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The Role of Cytokines in the Pathophysiology of Suicidal Behavior

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Abstract

Objective—Immune dysregulation has been implicated in depression and other psychiatric disorders. What is less clear is how immune dysregulation can affect risk of suicidal behavior. We reviewed the scientific literature concerning cytokines related to suicidal ideation, suicidal behavior and suicide, and surveyed clinical and neurobiological factors associated with cytokine levels that may modulate effects of inflammation on suicide risk.

Methods—We searched PubMed, Embase, Scopus and PsycINFO for relevant studies published from 1980 through February, 2015. Papers were included if they were written in English and focused on cytokine measurements in patients with suicidal behaviors.

Results—The literature search yielded 22 studies concerning cytokines and suicidal ideation, suicide attempts or suicide completion. The most consistent finding was elevated interleukin

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(IL)-6, found in 8 out of 14 studies, in CSF, blood, and *postmortem* brain. In one study, IL-6 in CSF was also found to be higher in violent than nonviolent attempters and to correlate with future suicide completion. Low plasma IL-2 was observed in 2 studies of suicide attempters, while divergent results were seen for tumor necrosis factor (TNF)- α , interferon (IFN)- γ , transforming growth factor (TGF)- β , IL-4, and soluble IL-2 receptors.

Conclusions—Given the complexity suggested by the heterogeneous cytokine findings, putative mediators and moderators of inflammation on suicidal behavior merit further study. Elevated IL-6 was the most robust cytokine finding, associated with suicidal ideation and both nonfatal suicide attempts and suicides. Future studies should evaluate the predictive value of high IL-6, consider how this may alter brain function to impact suicidal behavior, and explore the potential beneficial effects of reducing IL-6 on suicide risk.

Keywords

Cytokines; Suicide; Depression; Inflammation; Stress

1. Introduction

Suicide is a major public health concern. The World Health Organization (WHO) estimated that in the year 2000, approximately one million people died from suicide, and 10 to 20 times more attempted suicide, worldwide (WHO, 2002). Suicide and suicidal behaviors are cross-diagnostic, multifactorial phenomena. Several clinical, psychosocial and demographic factors have been shown to increase the risk for suicidal behaviors (Hawton et al., 2013). However, predictive value of known risk factors for accurate assessment of who will ultimately make suicide attempts remains low (May et al., 2012). Therefore, identification of relevant biomarkers has assumed increasing importance in suicide research, as objective markers of risk could significantly improve the chances of effective clinical intervention. Moreover, greater understanding of the biological processes impacting neural pathways involved of suicide risk could suggest new treatment approaches.

Even though 90% of suicides have a psychiatric diagnosis (Beautrais et al., 1996), only 5% of psychiatric patients die by suicide. A Stress-Diathesis Model of suicidal behavior was proposed by Mann et al (Mann et al., 1999), in which suicidal behavior was conceptualized as the result of the interplay between stressors such as acute episodes of psychiatric illness or psychosocial stressors, and the individual's constitutional vulnerability to respond with suicidal behavior. This model thus implicates the stress-response system as a potential contributor to the pathophysiology of suicidal behavior. In humans, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system play key roles in adaptation to physical or psychological stress, acting on numerous systems to maintain homeostasis through the release of corticosteroids and catecholamines (McEwen, 2008). However, chronic stress states in vulnerable individuals can produce alterations of basal and reactive cortisol which, in turn, can have deleterious effects on health. Maladaptive stress responses have been implicated in the pathophysiology of suicidal behavior (Oquendo et al., 2014). As the stress response is intrinsically linked with the immune system, the involvement of inflammatory responses must be considered in suicide-related pathophysiology.

Within the immune system, cytokines such as interleukins (IL), interferons (IFN), and tumor necrosis factor (TNF) play pivotal roles as signaling proteins mediating innate and adaptive immune responses (Commins et al., 2010). T-cell derived cytokines from the Th1 lineage are involved in cellular mediated immune processes (IL-1 α , IL-1 β , IL-2, IFN- γ , TNF- β) whereas those derived from the Th2 lineage promote humoral immune response (IL-4, IL-6, IL-10) and are implicated in allergic reactions (Chaplin, 2010). Certain cytokines can be functionally categorized as pro-inflammatory (IL-1, IL-6, TNF- α) or anti-inflammatory (IL-4, IL-10, IL-13) (Commins et al., 2010).

The role of cytokines in the pathophysiology of psychiatric disorders was postulated after observations that patients with inflammatory diseases had a higher prevalence of depression, and that symptoms similar to those observed in major depression could be provoked by administration of therapeutic cytokines, such as IFN- α (reviewed in (Raison et al., 2005)). Depression has been associated with increased inflammatory markers, including cytokines such as IL-6 and TNF- α (Liu et al., 2012), although inflammation may be implicated in only a subset of depressed patients (Raison and Miller, 2013).

In recent years, inflammation has emerged as potentially relevant in the pathophysiology of suicidal behavior. The earliest suggestions came from reports of suicidal ideation induced after medical treatment with therapeutic cytokines (Dieperink et al., 2004). A parallel set of discoveries stems from well-replicated findings that the incidence of suicide peaks during the spring, an initially baffling phenomenon later noted to covary with peak season for allergens (Postolache et al., 2008). Additional studies have directly linked allergic conditions to suicide completion (Qin et al., 2011; Timonen et al., 2004). Corroborative evidence is provided from an ecological study showing associations between intranasal corticosteroid anti-inflammatory therapy and lower suicide rates (Woo et al., 2011). In this review, we will focus on the contribution of later studies measuring inflammatory cytokines associated with suicidal behaviors *in vivo* or, in the case of completed suicide, on *postmortem* findings. We provide a critical overview of the literature and offer a contextualized interpretation of findings on how cytokine changes may alter brain function to favor suicidal behavior.

Identifying specific inflammatory markers and important contextual factors could inform suicide risk prediction. Treatments targeting constituents of the inflammatory pathway are currently undergoing testing for a variety of psychiatric conditions, and this approach could be developed as a novel therapeutic tool for the prevention of suicide.

2. Methods

Articles eligible for this review were identified by two investigators (L.G. and S.C.-T.) who independently performed database searches of PubMed from 1980 through February 2015, and Embase, Scopus and PsycINFO from 1980 until 2015 for articles in English (see Figure 1). The final search strategy comprised the following (with slight differences for individual database logic rules): (suicid* AND (inflammat* OR cytokines OR chemokines OR “receptors, cytokines” OR “tumor necrosis factor” OR interferon OR interleukin OR neuroglia) NOT (apoptosis OR “suicide gene” OR genet* OR cancer OR hepatitis OR “multiple sclerosis”)). The reference lists of the retrieved publications were examined for

other eligible articles. Publications were included if they met the following criteria: a) evaluated suicidal ideation, completed suicide or suicide attempts, and b) focused on the relationship of suicidal behaviors to cytokines, and publications were excluded if a) the inflammatory markers measured in relation to suicidal ideation, complete suicide or suicide attempts did not include cytokines, or b) if the publications presented sample overlap with other included studies. Manual bibliography search did not reveal any additional articles. Four articles were excluded due to overlapping samples (Grudet et al., 2014; Isung et al., 2014; Janelidze et al., 2015; Lee and Kim, 2010).

