative mood (Williams, Barnhofer, Crane, & Beck, 2005), and were not predictive of repetition of self-harm (Cates et al., 2017).

Finally, a *meta*-analysis confirmed reduced (semantic) verbal fluency in suicide attempters relative to patient controls (but not in patient controls vs. healthy controls) (Richard-Devantoy, Berlim, & Jollant, 2014). Although

these tests do not directly measure social components, verbal fluency has been regularly associated with social skills and functioning in mental disorders (Mahmood, Burton, Vella, & Twamley, 2018). In depressed patients who recently attempted suicide, verbal fluency was associated with activation in anterior prefrontal, parietal, and cingulate cortices in a single-photon emission computed tomography (SPECT) study (Audenaert et al., 2002). A positron emission tomography (PET) study in suicide attempters found a correlation between verbal fluency and mid-cingulate and superior frontal gyrus activity, an effect moderated by serotonin manipulation (fenfluramine) but not depression (Oquendo et al., 2003). A recent study using near-infrared spectroscopy reported lower responses in the left precentral gyrus during a verbal fluency task in suicide attempters relative to nonattempter patients (Tsujii et al., 2017).

2.1.3 Other cognitive processes: memory, attention, and cognitive inhibition

A *meta*-analysis (Richard-Devantoy, Berlim, & Jollant, 2015) showed that autobiographical memory, long-term memory, and working memory were all more impaired in suicide attempters than patients controls whereas patient controls also showed more impairments than healthy controls.

Attentional bias toward suicidal cues (as measured with a specific Implicit Association Task or a modified Stroop test with suicide words) were also reported (Cha, Najmi, Park, Finn, & Nock, 2010; Nock & Banaji, 2007; Richard-Devantoy, Ding, Turecki, & Jollant, 2016). Effects tended to be higher in suicide attempters than nonattempters or suicide ideators. Interestingly, both tests predicted suicide reattempt within 6 months (Cha et al., 2010; Nock et al., 2010). General attention deficits as measured by the Stroop test were also found in suicide attempters although a patient effect was also found (Richard-Devantoy et al., 2014).

Deficits in cognitive inhibition likely play a significant role in the transition from suicidal ideas to acts (Saffer & Klonsky, 2018). One *meta*-analysis (Richard-Devantoy et al., 2014), however, suggests a depression effect with no significant difference between attempters and nonattempters and a neuroimaging study reported mixed results with significant behavioral differences at the Go-NoGo task between both groups, but no activation differences (Richard-Devantoy, Ding, Lepage, Turecki, & Jollant, 2016). During the task, different activations between depressed patients and healthy controls were found in the inferior frontal gyrus, orbitofrontal cortex, and parietal cortex.

Reduced skills in cognitive inhibition (but also working memory, autobiographical memory, and attention including bias toward suicide-related words) may therefore be particularly heightened by a negative emotional / depressive state (and alcohol / drug use), although trait-alterations may also preexist at various levels in many individuals.

2.1.4 Resting state neuroimaging studies

Fourteen MRI studies using resting state sequences have been published over the last 5 years in suicide attempters or ideators. In comparison to nonattempter patients, suicide attempters showed increased amplitude of low-frequency fluctuation (ALFF) in the right superior temporal gyrus, left middle temporal gyrus, and left middle occipital gyrus; and decreased amplitude in right ventral medial frontal gyrus (Cao et al., 2016; Fan, Wu, Yao, & Dong, 2013). Independent component analyses (ICA) showed increased coherence in the left cerebellum and the left lingual gyrus and decreased coherence in the right precuneus (Zhang et al., 2016). Two studies showed increased functional connectivity of the left amygdala with the right insula and left superior orbitofrontal area, and of the right amygdala with the left middle temporal area (Kang et al., 2017). The limited number of studies and the variety of analytic methods used prevent a simple summary of findings.

Using a graph theory model, (Wagner et al. (2019) found changes in the global functional properties of the brain of both suicide attempters and relatives of suicide victims, notably reduced assortativity—a marker of network resilience. These deficits affected several connections in the anterior brain in both groups, and in the posterior brain in suicide relatives only. These findings support the notion of widespread brain functional alterations in suicidal behavior.

