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# The aetiology of social deficits within mental health disorders: The role of the immune system and endogenous opioids

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ABSTRACT

The American National Institute for Mental Health (NIMH) has put out a set of research goals that include a long-term plan to identify more reliable endogenous explanations for a wide variety of mental health disorders (Insel, 2013). In response to this, we have identified a major symptom that underlies multiple mental health disorders – social bonding dysfunction. We suggest that endogenous opioid abnormalities can lead to altered social bonding, which is a symptom of various mental health disorders, including depression, schizophrenia and ASD. This article first outlines how endogenous opioids play a role in social bonding. Then we show their association with the body's inflammation immune function, and review recent literature linking inflammation to mental health 'immunophenotypes'. We finish by explaining how these immunophenotypes may be caused by alterations in the endogenous opioid system. This is the first overview of the role of inflammation across multiple disorders where we provide a biochemical explanation for why immunophenotypes might exist across diagnoses. We propose a novel mechanism of how the immune system may be causing 'sickness-type' behaviours (fatigue, appetite change, social withdrawal and inhibited motivation) in those who have these immunophenotypes. We hope that this novel aetiology can be used as a basis for future research in mental health.

## 1. Background

While the aetiology of many disorders is still not well-understood, psychiatrists are more widely accepting that there are 'subtypes' of different mental health disorders, such as for depression (Kessing, 2007; Preskorn, 2011). On top of this, Allsopp et al. (2019) have argued that there is a large amount of 'symptom overlap' between different mental health diagnoses (p. 19), which suggests that simple diagnostic labels such as depression are catch-all terms that are not entirely useful. It is also likely that different 'subtypes' require different treatments (Fried, 2017). Allsopp et al. (2019) conclude that "by focusing on diagnostic categories … specific causal pathways may be obscured" (p. 21). This may be why, even with the current symptom-based approach to labelling mental health disorders, the use of 'depression' as an umbrella diagnosis has been shown to lead to an unreliable description of symptoms, where there can be 1030 unique symptom-profiles across 3703 patients (Fried and Nesse, 2015). The unreliability of a label predicting symptom profiles is still not removed when using 'subtype' terms such as 'melancholic' or 'atypical' depression (Łojko and Rybakowski, 2017). This variety of symptom profiles for the same diagnosis suggests that diagnostic labels, in their current form, may not be appropriate for describing a patient's condition.

Depression is not unique among mental health disorders in this regard; other common disorders have had related criticisms levied against them. One of these disorders is schizophrenia, which is seen by some as an umbrella term for multiple conditions with similar presentations that have different causal factors and treatment directions (Gillespie et al., 2017; Lasalvia and Tansella, 2013; van Os et al., 1999; Wimberley et al., 2016). Autism spectrum disorder (ASD) has been proposed to have multiple possible endocrinological causes, where either low or excessive levels of certain neurotransmitters give rise to ASD-like presentation (e.g. Pellissier et al., 2018). Social anxiety disorder (SAD; aka social phobia) likely has a subtype where serotonin plays a key role, while other subtypes have unknown aetiologies (Stein and Andrews, 2015).

The use of umbrella-term diagnoses based on wide-ranging symptoms, instead of an aetiology-based diagnosis, means that the direction of treatment that is chosen for patients is frequently not effective. For example, those with so-called 'treatment resistant' depression. This is a term used to describe those who have depression that do not respond to at least one treatment. By definition, these patients do not benefit from

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the initial treatments usually used for a depression diagnosis, yet they make up a large proportion of those with a depression diagnosis (Nemeroff, 2007; Murphy et al., 2017), with only 35% of patients going into full remission with their first pharmacological treatment (Kautzky et al., 2019). It is only upon attempting more than one treatment method that the remission rates lower (Murphy et al., 2017). 'Treatment resistance' that can go into remission when using a second or third treatment option implies that 'treatment resistant' is a misnomer. That it can be treated, but only with different therapies, suggests that the initial treatment given to these patients was not appropriate for the aetiology of their mental health condition. Thus, much 'treatment resistance' is likely to stem from providing a treatment that, while attempting to address the diagnostic label, fails to tackle the actual neurochemical causes of the symptoms in each patient.

In light of this, it is important that healthcare providers and researchers start to explore different methods of deciding initial treatment plans for those with mental health disorders. Instead of using the umbrella diagnostic labels as the main determinant of treatment direction, there should be an attempt to determine the aetiology of the disorder first. This will then allow for a more appropriate treatment plan, which will in turn save patients and healthcare professionals time, money and possibly lives. This is why the NIMH has a long-term plan to identify more reliable endogenous explanations for a wide variety of mental health disorders (Insel, 2013).