3. Results

3.1. Literature search

We found 22 articles that directly examined relationships between cytokines and suicidal ideation, suicidal behavior or suicide, that fulfilled the inclusion criteria, involving 1813 research participants. Ten articles concerned cytokines in suicide attempts (Huang and Lee, 2007; Isung et al., 2012a; Janelidze et al., 2011; Kim et al., 2008; Li et al., 2013; Lindqvist et al., 2011; Lindqvist et al., 2009; Nässberger and Träskman-Bendz, 1993; Rothenhäusler et al., 2006; Vargas et al., 2013), with a total of 1077 research participants: 423 suicide attempters, 353 non-attempters; and 301 normal controls. Four articles concerned *postmortem* studies (Hoyo-Becerra et al., 2013; Pandey et al., 2012; Tonelli et al., 2008; Torres-Platas et al., 2014) of cytokines in 85 suicides and 61 comparison participants. Two prospective studies (Isung et al., 2012b; Lindqvist et al., 2011) concerned the ability of baseline cytokine levels, among 182 individuals with a history of suicide attempt, to predict 16 subsequent suicides. Seven articles concerned suicidal ideation (Gabbay et al., 2009; Juengst et al., 2014; Karlovi et al., 2012; Martinez et al., 2012; Mendlovic et al., 1999; Monfrim et al., 2014; O'Donovan et al., 2013) in 499 research participants: 156 patients with suicidal ideation, 188 patients with no suicidal ideation, and 176 normal controls. See Tables 1-3 for a description of the included studies. Additionally, two recently published meta-analyses concerning cytokines related to suicidal ideation, suicidal behavior and suicide were identified (Black and Miller, 2015; Ducasse et al., 2015). We have summarized findings for individual cytokines in section 3.2. and in Table 4.

3.2. Results for individual cytokines

3.2.1. Interleukin-6—The cytokine most frequently associated with suicidality was IL-6, elevated in eight (Hoyo-Becerra et al., 2013; Janelidze et al., 2011; Karlovi et al., 2012; Lindqvist et al., 2011; Lindqvist et al., 2009; Martinez et al., 2012; O'Donovan et al., 2013; Pandey et al., 2012) of the thirteen studies. One study only (Kim et al., 2008) reported lower IL-6 in suicide attempters; we note that in this study, blood was collected from depressed suicide attempters at the time of arriving in the emergency room, whereas in the comparator groups—and in all the other studies in which this cytokine was measured in blood or CSF—specimens were collected in the morning in a fasted state. This might have created a confound, since a biphasic diurnal variation has been described for IL-6 with morning and evening peaks (Vgontzas et al., 2005). Another potential explanation is that as samples were collected in the emergency room directly following suicide attempts, resulting acutely high cortisol levels could account for lower IL-6 levels (Coutinho and Chapman, 2011). Finally,

unlike any other studies reviewed, Kim et al. utilized mitogen-stimulated whole blood, which may yield different results than plasma levels. The remaining studies found no differences in IL-6 CSF or blood levels in adult suicide attempters compared with controls (Isung et al., 2012a; Martinez et al., 2012; Vargas et al., 2013), in adolescents with active suicidal intent and a high lethality plan compared with depressed, non-suicidal peers (Gabbay et al., 2009), or with regard to mRNA expression in prefrontal cortex (Tonelli et al., 2008) or plasma (Isung et al., 2012b) of suicides compared with controls. It may be relevant to interpretation of the *postmortem* studies that differences in mRNA expression for IL-6 were found in hippocampus (Hoyo-Becerra et al., 2013), while a lack of group differences was seen in a study of adult prefrontal cortex (Tonelli et al., 2008).

3.2.2. Tumor necrosis factor- α —Only three of fifteen studies found higher TNF- α associated with suicidal behavior (Janelidze et al., 2011), suicidal ideation (Martinez et al., 2012), or suicide (Pandey et al., 2012). Lower levels were found in only one small study of depressed adolescents with high suicidal ideation (a group that included recent suicide attempters), compared with depressed non-ideators (Gabbay et al., 2009). In another study (Li et al., 2013), TNF- α levels were higher in MDD than in controls but did not distinguish ‘suicidal’ MDD from ‘non-suicidal’ MDD non-attempters, in which ‘suicidality’ comprised persistent thoughts of suicide or death, specific suicide plan, and suicide attempt or completion. The remainder of the studies (Hoyo-Becerra et al., 2013; Huang and Lee, 2007; Isung et al., 2012b; Karlovič et al., 2012; Lindqvist et al., 2009; O'Donovan et al., 2013; Tonelli et al., 2008; Torres-Platas et al., 2014; Vargas et al., 2013) found no group differences with respect to TNF- α .

3.2.3. Interleukin-2 and interleukin-2 soluble receptor (sIL-2R)—IL-2 levels were lower in depressed suicide attempters than depressed non-attempters and healthy controls in both studies where this cytokine was measured (Janelidze et al., 2011; Kim et al., 2008). No differences were found between groups in studies measuring suicidal ideation (Mendlovic et al., 1999). In a prospective study of 58 suicide attempters, IL-2 levels were lower in those who suicided at follow-up (N=7); this reduced to a trend when covariates were included in the model (Isung et al., 2012b). Among the two studies which measured sIL-2R, Nassberger and Traskman-Bendz (Nässberger and Träskman-Bendz, 1993) found higher levels in suicide attempters with mood disorders or other psychiatric diagnoses, when compared to healthy controls. Increased sIL-2R binding and consequent cellular internalization of the sIL-2R/IL-2 complex could account for the decreased IL-2 levels found in the above-mentioned studies. However, Rothenhäusler et al. (Rothenhäusler et al., 2006) found no difference in sIL-2R levels between formerly depressed patients with previous suicide attempts and healthy controls.

3.2.4. Interleukin-1 β —Three out of nine studies found higher levels of IL-1 β , but seven found no association with suicidal ideation and behavior in samples of CSF (Martinez et al., 2012) and serum (Monfrim et al., 2014), or with suicide, in *postmortem* tissue (Pandey et al., 2012).

3.2.5. Interferon- γ and transforming growth factor- β —Higher levels of IFN- γ were found in depressed patients with suicidal ideation compared to depressed non-suicidal and healthy controls in one of two studies (Mendlovic et al., 1999). For both IFN- γ (Gabbay et al., 2009; Kim et al., 2008) and TGF- β (Kim et al., 2008; Lee and Kim, 2010; O'Donovan et al., 2013), there was no difference in blood levels between depressed attempters and non-attempters, but cytokine levels did distinguish depressed patients from healthy controls (Gabbay et al., 2009; Kim et al., 2008; Lee and Kim, 2010), indicating more of a role as biomarkers for depression than suicide.

3.2.6. Interleukin-4, interleukin-13 and interleukin-8—In the only *postmortem* study that looked at IL-4 and IL-13 in the prefrontal cortex of suicides, both IL-4 and IL-13 were higher than in death by cardiac events (Tonelli et al., 2008). Three other studies found no differences for IL-4 in patients with suicidal ideation (Gabbay et al., 2009; Mendlovic et al., 1999) or suicide (Isung et al., 2012b) compared to the control groups. Low IL-8 was seen in one (Isung et al., 2012a) of two studies of suicide attempters; however, in another study by the same group, IL-8 did not differentiate those who went on to complete suicide from individuals who did not (Isung et al., 2012b).