Several groups focused on suicidal ideation. Suicide ideators showed modified coupling between parts of the anterior and posterior cingulate (Chase et al., 2017), and decreased functional connectivity between the rostral anterior cingulate, the orbitomedial prefrontal cortex, and the right middle temporal pole (Du et al., 2017). Suicidality was also positively associated with functional connectivity between left precuneus and left primary motor and somatosensory cortices, and middle and superior frontal gyri; and negatively between left posterior cingulate and left cerebellum, lateral occipital cortex, and fusiform gyrus (Schreiner, Klimes-Dougan, & Cullen, 2019). One study using a graph theory model showed decreased connectivity in the left superior frontal gyrus (pars orbitalis), left thalamus, and right thalamus, regions also negatively correlated with severity of suicidal ideation (Kim et al., 2017). One study using ICA found lower coherence in the left executive, anterior default-mode, and salience networks (Ordaz, Goyer, Ho, Singh, & Gotlib, 2018). Finally, suicidal ideators showed less temporal variability (dynamic ALFF) in the dorsal anterior cingulate cortex, the left orbital frontal cortex, the left inferior temporal gyrus, and the left hippocampus (Li, Duan, Cui, Chen, & Liao, 2018). Summarizing these finding is challenging. Suicidal ideation may be related to a set of dysfunctional connections between midline structures (superior frontal gyrus, anterior and posterior cingulate, precuneus) and the orbitofrontal, temporal and occipital regions, as well as thalamus, hippocampus, and cerebellum. Identified regions overlap

with regions associated with self-reference / rumination (Nejad, Fossati, & Lemogne, 2013) and mental pain (van Heeringen, Van den Abbeele, Vervaet, Soenen, & Audenaert, 2010), two predictors of suicidal ideas. Hippocampus may notably be involved in overgeneral autobiographical memory (Keresztes, Ngo, Lindenberger, Werkle-Bergner, & Newcombe, 2018). A recent study using ALFF and directly comparing ideators and attempters suggest significant differences between both groups (notably decreased values in frontoparietal network, and increased values in subcortical regions in the latter group), supporting the concept of suicidal transition (Wagner et al., 2021).

2.1.5 Pharmacological neuroimaging studies

Twenty-one articles have been published to date using PET or SPECT to measure various biochemical compounds. Main limitations comprise small sample size, the fact that suicidal behavior was often investigated as part of secondary analyses and the frequent lack of a patient control group. Almost all studies have investigated the serotonergic system. Overall, results have been mixed with several nonsignificant group comparisons (Sullivan et al., 2015). However, heterogeneity among suicide attempters may explain these findings. For instance, $5HT_{1A}$ binding was higher in the raphe nucleus of high versus low lethality attempters (Sullivan et al., 2015) and predicted higher lethality of subsequent acts (Oquendo et al., 2016).

More recently, proton magnetic resonance spectroscopy has been used in four studies investigating various brain regions but, while being an interesting technique, the number of studies remains too limited to be discussed here.

2.1.6 Structural neuroimaging studies

T_1 structural MRI represents a potentially interesting clinical tool due to the relative simplicity of acquisition and analysis. However, results of 38 studies have been mixed. A *meta*-analysis of 12 studies (whole brain-analyses using voxel-based morphometry) (Jollant et al., 2018) and a large study from the ENIGMA consortium of more than 3000 subjects focusing on subcortical structures (Rentería et al., 2017) even reported a lack of group difference between suicide attempters and nonattempters. Within-group heterogeneities may explain these disappointing results as both the use of a violent suicidal means (vs nonviolent methods) and a family history of suicide were associated with significant structural alterations (increased bilateral caudate and left putamen volumes; decreased bilateral temporal regions, right dorsolateral prefrontal cortex, and left putamen volumes, respectively) (Jollant et al., 2018).

A few studies using T_2 MRI sequences in different age groups showed more periventricular white matter hyperintensities in those with a history of

suicide attempt (Ahearn et al., 2001; Pompili et al., 2008). Although the nature of these lesions is unknown, it is suggested that they may infer with connectivity tracks.