One possible way forward is provided by Akil et al. (2018), who have suggested the use of a multi-scale systems approach, which focuses on "identifying the brain circuits that are dysfunctional in several animal models of depression as well the changes in gene expression that are associated with these models" (p. 272). We build on this approach by using evidence from multiple sub-fields to propose an aetiology for a subset of those with apparently separate mental health diagnoses that have a similar central symptom – social bonding deficits. To do this, we explore the role of inflammation and endogenous opioids (EOs) as possible neurochemical mechanisms for these deficits.

We will first look at the role of EOs in social bonding to establish a theoretical basis for EO abnormalities as a potential aetiology for deficits in social bonding. After this, we will show the role EOs play in the body's inflammation immune function. Then, we will outline recent research showing the role of the immune system, in the form of inflammation, on mental health disorders and, finally, we provide evidence that EO abnormalities are a possible cause for subtypes of mental health disorders that involve social bonding deficits. In doing this, we not only hope to help further the NIMH's long-term plan to find endogenous causes for mental health disorders, but also answer calls from other researchers to integrate inflammation and social bonding research (Gassen and Hill, 2019) while ensuring that we do so in a more pragmatic approach to mental health (Allsopp et al., 2019).

## 2. Endogenous opioids and social bonding

Endogenous Opioids (EOs) are a type of neurotransmitter that consist of different 'families', endorphins, enkephalins and dynorphins being the three best-known of these (see Benarroch, 2012 for a review of their chemical precursors, production and release as well as information on the other families). These families each preferentially bond to one of 3 types of opioid receptors. Endorphins have a preferential binding specificity for the μ-opioid receptor (MOR), enkephalins for the δ-opioid receptor (DOR), and dynorphins for the κ-opioid receptor (KOR).

Jaak Panksepp was first to note that opioids likely play a role in bonding processes (Panksepp et al., 1978, 1980a, 1980b; Nelson and Panksepp, 1998). He noted that "brain opioids constitute the brain neurochemical system for which we have the most extensive evidence for a key role in the specific control of social-affective processes" (Panksepp et al., 1986 p. 20). While his research was largely based on mother-infant bonding, many others have argued that the link between EOs and all types of social bonding has parallels with the behaviour of narcotics addicts and those who form close relationships (Panksepp, 1999; Insel, 2003; Burkett and Young, 2012). Burkett and Young (2012) go so far as to argue that 'social attachment may be understood as a behavioural addiction' (p. 1) in some sense, where they also provide a comparison of each of the diagnostic criteria for substance (opioid) addiction from the DSM at the time (DSM IV-TR) with a related behaviour in social attachments (p.43).

More recently, the 'Brain-Opioid Theory of Social Attachment' (BOTSA) has re-popularised in the context of primate and human social bonding (Dunbar, 2009; Machin and Dunbar, 2011). In BOTSA, Machin and Dunbar (2011) suggest that it is EOs that play the key role in social bonding over oxytocin and other nonapeptides like arginine vasopressin, which attracted considerable research interest in the early 21st century (Dunbar, 2007), whose effects have been overstated (Bakermans-Kranenburg and van IJzendoorn, 2013; Bakermans-Kranenburg and van IJzendoorn, 2014; Benjamin et al., 2012; Nave et al., 2015). EOs have been linked to maternal and infant bonding (Panksepp et al., 1980a, 1980b; Kalin et al., 1995; Barr et al., 2008), grooming behaviour (Martel et al., 1995), as well as kin relationships, separation anxiety and play behaviour (Vanderschuren et al., 1995). One of the key opioid neurotransmitters that Machin and Dunbar (2011) highlight is the MOR-preferred $\beta$-endorphin ($\beta$e; Keverne et al., 1989).

Evidence for BOTSA comes from multiple fields, including work in animal models. It has been found that MOR receptors play a necessary role in adult social bonding (Burkett et al., 2011, p. 2207), a finding which has been confirmed with other non-primate animal models (Garduño-Gutiérrez et al., 2013; Kelm-Nelson et al., 2013; Kobayashi et al., 2013; Parra-Gámez et al., 2013; Resendez et al., 2013). Other studies have used nonhuman primates to understand the role of EOs in the social bonding process. Ragen et al. (2015) looked at monogamous titi monkeys in two experiments. They found that a MOR agonist reduced separation anxiety, while a MOR antagonist lead to increases in stress hormone release during separation, suggesting a role of EOs in bonding maintenance and the stress response.

Another field of research that has explored the role of EOs on social bonding is research with human participants. For example, Nummenmaa et al. (2015) found that MOR density correlates with attachment style. Mu-opioid ligands are natural painkillers (Zubieta et al., 2001; Zubieta et al., 2003a,b), but do not readily pass through the blood brain barrier (Witt and Davis, 2006). As a result, pain threshold or pain tolerance has been used as an experimental proxy for mu-opioid release in the central nervous system (Cohen et al., 2010; Tarr et al., 2015; Tarr et al., 2016). Cohen et al. (2010) found that pain threshold increased by a larger amount after group exercise compared to equally demanding solo exercise, suggesting that MOR release is related to group activity, not just exercise in general. Johnson and Dunbar (2016) found that pain threshold predicted social network size, which further suggests that MOR activity may be related to social bonding in some way.