3.2.7. Interleukin-5 and interleukin-10—None of the studies measuring IL-5 (Mendlovic et al., 1999; Tonelli et al., 2008) or IL-10 (Huang and Lee, 2007; Isung et al., 2012b; Mendlovic et al., 1999; O'Donovan et al., 2013; Torres-Platas et al., 2014) found any associations with suicidal ideation, attempts, or suicide for these cytokines.

3.3 Meta-analyses

Two meta-analyses (Black and Miller, 2015; Ducasse et al., 2015) were found and utilized for bibliographic searching. Black and Miller (Black and Miller, 2015) included 18 studies, 2 of which concerned chemokines exclusively, and the remainder covered cytokines; with respect to cytokines, their observations comprised *in vivo* (IL-1 β , IL-6, IL-10, CRP, and TNF- α) and *in vitro* (IL-2, IL-4, IFN- γ , TGF- β) determinations. They reported high IL-6 and IL-1 β , and low IL-2, in patients with 'suicidality' compared to patients without suicidality and healthy controls; and low CSF levels of IL-8 in patients with suicidality compared to healthy controls. Ducasse et al. (Ducasse et al., 2015) analyzed 11 articles, limiting their meta-analysis *a priori* to 6 cytokines (IL-2, IL-6, TNF- α , IFN- γ , IL-4, TGF- β). They likewise found low plasma IL-2 levels in patients with suicidal behaviors compared to the other two groups, and as well, reported lower IL-4 and higher TGF- β plasma levels in both suicidal and non-suicidal patients than in healthy controls. The studies included in the two meta-analyses mostly overlap, but Black and Miller (Black and Miller, 2015) included additional studies in which positive findings for IL-1 β (Monfrim et al., 2014) and IL-6 (Monfrim et al., 2014; Pandey et al., 2012) were found, possibly explaining the divergent results. We include in our review six additional studies that were not included in either meta-analysis (Hoyo-Becerra et al., 2013; Juengst et al., 2014; Lindqvist et al., 2009; Rothenhäusler et al., 2006; Torres-Platas et al., 2014).

4. Discussion

Taken together, the current literature suggests that inflammation plays a role in suicidal behavior, but the heterogeneity of specific findings, even among the two available meta-analyses, is considerable. Possible explanations for discrepancies among studies include the following: 1) different phenotypes of suicidal behavior may be associated with distinct biological inflammatory patterns, exemplified by findings of Karlovi et al. (2012), in which IL-6 levels differed among suicidal compared with non-suicidal patients and correlated with depression severity, but only in the presence of melancholic as opposed to atypical features. 2) Comparability of different cytokine indices may be questionable, e.g. in one study (Isung et al., 2014), plasma and CSF IL-6 levels were found not to be associated. 3) Control of confounders is extremely challenging, since blood cytokine and soluble cytokine receptor levels are affected by a large number of factors such as age, sex, socioeconomic status, acute exercise, excessive caffeine use, BMI, smoking, sleep quality and habits, alcohol use, psychotropic medications, and medical comorbidities (O'Connor et al., 2009b). 4) Different immunoassay techniques may yield different results (de Koning et al., 2012). 5) Genetic and epigenetic effects may strongly influence individual reactivity to inflammatory stimuli (Kim et al., 2013).

This level of heterogeneity can be considered an indicator of inherent complexity. Thus additional approaches are needed to parse out relevant factors that may act as mediators and moderators of the relationship between inflammation and suicide risk, some of which may have potential as intervention points. For example, pivotal to the vulnerability for suicidal behaviors is a disturbed stress response (reviewed by Oquendo et al. (Oquendo et al., 2014)), which has been described with the Stress-Diathesis Model (Mann et al., 1999). Two of the most powerful influences on stress response, including inflammatory responses, are genetics and early life experiences, considered in section 4.1.

4.1. Factors affecting stress response

4.1.1. Genetics and heritability—These factors appear to contribute as much as 30-50% to the broad suicidality phenotype (Mann et al., 2009). Genes that regulate activity in the serotonergic, dopaminergic and GABAergic systems, HPA axis, and BDNF have been the most extensively studied in suicide (Mann et al., 2009). Studies of relationships between functional polymorphisms in cytokine genes and suicide attempts are few and do not provide a consensus. Investigations of the functional polymorphism *TNF-α -308 (A/G)* variously have found no differences in suicide attempters with various psychiatric diagnosis ($n=193$) vs. healthy controls ($n=420$) (Sáiz et al., 2008); a positive association between the GG genotype and depressed suicide attempters ($n=204$) vs. depressed non-attempters ($n=97$); and (in a sample with both sexes) greater prevalence in male suicides ($n=28$) than in non-psychiatric controls ($n=46$) (Omrani et al., 2009). Similarly, one study (Lee and Kim, 2010) of *TGF-β1* functional polymorphisms found no differences in either codon 10 or codon 20 polymorphisms in depressed suicide attempters ($n=124$) compared with depressed non-attempters ($n=61$) or healthy controls ($n=125$), whereas another study (Omrani et al., 2012) found the *TGF-β1-10* polymorphism to be more prevalent in suicide completers ($n=145$) compared to non-psychiatric controls ($n=200$). Single reports found the *IL-10 -1082*

genotype higher in suicides than non-psychiatric controls and the *IFN- γ +874* genotype more prevalent in male suicides (Omrani et al., 2009), and no differences in polymorphisms of the IL-1 gene complex [*IL-1 α -889 C/T*, *IL-1 β +3953 C/T*, *IL-1RA (86 bp)_n*] between a mixed diagnostic group of suicide attempters ($n=193$) and healthy controls ($n=420$) (Sáiz et al., 2008).

4.1.2. Acute psychosocial stress—Recently, Frank et al. (Frank et al., 2013) proposed that after an acute stressful event, glucocorticoids prime microglia into an enhanced state of inflammatory sensitivity, promoting enhanced immune responses, such as microglial cytokine production, to subsequent challenges. Stress-induced effects on neuronal activation are reversed by administering the microglial activation inhibitor minocycline, suggesting that microglial activation may mediate the effects of stress on resulting depressive symptoms (Hinwood et al., 2012). Microglia also have been implicated more directly in suicide risk, as Steiner et al. (Steiner et al., 2008) found higher microgliosis in suicides, with no effect of diagnostic group (schizophrenia, depression or healthy). Thus we might speculate that microglial activation moderates effects of life events such as major depressive episodes and psychosocial stressors on suicide risk.

4.1.3. Early life adversity—This subset of psychosocial stress is a major contributor to enhanced vulnerability to suicidal behaviors later in life (Brodsky and Stanley, 2008) and is predictive of multiple suicide attempts (Brodsky et al., 2001). Biologically, early life adversity is associated with abnormal cortisol stress response, persistent high levels of pro-inflammatory cytokines including TNF- α and IL-6, low-grade elevations in other pro-inflammatory markers such as C-reactive protein (CRP), and greater inflammatory responses to later psychosocial stress (reviewed in Fagundes et al., 2013). An explanatory model has been proposed by Miller et al (Miller et al., 2011), which posits that early life stress modulates inflammatory cells (monocytes/macrophages) so they exhibit hyper-responsivity to challenges and muted responsiveness to inhibitory feedback, and are further affected by hormonal signals and behaviors that heighten inflammation later in life.