Diffusion tensor imaging studies have reported changes in structural connectivity between suicide attempters and patient controls. This concerns a large number of regions and tracks: white matter in the left orbitofrontal (Mahon et al., 2012), right dorsomedial prefrontal cortex (Olvet et al., 2014), ventral frontal (Johnston et al., 2017), left insula (Lee et al., 2016), left temporal lobe (Lee et al., 2016), and right cerebellum (Johnston et al., 2017); the internal (Jia et al., 2010; Kim et al., 2015; Lee et al., 2016) and left external capsules (Lee et al., 2016); the corona radiate (Kim et al., 2015; Lee et al., 2016); the thalamic radiations (Kim et al., 2015; Lee et al., 2016); the sagittal stratum (including the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) (Kim et al., 2015; Lee et al., 2016), the superior longitudinal fasciculus (Kim et al., 2015; Lee et al., 2016); the connection between left olfactory cortex and left anterior cingulate gyrus (Bijttebier et al., 2015); the left cerebral peduncle (Lee et al., 2016); the bilateral uncinate fasciculus (Johnston et al., 2017). The role of the corpus callosum is debated (Cyprien et al., 2016; Gifuni et al., 2017).

2.1.7 Using neuroimaging studies for classification

One study used support vector machine classification with resting state data and showed various functional connectivities between the default mode and the limbic, salience, and central executive networks to discriminate recent (but not past) suicide attempters and suicidal ideators (Cáceda, Bush, James, Stowe, & Kilts, 2018). Another study used machine learning and brain responses to various words, and showed that three words ("death," "lifeless" and "carefree") allowed discriminating suicide attempters from suicide ideators on the basis of clusters in inferior parietal and inferior frontal gyri (Just et al., 2017). More studies with larger samples and an independent group for machine training will be necessary to clarify the clinical utility of these methods.

2.1.8 A tentative neuroanatomical summary of suicidal acts (Fig. 2.1)

- *Risky decision-making* may be related to a deficient "*valuation network*" on the anterior brain including the ventral and dorsal prefrontal cortex and the striatum (putamen, caudate, nucleus accumbens) as part of corticostriatal loops.
- *Deficient cognitive control* may be related to the "*cognitive control network*" (Li et al., 2017) encompassing the superior frontal cortex, the anterior cingulate, the insula, the parietal cortex, and the occipital cortex.
- *Deficient social perception and response* may be related to a deficient "*extended social network*" including the amygdala, the prefrontal cortex,

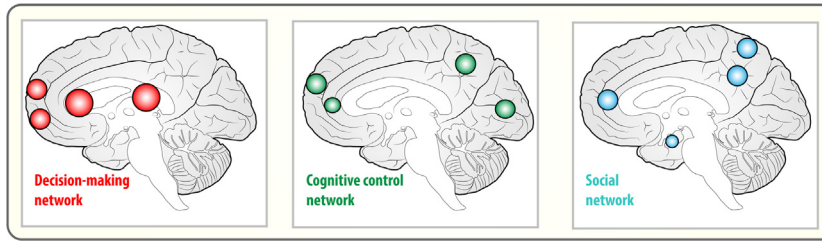

FIGURE 2.1 Schematic representation of the three brain systems hypothetically underlying the vulnerability to suicidal behavior: valuation, cognitive control, and extended social networks.

the anterior and posterior insula, the anterior cingulate, the posterior cingulate and precuneus, and the parietal cortex (and possibly the temporal cortex).

- Dysfunction of these various networks may rely on diffuse impairments in *functional and structural connectomics*, and lead to limited resilience of the system to stress.
- *Biochemical systems* involved may notably include the serotonergic and dopaminergic systems and the hypothalamic–pituitary–adrenal (HPA) axis, but also inflammatory processes (see below) (Brundin, Bryleva, & Thirtamara Rajamani, 2017), and the opioid system (Lutz, Courtet, & Calati, 2018).