Løseth et al. (2014) created a model that builds on BOTSA, which they described as the 'State-dependent μ-Opioid Modulation of Social Motivation Model' (Løseth et al., 2014, p. 9). They suggest that the MOR system differentially modulates positive and negative affect in relation to social bonding. Rejection, a negative stimulus, causes activation of MORs in the bilateral amygdala, periaqueductal grey area and the ventral striatum (Hsu et al., 2013), whilst acceptance, a positive stimulus, leads to increased MOR activation in the right insula and the left amygdala (Hsu et al., 2013). They cite the role of EOs as pain modulators to suggest that MOR activation plays a key part in social motivation by either alleviating distress (if one has an initial state of distress) or increasing resistance to rejection (if one is initially comfortable). The understanding of the interplay between MOR activation and social motivation has been further developed by Pellissier et al. (2018) in their 'μ-opioid receptor balance' (MOR-Balance) model. The MOR-Balance model proposes a bell-curve for ideal MOR activation regarding social bonding (Fig. 1), where too little activation causes social withdrawal, and over-activation causes social indifference.

The purpose of this section was to summarise the role of the opioid system in bonding behaviour, with a focus on how the balance of MOR activation affects social bonding. This background knowledge is needed to understand how changes in MOR activation may affect social bonding function in those with mental health disorders.

## 3. Immune system and endogenous opioids

This section will focus on how MOR activity is regulated. There are multiple mechanisms that can change MOR activation, from MOR gene expression, to exposure to external opioid agonists or antagonists. However, one of the more common *endogenous* modulators of MOR activation is the feedback process it has with the immune system. Immune function is a complex system, split into the 'innate' and 'adaptive' immune response that is regulated by multiple hormones and neurotransmitters. As part of this complex network, the immune system uses a feedback loop with MOR activation to help regulate itself. This section will briefly explain this interplay, with a focus on inflammation.

Inflammation is a key function of the immune system, which is usually well-regulated by the innate immune response (Barton, 2008). The purpose of inflammation is three-fold; (1) it allows the host to defend against infection; (2) it activates the tissue repair response; and (3), as a response to stress and homeostatic change, it prompts the host's homeostatic mechanisms (Medzhitov, 2008). The third of these, stress, is considered an endogenous trigger for inflammation while pathogens and tissue damage are exogenous triggers (Medzhitov, 2008 p. 430). Inflammation is regulated by a different part of the immune system that is brought into action during the inflammation process via the release of various neurotransmitters by immune cells. One type of neurotransmitter released in this process is opioids. Both the innate and adaptive immune systems have methods of releasing opioids during inflammation for this regulation (Plein and Rittner, 2018, p. 2722).

In a recent review article, Liang et al. (2016) developed an overview of how opioids and the immune system interact, suggesting that the EO system plays a direct role on immune system function. They highlight that there is an abundance of research showing that many immune cells have opioid receptors (Börner et al., 2009; Li et al., 2009; Wybran et al., 1979), especially MOR receptors (Roy et al., 2006; Börner et al., 2013) that directly change immune cell activity. For example, Sarkar et al. (2012) have shown that opioids trigger the release of Natural Killer (NK) cells that fight off potential pathogens. Given that the immune system also releases opioid ligands into the body, a feedback loop is created between level of inflammation and level of circulating opioids. Under normal conditions, this feedback loop is well-regulated. However, under chronic stress this immune response may be altered such that there is an increase in overall inflammatory activity (Glaser and Kiecolt-Glaser, 2005), causing longer-term damage to the organism and increasing risk for numerous major physical diseases (Manabe, 2011). Various problems may arise if the feedback loop is dysfunctional. For example, an overabundance of MOR agonists can lead to an increase in the rate and levels of inflammation (Nguyen et al., 2014). This interplay between the inflammatory immune response and MOR agonists has also been observed in animal models (Sacerdote, 2006; Alves et al., 2012).

The feedback-loop between the inflammation response and EOs is further demonstrated by the fact that multiple inflammation diseases are linked to an up-regulation of opioid receptors (Jiménez et al., 2006), where inflammation is associated with increased peripheral MOR sensitivity (Hipólito et al., 2015), as well as changing MOR sensitivity in the brainstem (Hipólito et al., 2015). In related work, Cahill and Taylor (2017) have argued that this 'neuroinflammation' – the brain's biological response to inflammation-related pain and stress - may be the cause of dysphoric symptoms seen in chronic exogenous opioid users. More specifically, they suggest these symptoms arise via mesocorticolimbic pathway changes caused by neuroinflammation (Cahill and Taylor, 2017). The interplay between MOR activation by exogenous opioids and an altered immune response has been the focus of other studies, which show that some exogenous μ-opioids may cause immunosuppression (Plein and Rittner, 2018). The changes to immune function that exogenous opioids make provide further evidence for the regulatory role of MOR activity in immune function, though it should be noted that we don't yet have a complete understanding of the role of opioid receptor activity on the immune system. For example, while some exogenous μ-opioids can cause immunosuppression (Plein and Rittner, 2018), not all do (Sacerdote, 2006), and it is not clear why this is the case.