4.1.4. Chronic social stress—Extensively studied with regard to both suicide risk and inflammatory changes, chronic psychosocial stress is associated with glucocorticoid receptor resistance. Furthermore, pro-inflammatory cytokines can induce glucocorticoid receptor resistance, thus creating a perpetuating cycle of enhanced inflammatory states. For example, individuals in a chronically stressful adult care-giving role exhibit elevated IL-6 (Kiecolt-Glaser et al., 2003). A recent study reported increased suicidal ideation in dementia family care-givers (O'Dwyer et al., 2013).

4.1.5. Clinical depression—Depressed patients exhibit changes in multiple inflammatory indices, such as elevated CRP (Scrandis et al., 2008), loss of brain astroglia and activation of microglia (McNally et al., 2008), and altered circulating levels of inflammatory cytokines and their soluble receptors, including soluble IL-2-receptor (sIL-2R), IL-6 and TNF- α (Liu et al., 2012). Severity of depressive symptoms also has been shown to correlate positively with levels of pro-inflammatory cytokines and chemokines (Suarez, 2003). Among patients receiving pro-inflammatory agents such as chronic IFN- α

therapy for the treatment of infectious diseases or cancer, 20% to 50% develop clinically significant depression (Capuron et al., 2002). Conversely, anti-inflammatory therapy has been shown to have antidepressant activity (Muller et al., 2006).

However, not all depressed patients show changes in inflammatory markers (Miller et al., 2013). It may be instructive to identify additional phenotypes associated with depression, inflammation, and suicidality. For example, increased inflammatory markers are more prominent in depressed patients with a history of childhood adversity (Fagundes et al., 2013), treatment resistance (Lanquillon et al., 2000) and obesity (Shelton and Miller, 2010), all factors that have been linked to suicidal behavior (Brodsky and Stanley, 2008; Klinitzke et al., 2013; Olin et al., 2012).

4.2. Symptom domains and inflammation

4.2.1. Illness severity—Depression severity could potentially be a major confound, as inflammatory changes could represent a function of severity rather than suicidal behavior *per se* (Lindqvist et al., 2009; Martinez et al., 2012). However, results of several studies indicate that severity cannot account for the findings. In one study where depressed patients with suicidal ideation also reported higher symptom severity (even when omitting the HDRS suicide evaluation item), this did not significantly account for variations in inflammatory index between groups (O'Donovan et al., 2013). Moreover, in another study in which depressed suicide attempters had elevated inflammatory markers compared with depressed non-attempters (Janelidze et al., 2011), a trend was seen toward higher severity MADRS scores in depressed *non*-attempters compared to attempters. Five additional studies found no effect of depression symptom severity (Gabbay et al., 2009; Isung et al., 2012a; Isung et al., 2012b; Kim et al., 2008; Li et al., 2013). Thus depression severity does not seem to explain the relationship between inflammation and suicidal behavior.

4.2.2. Anhedonia—Anhedonia has been shown to predict suicide (Winer et al., 2014). Moreover, on magnetic resonance imaging (MRI), structural and functional correlates of anhedonia are seen in stress-sensitive brain regions such as the nucleus accumbens and anterior cingulate gyrus, in both healthy (Wacker et al., 2009) and depressed subjects (Keedwell et al., 2005). In a rat model, microglial activation has been demonstrated in analogous brain regions, in the context of restraint stress that induces anhedonia, as modeled by reduced sucrose intake (Tynan et al., 2010). Whether anhedonia is linked to microglial activation in these brain areas in humans has not yet been studied.

4.2.3. Trait aggression—This characteristic has been associated with suicide (Dumais et al., 2005), suicide attempts (Dumais et al., 2005; Oquendo et al., 2004) and future suicidal behavior (Oquendo et al., 2004), and also with inflammatory changes. Aggression, anger, and hostility were positively associated with monocyte-associated TNF- α expression following lipopolysaccharide (LPS) stimulation (Suarez et al., 2002) in healthy men. Hostility also has been associated with higher IL-6 in men (Suarez, 2003) and greater LPS-stimulated expression of IL-1 β , IL-8 and IL-1 β in women (Suarez et al., 2004), with highest inflammation levels among depressed individuals. Although one study found an association between IL-6 and violent suicide methods (Lindqvist et al., 2009), none of the reviewed

studies above evaluated trait aggression in participants, suggesting an important direction for future investigation.

4.2.4. Impulsivity—Frequently, impulsivity is characteristic of individuals who engage in suicidal behaviors (Gvion and Apter, 2011) and has been recently associated with increased inflammatory markers as well. Isung et al (Isung et al., 2014) found increased plasma IL-6 in suicide attempters with high impulsivity and sensation-seeking personality traits. Whether these characteristics constitute a behavioral link between inflammation and suicidal behavior requires further study.

4.2.5. Hopelessness—Another emotional state that may increase vulnerability to suicidal behavior, hopelessness was also positively related to IL-6 levels (Sjögren et al., 2006). Studies with a longitudinal design could clarify the relationship between inflammation, suicidal behavior and hopelessness.

4.3. Mechanistic considerations

4.3.1. Peripheral vs central cytokines—As cytokines are rather large molecules that do not easily cross the blood brain barrier (BBB) (Haroon et al., 2012), the relationship between blood and CSF cytokine levels may not be a simple one, complicating the interpretation of studies of peripheral cytokines and suicidal behaviors. Increased circulating cytokines may affect brain and behavior through several mechanisms, including entry through “leaky” regions or by active transport (reviewed in (Haroon et al., 2012)). Alternatively, within-brain cytokine production could be increased by external factors such as stress-induced microglial activation (Frank et al., 2007). Although CSF measures of cytokines and chemokines would seem to be a better index of brain inflammation, nevertheless procedural feasibility, lower invasiveness burden for research participants, and ability to perform repeated measures make blood sampling more attractive. Surprisingly, none of the studies reported herein measured both CSF and peripheral cytokine levels; such studies are essential to clarify this issue.

4.3.2. Polyunsaturated fatty acids (PUFAs)—These essential dietary nutrients play a key role in the regulation of inflammation, largely through the actions of their metabolites, and have been implicated in depression and suicide risk. Omega-6 (n-6) PUFA metabolites include the primarily pro-inflammatory eicosanoids, while omega-3 (n-3)-PUFA-derived metabolites are the generally anti-inflammatory docosanoids (Calder, 2015). In humans, plasma omega-3 PUFA levels correlate negatively with levels of pro-inflammatory cytokines and positively with levels of anti-inflammatory cytokines (Ferrucci et al., 2006). Among *in vitro* studies, pre-incubation with long-chain omega-3 PUFA results in reduction of TNF- α and IL-6 expression and enhanced secretion of anti-inflammatory IL-10 (Oliver et al., 2012). Omega-3 PUFAs are lower in suicides (Lewis et al., 2011) and in suicide attempters in a concentration-dependent manner (Huan et al., 2004). Low levels of the omega-3 species docosahexaenoic acid (DHA) and an increased omega-6/omega-3 ratio also have been shown to predict suicide attempts in depression (Sublette et al., 2006). In studies of self-harming individuals, omega-3 fatty acid supplementation has been shown to reduce suicidal ideation (Hallahan et al., 2007). Specific effects of omega-3 PUFA supplementation on

cytokines include reduction of IL-6 responses to test-taking stressors (Kiecolt-Glaser et al., 2011).