2.2 Postmortem brain research: exploring the cellular and molecular roots of suicide

There has been considerable interest in investigating the microscopic underpinnings of the suicide-associated structural and functional changes in the brain presented above. Since neuroimaging approaches do not offer sufficient spatial resolution to analyze the cellular and subcellular makeup of cerebral networks, postmortem research with well-characterized brain tissues remains the gold standard for such investigations. In addition to offering increased resolution, this approach allows the study of human cell types and connections that are different or even absent in rodents (Boldog et al., 2018; Oberheim et al., 2009). The latter remain nonetheless highly useful to help understand the fundamental biology of mood disorders (Kang et al., 2012; Labonté et al., 2017). We must however keep in mind that three major conditions must be fulfilled in order to carry out meaningful postmortem brain suicide studies: (1) matched case and control tissues must be of quality, as measured by tissue pH and RNA integrity; (2) control samples must come from healthy individuals having died suddenly in order to avoid biochemical changes occurring in the brain during the agonal period; and (3) all samples must be accompanied by detailed clinical, psychosocial, and toxicological information. Furthermore, an important limitation when setting up and

interpreting such studies is that the majority of individuals having died by suicide were affected by psychopathologies, and notably by MDD (Arsenault-Lapierre, Kim, & Turecki, 2004), thus often making it difficult to specifically associate experimental observations with suicide. Despite this, postmortem brain investigations using a variety of histological and molecular approaches have allowed to uncover fine neuroanatomical and molecular alterations in the brains of suicide victims (Bach & Arango, 2012; Maheu, Davoli, Turecki, & Mechawar, 2013; Turecki, 2013). Previous reviews have discussed postmortem findings supporting the hypothesis of altered neurotransmission, neuroplasticity, or glial cell function in suicide (Ernst, Mechawar, & Turecki, 2009; Lutz, Mechawar, & Turecki, 2017). Below, we will focus specifically on some of the literature implicating microglia and neuroinflammation in suicide and see how these findings can be reconciled with the neurocognitive studies.

2.2.1 Evidence of activated microglia/macrophages

Microglia, the resident immune cells of the brain, were first directly implicated in suicide by the study of Steiner and colleagues (Steiner et al., 2008), which provided immunohistological evidence of microgliosis in brain samples from suicide victims, compared to matched healthy controls, irrespective of their psychiatric illness (schizophrenia, MDD, bipolar disorder). The authors evidenced microgliosis by examining HLA-Dr-immunoreactive microglia in sections of dorsolateral prefrontal cortex, anterior cingulate, mediodorsal thalamus, and hippocampus, and found no region specificity to the phenomenon, as microgliosis was significantly higher in all regions (except for the hippocampus, in which there was a strong trend) than in control samples. More recently, Iba1-IR microglia in the anterior cingulate white matter of depressed suicides were found to more frequently display a primed phenotype (increased cell body size) compared to those examined in matched controls (Torres-Platas, Cruceanu, Chen, Turecki, & Mechawar, 2014). The following year, a PET visualization of translocator protein (TSPO) availability in prefrontal, anterior cingulate, and insular cortices revealed that this molecular index of microglial activation (but see Owen et al., 2017) was significantly increased in patients experiencing a major depressive episode (Setiawan et al., 2015). Similar findings were later reported by Li and colleagues (Li, Sagar, & Kéri, 2018). Another independent group replicated the findings of Setiawan et al. (2015), but further showed that TSPO was significantly increased in the anterior cingulate and insula of patients with suicidal thoughts compared to those without (Holmes et al., 2018). Taken together, these results strongly suggest microglial activation as a cellular feature of depression, which is exacerbated with suicidal thoughts.

The study by Torres-Platas et al. (2014) also found that a significantly greater number of blood vessels in this region were surrounded by a high

density of Iba1-IR macrophages in depressed suicides compared to controls. In their study of prefrontal cortex samples from individuals affected with mood disorder and schizophrenia, Schnieder and colleagues (Schnieder et al., 2014) also reported that dorsal prefrontal white matter displayed increased numbers of perivascular Iba1-IR macrophages in suicides compared to controls. The increase of macrophages in the perivascular space may reflect increased infiltration in the brain of suicides of circulating bone marrow-derived monocytes, similar to the phenomenon described in a preclinical model of depression and associated with anxiety-like behavior (Wohleb, Powell, Godbout, & Sheridan, 2013). Interestingly, this mouse model (repeated social defeat) was recently found to lead to a more permeable blood–brain barrier (Menard et al., 2017), suggesting that increased neuroinflammation in the periphery could more directly influence the brain. These data are consistent with the findings of Rajkowska and colleagues (Rajkowska, Hughes, Stockmeier, Javier Miguel-Hidalgo, & Maciag, 2013) showing that astrocytic endfeet coverage of blood vessels is significantly reduced in the orbitofrontal cortex of MDD patients, most of whom had died by suicide, compared to matched controls.