While neuroimmune pharmacology is a young discipline, especially regarding opioid ligand function, our understanding is rapidly growing (see Cosentino and Marino, 2018). We now are aware that the EO system, especially MOR activation, plays a key role in the inflammation that takes place during the immune response. Combining the knowledge of the role of MOR activation on both social bonding and on the immune system may allow us to better contextualise the link that has been found between inflammation, immune biomarkers, and mental health disorders.

## 4. Mental health and the immune system

It has recently been suggested that there are subtypes of mental health disorders where immunological irregularities are apparent (Miller et al., 2013; Lamers et al., 2018a,b). These subtypes have been called 'immunophenotypes' (Pennix et al., 2018). This realisation occurred as research emerged showing that various mental health disorders are correlated with abnormal levels of immune biomarkers (for an overview of the depression-inflammation literature, see Pariante, 2017). This research has led scientists with different clinical foci to propose immunological aetiologies for their mental health disorders of interest. For example, Slavich and Irwin (2014) provide a plausible explanation for the onset of depression by citing stress as a causative factor of inflammation, which leads to depressive symptomology. They cite work linking inflammation biomarkers to depression (e.g. Pariante and Lightman, 2008; Pariante and Miller, 2001), with other work outlining possible roles of the stress-immune response on mental health in general (Godoy et al., 2018). However, in much of the research this is only true for a subset of those with depression (Miller et al., 2013), i.e. this immunophenotype is a subtype of depression, not an explanation of all depression.

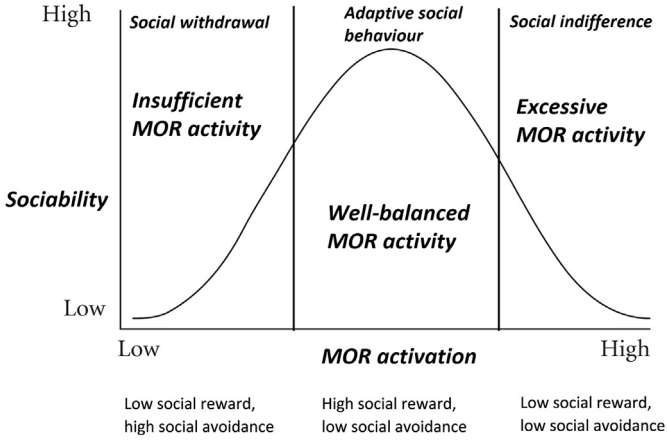


**Fig. 1.** The μ-receptor balance model (adapted from Pellissier et al., 2018): Activity of μ-opioid receptors (MOR) competes with social avoidance systems (SAS) to drive social behaviours. In a window of optimal functioning, MOR activity is balanced with SAS to allow adaptive social behaviour. These conditions are ideal to detect social reward. On the left part of the curve, low MOR activity, e.g. due to social distress, pharmacological antagonism or genetic anomaly, leads to reduced social reward and leaves the field clear for SAS to elicit social withdrawal. On the right part of the curve, excessive MOR activity, due to intense and/or prolonged exposure to opioid ligands or increased MOR expression, saturates the reward system and produces social indifference. Importantly, under this model, blocking MOR activity in the case of excessive tone, or stimulating MOR when the tone is too low can restore normal, adaptive social behaviour.

Similarly, in their review of possible biochemical mechanisms behind Autism Spectrum Disorders (ASD), Griffiths and Levy (2017) touch on possible mechanisms that stem from mitochondrial dysfunction. One of these explanations involves immune dysfunction and inflammation (p. 6–7). They note that a large body of research reports that abnormal inflammation and immune dysfunction is more common in those with ASD than in the general population (Elias et al., 2015; Gesundheit et al., 2013; Onore et al., 2012; Rossignol and Frye, 2014; Stigler et al., 2009). Rossignol and Frye (2014) highlight that a number of studies report evidence of immune dysregulation and/or inflammation in individuals with ASD and that in some studies, "biomarkers of inflammation or immune dysregulation have been correlated with ASD severity" (p. 2), including some showing neuroinflammation (e.g. Suzuki et al., 2013; Wei et al., 2011), with evidence mounting for some to describe subtypes of ASD to be immune disorders (Meltzer and Van de Water, 2017) or even autoimmune disorders (Ashwood and Van de Water, 2004a; Ashwood and Van de Water, 2004b). Bjørklund et al. (2016) conducted a literature review where they outline the various differences seen in multiple immune cells, such as NK cells, T cells and B cells, of those with ASD. In this review, Bjørklund et al. (2016) describe the link between immune dysregulation, neuroinflammation and ASD presentation and compare this with the immune cells and inflammation of those with neurotypical development.