4.3.3. Neurocircuitry—Increased cytokine levels could enhance suicidal behaviors by affecting specific areas in the brain or specific neurochemical processes associated with suicidality. For example, using positron emission tomography with [^{18}F] fluorodeoxyglucose (FDG-PET) in an MDD population, we found 1) lower regional cerebral metabolic rates of glucose (rCMRglu) in right dorsolateral prefrontal regions in suicide attempters, and higher rates in ventromedial regions in non-attempters (Sublette et al., 2013); and 2) lower rCMRglu in high-lethality suicide attempters than in low-lethality attempters in ventral, medial, and lateral prefrontal cortex (Oquendo et al., 2003). In a recent meta-analysis of twelve MRI studies (van Heeringen et al., 2014), structural changes in the left superior temporal gyrus, rectal gyrus and caudate nucleus, and functional changes in the anterior and posterior cingulate were associated with suicidal behavior. This distribution partially overlaps with brain regions reportedly targeted by cytokines in the brain: basal ganglia (especially ventral striatum) and anterior cingulate cortex (Miller et al., 2013). In patients with hepatitis C treated with IFN- α compared with untreated patients, left-sided activation was seen on fMRI during a visuospatial attention task in the inferior frontal gyrus and dorsal anterior cingulate (Capuron et al., 2005); and extensive bilateral rCMRglu increases were seen on FDG-PET in subcortical regions including basal ganglia and cerebellum (Capuron et al., 2007) studies.

Decreased brain volumes in the prefrontal cortex of suicidal patients also have been described (Ding et al., 2015), possibly reflecting neuroplasticity impairment. Pro-inflammatory cytokines are associated with decreased neurogenesis and induce reductions in BDNF expression, mRNA and protein levels (Calabrese et al., 2014). BDNF, the most relevant neuroplasticity mediator, affecting neuronal survival, growth and neurogenesis (Bramham and Messaoudi, 2005), also has been linked to suicidal behaviors. Reduced prefrontal cortex BDNF mRNA and protein levels, regardless of psychiatric diagnosis (Dwivedi et al., 2003) and increased BDNF gene DNA methylation (Keller et al., 2010) have been reported in suicides, and lower peripheral BDNF levels have been noted in suicidal patients. Volumetric changes also may be mediated through cytokine effects on corticoid secretion (Goshen et al., 2008), as increased cortisol levels are associated with decreased volumes in the prefrontal cortex and other brain areas.

Unlike neuroimaging methodologies, *postmortem* techniques necessitate *a priori* choice of single or few brain regions for study and thus cannot provide larger-scale information about regional interconnectedness. The small number of studies focused on brain inflammatory components related to completed suicide all found evidence of increased inflammation, instantiated by measurements of cytokine activity in the prefrontal cortex (Pandey et al., 2012; Tonelli et al., 2008), microglial priming and macrophage recruitment (Torres-Platas et al., 2014) and hypertrophy of astrocytes in the dorsal anterior cingulate (Torres-Platas et al., 2011), and toll-like receptor (TLR) expression in the dorsolateral prefrontal cortex (Pandey et al., 2014). Elevated mRNA expression of IL-4 and IL-13 (Tonelli et al., 2008), and mRNA and protein expression of IL-1 β , IL-6 and TNF- α (Pandey et al., 2012) were seen among suicides with a variety of diagnoses compared with normal controls dying of other causes.

Elevated microglial priming, macrophage recruitment (Torres-Platas et al., 2014), and hypertrophic astrocytes (Torres-Platas et al., 2011) were seen in the dorsal anterior cingulate of depressed suicides compared to psychiatrically healthy controls; however, since all case subjects were depressed suicides, no conclusions could be drawn regarding specificity for suicidal behavior as opposed to depression. In contrast, a study of TLRs compared depressed suicides, non-depressed suicides, depressed non-suicides, and controls (Pandey et al., 2014). TLRs are innate immune receptors that recognize pathogen- or damage-associated molecular patterns and stimulate microglia to release pro-inflammatory cytokines. Elevated TLR3 and TLR4 mRNA expression was seen in all depressed patients, irrespective of cause of death, compared with controls, while elevated TLR3 and TLR4 protein levels were seen in both suicide groups compared with non-suicides irrespective of diagnosis (Pandey et al., 2014).

4.3.4. Monoaminergic neurotransmission—One of the mechanisms by which cytokines may influence suicidal behavior is through effects on monoaminergic neurotransmission, extensively associated with both depression and suicidal behaviors (reviewed in (Mann, 2003)). For example, increased serotonin transporter (SERT) mRNA is seen after IFN- α administration in mice (Morikawa et al., 1998). Additionally, there is evidence suggesting that genetic SERT variants may be more susceptible to the actions of pro-inflammatory cytokines: hepatitis C patients with the *SLC6A4* (SERT) genetic variant are more likely to develop a depressive episode during INF- α treatment (Lotrich et al., 2009; Pierucci-Lagha et al., 2010).

Another critical link between inflammatory and serotonin systems is provided by cytokine-activated enzyme indoleamine-2,3-dioxygenase (IDO), which catalyzes the production of kynurenine from tryptophan. Activation of this pathway could reduce generation of serotonin, the other downstream tryptophan product (Maes et al., 1993). Many of the cytokines studied in relation to suicide (Janelidze et al., 2011; Kim et al., 2008; Lindqvist et al., 2009; Tonelli et al., 2008) are known stimulators of IDO, and knockout mice for the IDO gene fail to express depressive-like symptoms despite immune activation (O'Connor et al., 2009a). However, high levels of kynurenine also have been associated with suicide attempts without evidence of tryptophan depletion (Sublette et al., 2011), suggesting an alternative mechanism whereby elevations of kynurenine or its metabolites, quinolinic acid and kynurenic acid, may influence mood and suicide risk through direct effects on brain. This is supported by a study showing that treatment with IFN- α increased CSF kynurenine, quinolinic acid and kynurenic acid without any decrease of CSF tryptophan (Raison et al., 2010). Moreover, quinolinic acid is an N-methyl-D-aspartate (NMDA) receptor agonist; and ketamine, a known NMDA receptor antagonist, reduced suicidality in some recent studies (DiazGranados et al., 2010; Larkin and Beautrais, 2011). This hypothetical pathway is illustrated in Figure 2.

4.3.5. Immune dysregulation mechanisms governing resilience—In addition to higher production of pro-inflammatory cytokines as a risk factor for suicidal behaviors, decreases in anti-inflammatory processes should also be considered. For example, low omega-3 PUFA intake may contribute to a perpetuation of immune dysregulation through lower production of the docosanoid metabolites, resolvins, protectins, and maresins, so

named because of their role facilitating resolution of inflammation (Calder, 2015). Other changes in resiliency systems may also confer vulnerability to disease. Following mild stress, BDNF^{+/−} mice did not increase production of the anti-inflammatory cytokine IL-10 or of the neuroprotective branch of the kynurenine pathway, contrary to wild-type mice (Dugan et al., 2015). More studies are needed to clarify these less investigated pathways.