2.2.2 Molecular evidence of increased inflammation in depression and suicide

Several independent studies have reported that a small but significant increase in proinflammatory cytokines can be measured in the blood of depressed patients compared to controls (Dowlati et al., 2010). Clinical research led by Brundin and colleagues with samples collected in the emergency room has revealed that the cerebrospinal fluid of suicide attempters contains significantly higher levels of interleukin-6 (IL-6) (Lindqvist et al., 2009). In line with these findings, studies measuring the expression of cytokines in postmortem brain samples have found significantly increased levels of IL-1β, IL-6, and TNF-α in the prefrontal cortex of both adolescent (Pandey et al., 2012) and adult (Pandey, Rizavi, Zhang, Bhaumik, & Ren, 2018) suicides compared to controls. The latter study also reported significantly increased expression of lymphotoxin B and decreased expression of the antiinflammatory cytokines IL-10 and IL-1RA (Pandey et al., 2018). Considered with evidence that IFN-α therapy to treat cancer or hepatitis is known to induce clinical depression in about half of the patients (Capuron & Miller, 2004), and that MDD is highly comorbid with neuroinflammatory disorders (Margaretten, Julian, Katz, & Yelin, 2011), these findings strongly suggest that chronic low-level inflammation may play an important role in depression and suicide (see also review of preclinical data in Hodes et al., 2015; Hodes, Kana, Menard, Merad, & Russo, 2015).

2.2.3 Inflammation and cognition

The converging lines of evidence linking depression and suicide to cerebral inflammation have mainly involved brain regions implicated in suicide (Fig. 2.1), such as the prefrontal and anterior cingulate cortices. Could there be a causal relationship between cerebral inflammation within these circuitries and their altered function leading to impaired mood and cognition? Clinical data from patients having received cytokine (IFN-α) therapy seem to support this hypothesis. Indeed, patients having developed MDD following treatment with this proinflammatory cytokine were found to perform more poorly than controls in a visuospatial task, and the number of task-related errors correlated significantly with anterior cingulate cortex activation in patients (but not in controls), as monitored by functional MRI during the task (Capuron et al., 2005). More recently Li, Sagar, et al. (2018) reported that increased TSPO in all brain regions investigated in depressed patients was negatively correlated with decreased cognitive ability as measured by an attention task. Further support for this hypothesis has come from experiments conducted with healthy individuals treated with minocycline, an inhibitor of microglial activation. Minocycline is a tetracycline antibiotic that influences microglial activity by selectively inhibiting microglial polarization to a proinflammatory state (Kobayashi et al., 2013). What Kanba's group showed in particular is that a short-term treatment with minocycline at daily doses normally used to treat infections modulated decision-making in different tests or situations (Kato et al., 2012; Watabe et al., 2013). These studies suggest that cognitive performance can be influenced by stimulating or inhibiting microglial activation.

2.2.4 Bipolar disorder

In recent years, fundamental neuroscience research has revealed that, in addition to their immune functions, microglia play a number of roles that shape brain circuitries in the developing and adult brain, in health and disease (reviewed in Stevens & Schafer, 2018). Ramified microglia, which used to referred to as "resting," are in fact constantly interacting with surrounding neurons and play an active role in neuroplasticity by shaping and modulating the strength of synaptic connections (Parkhurst et al., 2013; Rogers et al., 2011) and, ultimately, the function of cerebral networks. By interfering with these cellular processes, chronic, low-level cerebral neuroinflammation may contribute to the suicide-associated cognitive impairments, including risky decision-making.

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