It is not just depression and ASD that are linked to inflammation. There is also an abundance of research which shows increased levels of pro-inflammatory biomarkers or decreased levels of anti-inflammatory biomarkers in individuals with schizophrenia (Müller et al., 2015; Lee et al., 2017; Tanaka et al., 2017), bipolar disorder (Muneer, 2016; Rosenblat and McIntyre, 2016), borderline personality disorder (Kahl et al., 2006) and anxiety in response to social stimuli (Inagaki et al., 2012), leading to social anxiety disorder (Vogelzangs et al., 2013). Moreover, the link between abnormal inflammation function and general mental health dysfunction is further found in those with comorbid conditions. The role of inflammation in the comorbidity of ASD and schizophrenia is beginning to come to light (Prata et al., 2017; Zheng et al., 2018). Similarly, depression and schizophrenia have a high level of co-morbidity, where inflammation abnormalities have been suggested as a possible aetiology for the comorbidity (Kucerova et al., 2015; Upthegrove et al., 2017).

This section has provided a brief outline of the array of research that shows immune dysfunction, specifically inflammation, as a possible aetiology for subtypes of multiple mental health disorders, and for the high rates of comorbidity between mental health issues. In doing so, it is becoming clear that old understandings of mental health disorders having a single aetiology, such as dopamine abnormalities as *the* cause of schizophrenia, or monoamine deficiencies as *the* cause of depression, can no longer be used as the de facto basis of treatment plans.

## 5. The role of endogenous opioids in social bonding disorders

Given the role of opioids in social bonding and the immune system alongside the discovery of inflammation-based mental health disorders, the possibility that the opioid system plays a key role in some subtypes of social bonding-related mental health is of particular relevance for rethinking the aetiology and treatment of various conditions. As outlined in section 2, the EO system plays a major role in regulating social bonding and social behaviour. This is extremely relevant to mental health disorders because of the social deficits that are considered key symptoms for many such disorders. For example, a major symptom for depression is the loss of motivation for social contact (NHS, 2016), while negative symptoms of schizophrenia are anhedonia and asociality (Blanchard and Cohen, 2006). Similarly, social deficits are a definitional symptom in some disorders, such as ASD (Criterion A, DSM-5, American Psychiatric Association, 2013).

In the stress-inflammation aetiology for depression proposed by Slavich and Irwin (2014), much like most research linking the immune system and mental health issues, the focus is on inflammatory cytokines, such as IL-1, IL-6, and TNF-α. This focus on cytokines is prevalent throughout the literature associating immune function with mental health disorders (e.g. Lee et al., 2017; Pariante, 2017; Tanaka et al., 2017). As a result, these immune markers can be linked to the 'negative' symptoms of disorders, i.e. those symptoms which describe an absence of a behaviour, thought or feeling that is no longer present, by describing them as 'sickness behaviours' typical of mental health disorder subtypes (Moieni and Eisenberger, 2018). Examples of these sickness behaviours include social withdrawal, anhedonia, change of appetite and loss of motivation (e.g. Dantzer et al., 2008; Raison and Miller, 2013).

A recent large-scale study ($n = 15{,}071$) sought to test the 'sickness behaviour' hypothesis by collecting data about specific symptoms of those diagnosed with depression and concentration of the inflammation biomarker C-reactive protein (CRP; Jokela et al., 2016). They found that those who suffer from depression with increased levels of CRP are more likely to experience greater 'illness' symptoms such as fatigue, appetite change, social withdrawal, and inhibited motivation. The relationship between inflammation biomarkers and specific depression symptoms has been further supported by other studies. For example, Gallagher et al. (2017) conducted a longitudinal study on 562 participants and looked at CRP and specific symptoms. They found that those with greater levels of CRP had higher rates of amotivation, less sadness and greater medical co-morbidity over time than those with lower levels of CRP (also see Lamers et al., 2018a,b). Similar findings of increased levels of these 'sickness type' behaviours can be found in the ASD (Wei et al., 2011; Suzuki et al., 2013; Meltzer and Van de Water, 2017) and schizophrenia literature (Carrizo et al., 2008; Garcia-Rizo et al., 2012; Suvisaari et al., 2011; Meyer et al., 2011).

The link between inflammation and specifically the 'negative' symptoms of mental health disorders is important to note. The symptoms mentioned in these studies – fatigue, appetite change, social withdrawal, inhibited motivation and lowered levels of sadness – are the same as the side-effects of opioid drug use, especially mu-opioid drugs such as heroin, oxycodone and morphine. Given the similarity between mu-opioid narcotics users and those with an immunophenotype of depression, it is very likely that increased EO sensitivity or increased MOR activity play a role in the immunophenotype of mental health disorders. While an immunophenotype has multiple possible environmental or genetic causes for onset, the EO system is a strong candidate for an explanation for their onset. The remainder of this section will outline why we suspect that is the case.