4.4. Causality or Epiphenomenon?

These observations support a connection between alterations in cytokine levels, vulnerability factors, and suicidal behavior. What remains to be elucidated is the nature of this relationship. Thus, these findings could represent an epiphenomenon, in which increased cytokine concentrations observed in suicide attempters are the result of the stress response activation. For example, physical tissue damage, as may be seen in more violent suicidal attempts, could partly explain increased levels of circulating cytokines. Indeed, in one of the reviewed studies (Lindqvist et al., 2009), increased levels of IL-6 were greatest in violent suicide attempts. However elevated inflammatory markers are also seen in connection with high suicidal ideation independent of previous suicide attempts (O'Donovan et al., 2013). Therefore cytokine increases cannot be attributed solely to the physiologic consequences of a recent suicidal attempt, although they could arise from the stress and emotional pain that triggered the suicidal urge. For instance, increases in IL-1 β gene expression, plasma IL-6 (Brydon et al., 2005) and IL-2 (Wieck et al., 2014) occur following a purely psychologically challenging task. On the other hand, favoring a causal relationship in at least a subset of patients are reports describing suicidal behaviors in patients receiving treatment for medical conditions with therapeutic cytokines (Dieperink et al., 2004).

4.5. Effects of Suicidality Independent from Depression?

One of the most relevant remaining questions is whether specific changes in cytokines associate with suicidal ideation or behaviors independently from effects of psychiatric diagnosis. We found nine studies that directly compared depressed suicidal patients to depressed non-suicidal patients (see Table 5). On qualitative review, there is no clear suggestion that any particular cytokine abnormality distinguishes suicidal from non-suicidal depressed patients. Serafini et al. (Serafini et al., 2013) also reviewed the literature and tabulated cytokines “more frequently associated with MDD compared to those related to suicidality”. Each cytokine abnormality was reported in one or two studies, with the most prominent finding in suicidal MDD of higher TNF- α in 4 studies (Boehm et al., 2010; Janelidze et al., 2011; Li et al., 2013; Pandey et al., 2012); however, this is confusing as Pandey (Pandey et al., 2012) did not utilize a depressed control group; Li et al. (Li et al., 2013) report equal levels of TNF- α among suicidal and non-suicidal MDD; and Boehm et al. (Boehm et al., 2010) is not a study of depressed patients. These findings are in direct contrast with Black and Miller (Black and Miller, 2015), who, using quantitative meta-analytic methods, found a marked lack of effect with respect to TNF- α but did find significant differences in suicidal compared with non-suicidal patients in IL-1 β and in IL-6 after removing one study through sensitivity analysis for heterogeneity. Thus IL-1 β and IL-6 seem to be the most likely candidates for continued research. Once again, we note that control of confounders is of paramount importance in continuing studies to distinguish the interrelationships between cytokines, suicidal behavior, and depression. For instance, not

only cytokines (Raison and Miller, 2013) but many of the factors associated with suicidal behavior--such as acute and chronic stress, anhedonia, hopelessness, and differences in PUFAs, brain functioning and circuits, or monoaminergic transmission (Gelenberg, 2010)--are also linked to depression.

4.6. Limitations

The number of studies focusing on the relationship between cytokines and suicidal behaviors is still small, with modest sample sizes, and the methodologies employed are diverse. Accordingly, this review was non-quantitative in nature and cannot yield conclusions about effect sizes. Additionally, we did not address possible effects of publication bias. Recruitment bias is also a general issue in suicidal behavior studies, as differences may exist between participants who do or do not agree to participate. Caution is needed in interpreting combined results from suicide attempters and suicides since, although suicide attempt is a risk factor for completion, and suicides are obviously a subset of suicide attempters, it is unclear whether suicide completion is simply suicidal behavior on the extreme end of a severity continuum, or whether suicides represent a distinct neurobiological subtype. Different methods for suicide attempt or completion may also reflect differences in lethality and intent, and may be associated with distinct inflammatory patterns. In most studies presented in our review, suicide methods were not controlled. Also, interactions with other biological markers associated with suicidal behaviors, such as monoamines or HPA axis mediators, might create potential confounds that were not evaluated in the majority of the included studies. Moreover, it may be methodologically problematic to compare *in vivo* and *postmortem* results, since agonal processes may influence cytokines, and clinical information obtained through psychological autopsies are not directly comparable to psychiatric assessments of live patients. Other limitations to *postmortem* studies of suicide include prolonged *postmortem* intervals and effects of psychoactive medications (Pandey and Dwivedi, 2010). Finally, *a priori* hypotheses concerning specific cytokines were not comparable across all studies.

5. Conclusions

Suicide risk has been associated with chronic stress, HPA hyperactivity, serotonergic abnormalities, and in some studies, persistently elevated inflammatory markers, especially elevation of IL-6. Larger, methodologically rigorous studies are needed to draw definitive conclusions regarding the association of inflammatory proteins and suicide. Such studies would contribute to an integrated understanding of the interplay among these different elements, and allow the identification of proximate suicide risk factors that are potentially modifiable. For example, if immune responses such as IL-6 activation mediate the effects of chronic stress on suicide risk, then treatments that reduce IL-6 could have promise. Future studies using prospective designs could focus on whether IL-6 predicts risk of suicidal behavior. Associated clinical characteristics that could modulate the effects of IL-6 also should be taken into account. A better understanding of suicide risk factors that could be amenable to intervention, such as reducing inflammation or altering dietary intake of PUFAs, is of crucial importance as it could potentially decrease the devastating impact of suicidal behaviors on at-risk individuals, their families, and society.

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Highlights

- We reviewed 22 articles concerning cytokines and suicidal ideation, suicide attempts or suicide completion.
- The most consistent finding was elevated interleukin (IL)-6, found in 8 out of 14 studies, in CSF, blood, and *postmortem* brain, and associated with more violent attempts and future suicide completion.
- Considerable heterogeneity among cytokine results indicates a high level of complexity.
- Thus putative mediators and moderators of the effects of inflammation on suicide risk merit further study.

Figure 1. Algorithm employed to perform literature search and article selection process
This flowchart describes the databases used for article search, the number of retrieved articles and the process and criteria used to achieve the final article selection.

Figure 2. Hypothetical pathways through which pro-inflammatory cytokines may influence suicide risk

Stressors and constitutional factors associated with suicidal behaviors reciprocally interact with the immune system resulting in increased levels of pro-inflammatory cytokine in vulnerable individuals. Pro-inflammatory cytokines strongly induce IDO enzyme favoring the kynurenine pathway, which results in decreased serotonin and increased quinolinic acid, both associated with depression and suicidal behaviors. Abbreviations: 5-HT - 5-hydroxytryptamine (serotonin); IDO - Indoleamine 2,3-dioxygenase; NMDA - N-Methyl-D-aspartate.

Table 1**Studies of Cytokines and Suicidal Ideation.**

Study	Sample	Source	Results
Mendlovic et al., 1999	N=6 depressed with suicidal ideation; N=3 depressed without suicidal ideation; N=9 controls	PHA-stimulated lymphocytes	↑ INF- γ in suicidal depressed patients than healthy controls ↓ INF- γ in non-suicidal depressed than in healthy controls = IL-2, IL-4, IL-5, IL-10 in the 3 groups
Gabbay et al., 2009	N=12 suicidal depressed adolescents; N=18 depressed non-suicidal adolescents; N=15 healthy controls	Plasma	↓ TNF- α in suicidal depressed adolescents vs non-suicidal depressed patients = TNF- α in suicidal depressed vs controls ↑ IFN- γ in depressed suicidal and non-suicidal adolescents vs controls = IL-6, IL-1 β , IL-4 in the 3 groups
Martinez et al., 2012	N=18 depressed patients undergoing 8 week treatment protocol N=8 had IL-6 N=9 had TNF- α	CSF	+ correlation between IL-6, TNF- α and SSI scores after treatment; no correlation at baseline
O'Donovan et al., 2013	N=29 depressed with high suicidal ideation; N=45 depressed with low suicidal ideation; N=48 healthy controls	Plasma	↑ IL-6 and CRP depressed high suicidal ideation vs depressed low suicidal ideation and controls = TNF- α , TGF- β , IL-10 in the 3 groups = individual inflammatory markers for low suicidal ideation depressed vs controls
Monfrim et al., 2014	N=40 bipolar with suicidal ideation ^a ; N=40 bipolar without suicidal ideation ^a ; N=40 control patients	Serum	↑ IL-1 β in bipolar patients with suicidal risk vs both other groups
Juengst et al., 2014	N=37 participants with TBI and CSF levels at baseline N=32 at 6-month follow-up N=33 at 12-month follow-up	CSF	+ TNF- α levels at baseline predicted suicidal ideation ^b at 12-month but not 6-month follow-up
Li et al., 2013	N=33 depressed with suicidal ideation; N=12 depressed suicide attempters; N=19 depressed without suicidal ideation; N=64 healthy controls	Plasma	↑ TNF- α in depressed patients vs healthy controls on admission ↓ TNF- α in depressed patients post treatment ↓ TNF- α greater for responders vs non-responders to venlafaxine treatment = TNF- α levels between depressed patients with suicidal ideation vs depressed suicide attempters vs non-suicidal depressed patients
Karłovi et al., 2012	N=23 melancholic depressed with suicidal ideation ^c ; N=20 melancholic depressed without suicidal ideation ^c ; N=7 atypical depressed melancholic depressed with suicidal ideation ^c ; N=16 atypical depressed melancholic depressed without suicidal ideation ^c	Serum	↑ IL-6 in depressed melancholic with suicidal ideation ^c vs depressed melancholic without ideation ^c

^aReported as 'suicide risk'; defined as any positive answer(s) in the suicidality module of the Mini International Neuropsychiatric Interview (M. Kaster, personal communication).

^bReported as 'suicidal endorsement'.

^cReported as 'suicidal behavior'.

Abbreviations: CRP – C-reactive protein; CSF – cerebrospinal fluid; IL - interleukin; IFN - interferon; PHA - phytohemagglutinin; SSI – Scale for Suicidal Ideation; TGF – transforming growth factor; TNF – tumor necrosis factor.

Symbols: ‘↑’ - increased; ‘↓’ - decreased; ‘=’ - no change; ‘+’ – positive.

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Table 2**Studies of Cytokines and Suicide Attempts.**

Study	Sample	Source	Results
Nassberger and Traskman-Bendz, 1993	N=30 suicide attempters (various psychiatric disorders); N=25 healthy controls	Plasma	↑ sIL-2R in suicide attempters
Rothenhäusler et al., 2006	N=25 formerly depressed suicide attempters; N=25 healthy controls	Plasma	= sIL-2R in suicide attempters
Huang and Lee, 2007	N=11 depressed suicide attempters; N=31 depressed non-attempters; N=40 healthy controls	Serum	= IL-1 β , TNF- α , IL-10 between depressed suicide attempters and depressed non-attempters
Kim et al., 2008	N=36 depressed suicide attempters; N=33 depressed non-attempters; N=40 healthy controls	Mitogen stimulated whole blood	↑ IL-6 in depressed non-attempters vs depressed attempters and controls ↑ IL-6 in depressed attempters vs controls when correcting for sampling time ↓ IL-2 in suicide attempters vs non-attempters and controls ↓ IFN- γ and IL-4 total depressed patients vs controls ↑ TGF- β 1 total depressed patients vs controls
Lindqvist et al., 2009	N=63 suicide attempters (various psychiatric disorders); N=47 healthy controls	CSF	↑ IL-6 in suicide attempters = IL-1 β , IL-8 and TNF- α in both groups
Janelidze et al., 2011	N=47 depressed suicide attempters; N=33 depressed non-attempters; N=40 healthy controls	Plasma	↑ IL-6, TNF- α and ↓ IL-2 in depressed suicide attempters vs depressed non-attempters and controls
Lindqvist et al., 2011	N=124 suicide attempters at baseline Of these, at follow-up (mean 15 $\pm$ 4 years), N=31 were violent suicide attempters	CSF	Factor consisting of ↑ IL-6, 5-HIAA, HVA and ↓ orexin associated with violent suicide attempts
Isung et al., 2012a	N=43 suicide attempters (various psychiatric disorders); N=20 healthy controls	CSF	↓ IL-8, VEGF in suicide attempters = IL-6 in both groups
Martinez et al., 2012	N=18 depressed N=15 depressed with IL-1;	CSF	+ correlation between IL-1 and history of suicide attempts
Li et al., 2013	N=33 depressed with suicidal ideation; N=12 depressed suicide attempters; N=19 depressed without suicidal ideation; N=64 healthy controls	Plasma	↑ TNF- α in depressed patients vs healthy controls on admission ↓ TNF- α in depressed patients post treatment ↓ TNF- α greater for responders vs non-responders to venlafaxine treatment = TNF- α levels between depressed patients with suicidal ideation vs depressed suicide attempters vs non-suicidal depressed patients;
Vargas et al., 2013	N=141 suicide attempters; N=201 non-attempters (all outpatients at a smoking treatment clinic)	Serum	= IL-6, TNF- α in both groups

Abbreviations: CSF – cerebrospinal fluid; 5-HIAA – 5-hydroxyindoleacetic acid; HVA – homovanillic acid; IL – interleukin; IFN – interferon; PHA – phytohemagglutinin; sIL-2R – soluble interleukin receptor; TGF – transforming growth factor; TNF – tumor necrosis factor; VEGF – vascular endothelial growth factor.

Symbols: ↑ - increased; ↓ - decreased; = - no change.

Table 3

Studies of Cytokines and Suicides.

Study	Sample	Source	Results
Tonelli et al., 2008	N=34 suicide completers (various psychiatric diagnosis); N=17 controls	<i>Postmortem</i> orbitofrontal cortex brain tissue (RT-PCR for mRNA)	↑ IL-4 in female suicides ↑ IL-13 in male suicides = IL-1β, TNF-α, IL-6, IL-5
Pandey et al., 2012	N=24 adolescent suicides (various psychiatric disorders); N=24 controls	<i>Postmortem</i> prefrontal cortex brain tissue	↑ IL-6, IL-1β, TNF-α in suicides
Hoyo-Becerra et al., 2013	N=20 suicides (N=8 depressed, N=12 undisclosed diagnoses); N=13 controls	<i>Postmortem</i> hippocampus, amygdala and gyrus cinguli tissue	↑ IL-6 in suicides hippocampus = TNF- α
Torres-Platas et al., 2014	N=7 depressed suicides; N=7 controls	<i>Postmortem</i> dorsal anterior cingulate white matter	= IL-1β, IL-1Ra, TNF-α, IL-10 in both groups
Lindqvist et al., 2011	N=124 suicide attempters at baseline Of these, at follow-up N=9 suicides	CSF	↑ Factor consisting of IL-6, 5-HIAA, HVA and ↓ orexin associated with suicide
Isung et al., 2012b	N=58 suicide attempters at baseline (various psychiatric diagnosis); Of these, at follow-up, N=51 survivors N=7 suicides	Plasma	↓ IL-2 in suicides = IL-1α, IL-1β, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, MCP-1, EGF in both groups

Abbreviations: CSF – cerebrospinal fluid; 5-HIAA – 5-hydroxyindoleacetic acid; HVA –homovanillic acid; IL - interleukin; I FN - interferon; PHA - phytohemagglutinin; RT-PCR – reverse transcription polymerase chain reaction; TGF – transforming growth factor; TNF – tumor necrosis factor.