Stress is one of the environmental cues of interest in most research on immunophenotypes (Corcoran et al., 2003; Polter and Kauer, 2014; Slavich and Irwin, 2014). For example, the link between stress and depression has been suggested to be specific to 'atypical depression', a subtype of depression that is most associated with the immunophenotype (Rudolf et al., 2014; Lamers et al., 2018a,b). Those diagnosed with atypical depression are also noted to have a stronger reaction specifically to the stress of interpersonal rejection (Łojko and Rybakowski, 2017). This increased sensitivity to social-specific stressors in those most likely to have an immunophenotype of depression further emphasises the possibility that changes to the EO system could be a possible cause.

The effects of stress on opioid receptors are a further reason to consider that EO abnormalities play a role in mental health conditions. There is a growing body of work showing that stress can change the expression of MOR receptors via epigenetics (Nikulina et al., 1999; Nikulina et al., 2005; Chong et al., 2006; Hwang et al., 2009; Oertel et al., 2012). This epigenetic change is found more specifically in brain areas where EOs and dopamine are released to play a role in social reward and motivation – the ventral tegmental area (Nikulina et al., 1999). This, in combination with the μ-opioid role in the immune system, covered in section 3, indicates that the alterations in social behaviour seen in those who have the 'immunophenotype' of various mental disorders could be caused by changes in MOR receptor activity.

Another factor that points toward a link between EO abnormalities and mental health disorders, is that it has been noted that depression and

pain – an experimental proxy for EOs (Charles et al., in prep; Cohen et al., 2010; Tarr et al., 2015; Tarr et al., 2016) – have a strong link to one another (Li, 2015). There is a lower pain threshold (PT) in depressed patients (Adler and Gattaz, 1993; Marazziti et al., 1998) compared to their non-depressed counterparts. Though, PT differences in depressed patients are modality-specific: PT is increased for electric and heat-based pain, but reduced in ischemic pain (Bagnato et al., 2018; Bär et al., 2005; Thompson et al., 2016). The difference in threshold between pain modalities could be because different pain modalities are related to different types of opioid receptors (Scherrer et al., 2009). In mouse models, DORs are responsible for mechanical (ischemic) pain, whereas MORs are responsible heat-related pain (Scherrer et al., 2009; Wang et al., 2018). As such, a systematic up-regulation of MOR could explain the increased resistance to heat-related pain seen in depressed patients. Similarly, the decreased tolerance to ischemic pain may also suggest altered DOR functioning. This link between PT and depression is in addition to the increased rate of depression found in those with disorders related to pain perception, e.g. chronic pain (Lépine and Briley, 2004).

Similar findings of altered pain perception are shown in the schizophrenia literature, too (Sakson-Obada, 2017; Urban-Kowalczyk et al., 2015; Stubbs et al., 2015). Stubbs et al. (2015) conducted a meta-analysis of all research conducted on pain perception in those with schizophrenia compared to healthy controls and found a consistent, moderate effect that those with schizophrenia-spectrum disorder had elevated pain thresholds (Hedge's $g = 0.493$), with an even higher effect size in those who were not prescribed anti-psychotics ($g = 0.599$), and an increased pain tolerance ($g = 0.566$) and threshold ($g = 0.696$) in those with a diagnosis of schizophrenia. Something worthy of note is that most studies on schizophrenia and pain perception are conducted using electrical or thermal pain (Sakson-Obada, 2017), which suggests elevated MOR activity. This elevated level of MOR activation is supported by recent research showing increased concentrations of β-endorphin in both animal models of schizophrenia (Szűcs et al., 2016) and in patients with schizophrenia (Urban-Kowalczyk et al., 2015) as well as reduced MOR availability in brains of patients with negative symptoms of schizophrenia (Ashok et al., 2017).

Further evidence that mental health issues may be linked to EO differences comes from research suggesting that mental health disorders and pain sensitivity share neuroanatomical circuitry, specifically, the lateral habenula (LHb) (Li et al., 2016, 2017; Lawson et al., 2017; Morris et al., 1999). Li and colleagues (2016; 2017) have proposed that the LHb, a region believed to play a role in avoidance behaviours (Shumake et al., 2010) shows an altered activation in those with depression. Given the LHb has a different level of activation in depressed patients compared to healthy controls (Browne et al., 2018; Lawson et al., 2017; Morris et al., 1999), and is related to avoidance, it is possible that this brain region plays a role in the loss of social motivation seen in those with depression. The LHb isn't just related to depression; in animal models LHb lesions lead to schizophrenia-like symptoms (Li et al., 2019). Moreover, the volume of the bilateral Hb has been shown to be significantly lower in human patients with schizophrenia compared to healthy controls (Zhang et al., 2017).