Symbols: ‘↑’ - increased; ‘↓’ - decreased; ‘=’ - no change; RT-PCR – reverse transcription polymerase chain reaction.

Table 4

Results according to individual cytokines and outcome measures studied.

Cytokine	Suicidal ideation			Suicide attempt			Suicide		
	↑	↓	=	↑	↓	=	↑	↓	=
IL-6	(2) Martinez et al., 2012 (CSF); O'Donovan et al., 2013 (P) Karlovi et al., 2012 ^a (S)		(1) Gabbay et al., 2009 (P)	(3) Janelidze et al., 2011(P); Lindqvist et al., 2011 (CSF); Lindqvist et al., 2009 (CSF)	(1) Kim et al., 2008 (MSB)	(2) Vargas et al., 2013 (S); Isung et al., 2012a (CSF)	(3) Hoyo-Becerra et al., 2013 (PMB); Pandey et al., 2012 (PMB); Lindqvist et al., 2011 (CSF)		(2) Tonelli et al., 2008 (PMB); Isung et al., 2012b (P)
TNF-α	(1) Martinez et al., 2012 (CSF)	(1) Gabbay et al., 2009 (P)	(2) O'Donovan et al., 2013 (P); Juengst et al., 2014 (CSF)	(1) Janelidze et al., 2011 (P)		(3) Huang and Lee, 2007; Vargas et al., 2013 (S); Lindqvist et al., 2009 (CSF)	(1) Pandey et al., 2012 (PMB)		(4) Hoyo-Becerra et al., 2013 (PMB); Tonelli et al., 2008 (PMB); Torres-Platas et al., 2014 (PMB); Isung et al., 2012b (P)
IL-2			(1) Mendlovic et al., 1999 (PSL)		(2) Kim et al., 2008 (MSB); Janelidze et al., 2011 (P)			(1) Isung et al., 2012b (P)	
IL-1β	(1) Monfrim et al., 2014 (S)		(1) Gabbay et al., 2009 (P)	(1) Martinez et al., 2012 (CSF)		(2) Huang and Lee, 2007(S); Lindqvist et al., 2009 (CSF)	(1) Pandey et al., 2012 (PMB)		(3) Tonelli et al., 2008 (PMB); Torres-Platas et al., 2014 (PMB); Isung et al., 2012b (P)
INF-γ	(1) Mendlovic et al., 1999 (PSL)		(1) Gabbay et al., 2009 (P)			(1) Kim et al., 2008 (MSB)		(1) Isung et al., 2012b (P)	
IL-4			(2) Mendlovic et al., 1999 (PSL); Gabbay et al., 2009 (P)				(1) Tonelli et al., 2008 (PMB)		(1) Isung et al., 2012b (P)
IL-13							(1) Tonelli et al., 2008 (PMB)		
IL-8					(1) Isung et al., 2012a (CSF)	(1) Lindqvist et al., 2009 (CSF)			(1) Isung et al., 2012b (P)
IL-10			(2)			(1)			(2)

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Cytokine	Suicidal ideation	Suicide attempt	Suicide
	↑ ↓ =	↑ ↓ =	↑ ↓ =
	Mendlovic et al., 1999 (PSL); O'Donovan et al., 2013 (P)	Huang and Lee, 2007 (S)	Torres-Platas et al., 2014 (PMB); Isung et al., 2012b (P)
TGF-β	(1) O'Donovan et al., 2013 (P)	(1) Kim et al., 2008 (MSB)	

^aReported as 'suicidal behavior'.

Abbreviations: CSF - cerebrospinal fluid; MSB - mitogen stimulated blood; P - plasma; PMB - *postmortem* brain; PSL - phytohemagglutinin-stimulated lymphocytes; S - serum.

Symbols: (#) - number of studies; '↑' - increased; '↓' - decreased; '=' - no change.

Table 5

Cytokine findings with respect to group comparisons among studies that compared suicidal major depressive disorder (MDD) to non-suicidal MDD or healthy controls.

Study	Source	Suicidal MDD vs. Non-Suicidal MDD/BD	Suicidal MDD vs. Controls	Non-Suicidal MDD vs. Controls
Suicide Attempts				
Huang and Lee, 2007	Plasma	= IL-1 β = TNF- α = IL-10		
Janelidze et al., 2011	Plasma	$\uparrow$ IL-6 $\uparrow$ TNF- α $\downarrow$ IL-2	$\uparrow$ IL-6 $\uparrow$ TNF- α $\downarrow$ IL-2	
Kim et al., 2008	Mitogen-stimulated whole blood	$\downarrow$ IL-6 $\downarrow$ IL-2	$\downarrow$ IL-2 $\downarrow$ IL-4 $\downarrow$ IFN- γ $\uparrow$ TGF- β 1	$\uparrow$ IL-6 $\downarrow$ IL-4 $\downarrow$ IFN- γ $\uparrow$ TGF- β 1
Li et al., 2013	Plasma	= TNF- α	$\uparrow$ TNF- α	$\uparrow$ TNF- α
Suicidal Ideation				
Gabbay et al., 2009	Plasma	$\downarrow$ TNF- α = IL-1 β = IL-4 = IL-6	$\uparrow$ IFN- γ = IL-1 β = IL-4 = IL-6	$\uparrow$ IFN- γ = IL-1 β = IL-4 = IL-6
Karlovic et al., 2012	Serum	$\uparrow$ IL-6		
Martinez et al., 2012	CSF	$\uparrow$ IL-1 β		$\uparrow$ IL-6 $\uparrow$ TNF- α
Mendlovic et al., 1999	PHA-stimulated lymphocytes	$\uparrow$ IFN- γ ($\downarrow$) IL-4 ($\downarrow$) IL-5 = IL-2 = IL-10	$\uparrow$ IFN- γ = IL-2 = IL-4 = IL-5 = IL-10	$\downarrow$ IFN- γ = IL-2 = IL-4 = IL-5 = IL-10
O'Donovan et al., 2013	Plasma	$\uparrow$ IL-6 = IL-10 =TNF- α =TGF- β	$\uparrow$ IL-6 = IL-10 =TNF- α =TGF- β	= IL-6 = IL-10 =TNF- α =TGF- β

Postmortem studies were not included because they did not utilize non-depressed control groups.

Abbreviations: CSF – cerebrospinal fluid; IL - interleukin; IFN - interferon; PHA - phytohemagglutinin; TGF – transforming growth factor; TNF – tumor necrosis factor.

Symbols: ' $\uparrow$ ' - increased; ' $\downarrow$ ' - decreased; '=' - no change