But how does this relate to EO release? The LHb has lowered activation with the administration of the MOR agonist morphine (Benabid and Jeaugey, 1989; Ma et al., 1992), and increased activation on morphine withdrawal (Neugebauer et al., 2013). These findings are reported to be related to MOR-related inhibition of LHb neurones in a patch-clamp recording study (Margolis and Fields, 2016). The LHb receives differential input from, among other brain regions, the nucleus accumbens and has a feedback loop with the ventral tegmental area (Bianco and Wilson, 2009). These are two major brain regions linked to reward and motivation. Furthermore, Le Foll and French (2018) provide evidence of certain genes related to inflammation are up-regulated in the LHb for those more likely to have anhedonia - a symptom that appears in both depression and psychosis that is more likely to be found in those with the immunophenotype of the disorders (Garcia-Rizo et al., 2012; Jokela et al., 2016). Le Foll and French (2018) also note that some inflammation of the LHb may be linked to opioid drug use. This provides further evidence that an immunophenotype could be related to altered MOR activation.

The MOR-Balance model for social bonding (Pellissier et al., 2018), mentioned briefly in section 2, was originally proposed in the context of ASD. In this model, Pellissier et al. (2018) provided a synthesis of many studies that looked at the role of the opioid system's role in ASD. In their synthesis, they note an inconsistency in the literature as to whether it is excess or insufficient MOR activity that leads to ASD presentation. There were paradoxical findings from studies showing support for both possible roles of MOR activity in ASD presentation. To account for this apparent paradox, they proposed the MOR-Balance model (Fig. 1) for ASD, which could explain the presence of ASD in a subset of those with neuroatypical development. Given that ASD also has an immunophenotype (Wei et al., 2011; Suzuki et al., 2013; Meltzer and Van de Water, 2017), the possibility of EOs playing a role in social bonding mental health disorders is one that should be considered seriously.

One final piece of evidence in support of the role of EOs in mental health disorders concerns research on opioid-based treatments that exist for depression and ASD. Research on EO-based treatments for mental health disorders is occurring, but it is still either in early stages or has fallen out of favour. Browne and Lucki (2019) published a comprehensive breakdown of the evidence that endogenous opioid tone links to depression and then cover research on new drugs currently going through clinical trials. The four drugs that they cover in their paper are Buprenorphine, ALKS-5461, JNJ-67953964 and BTRX-246040. The first of these, Buprenorphine, may have some abuse potential, but at least one derivative has been made that appears to reduce this issue, without losing the anti-depressant effects (Almatroudi et al., 2018). The second of these drugs, ALKS-5461, is a combination of Buprenophine with the MOR-antagonist samidorphan. This combination is used to further reduce abuse potential. While early research is positive, the Drugs Advisory Committee of the FDA in the USA recommended that the drug's benefit-risk profile was not adequate to support approval. The third drug they cover, JNJ-67953964, is a KOR antagonist. Evidence suggests that the drug is more effective as a means to reduce substance abuse than for specifically anti-depressant purposes. The fourth drug, BTRX-246040, is a nociceptin-opioid receptor antagonist (note that NORs are mainly related to pain perception) currently undergoing phase 2 trials. Research on these opioid-based treatments for depression is still very much in its early stages but it is a promising area.

In the late 20th century, research focus on the relationship between ASD and inflammation used the ratio of CD4 to CD8 cells as a biomarker for inflammation. This biomarker has since been superseded by others, such as inflammatory cytokines. However, during this time, Scifo et al. (1996) found that the use of Naltrexone, a MOR antagonist, produced a significant reduction in ASD symptomology. They noted that the "behavioural change was also accompanied by an increase of T-helper-inducers and decrease in T-cytotoxic-suppressor, resulting in a normalization of the CD4/CD8 ratio" (p. 351). Other research looking at the effect of Naltrexone on ASD also shows some improvement (Bouvard et al., 1995; Campbell et al., 1993; Kolmen et al., 1995), especially with self-injurious behaviour (Eichaar et al., 2006; Sandman and Kemp, 2011) but only in a subgroup of those with ASD (Roy et al., 2015). Given the MOR-Balance model of ASD proposed by Pellissier et al. (2018), this subgroup may be the one with excessive MOR activity, compared to others with ASD who have insufficient MOR activity or some other biochemical cause of their symptoms. As the treatment only appeared useful in a subgroup of those with ASD, not much more research on the effectiveness of opioid agonists or antagonists for ASD has been conducted. We would recommend that more research looks at their effectiveness in sub-populations that appear to have an immunophenotype or excessive circulating opioids. We believe that one avenue of research that should receive greater prominence is pharmacological treatments for mental health disorders that address dysfunctional opioid activity.

This section has offered several lines of evidence which suggest that altered MOR activity plays a role in various mental health disorders: (1)

Behavioural/symptomatic similarities between 'sickness-type' inflammation disorders and chronic opioid drug users; (2) The role of stress on MOR epigenetics, which could provide an explanation of the link between stress and the onset of mental health issues; (3) The link between increased tolerance of heat-related pain, which is controlled by MOR activation, and depression & schizophrenia; (4) The role of brain regions that have MOR input, such as the LHb, in social reward and social avoidance and the link between these regions and mental health issues; (5) Differential MOR activation in those with social deficits in ASD; and (6) Evidence of some remission from early stage research of opioid-based pharmaceutical treatments for depression and ASD (see Fig. 2 for a visual representation of these lines of evidence). These pieces of evidence add up in the argument we make throughout this article, namely that changes in the EO system, specifically abnormal MOR activity, is a possible neurochemical mechanism behind the behaviour changes seen in those with immunophenotypes of various mental health disorders.

## 6. Conclusion

Clinical applications of psychology have long struggled with the tension between an understanding that mental health disorders have various subtypes and treatment plans which treat these disorders as monolithic, with a single aetiology. This problem arises, in part, from the key-symptom-focused approach of the field, where individuals with similar core cognitive-behavioural symptoms are reported to suffer from the same disorder, without a precise understanding of the aetiology of the other surrounding symptoms. We are not alone in pointing out the importance of changing this approach: the American National Institute of

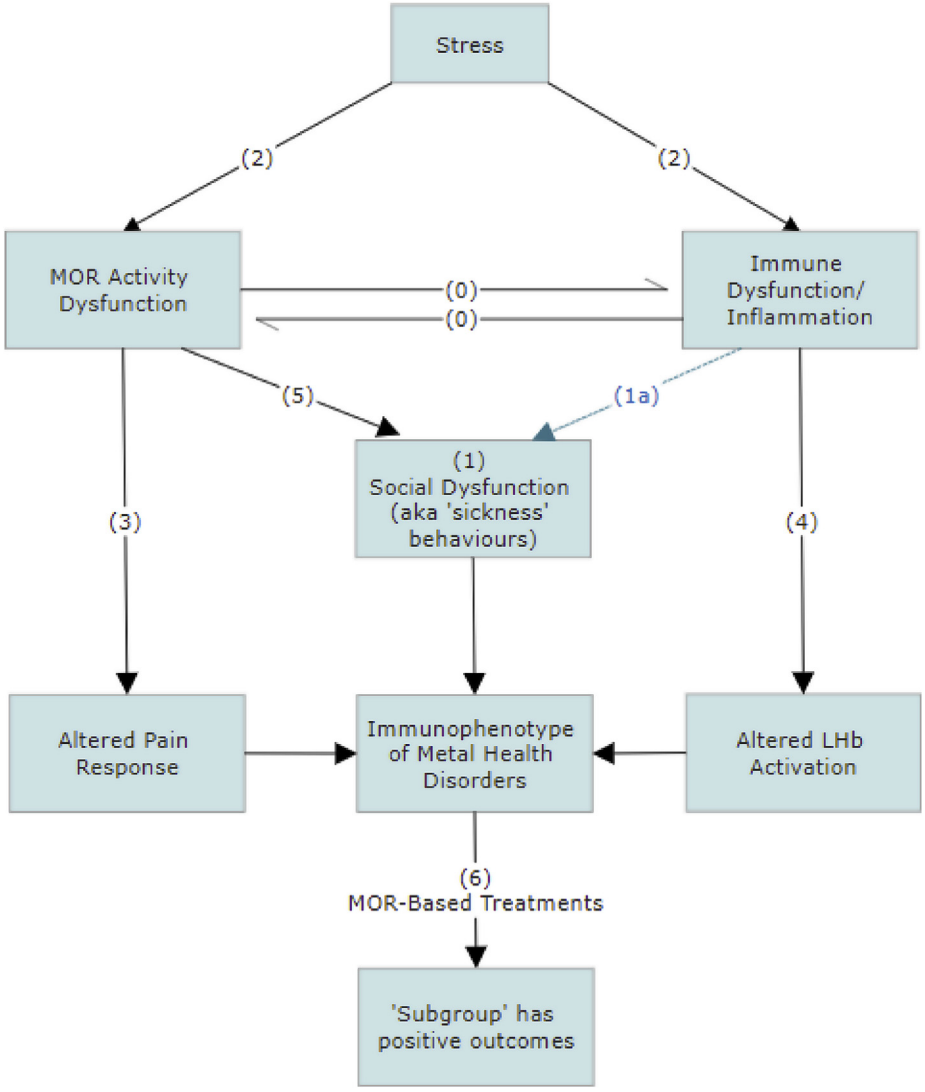


**Fig. 2.** A visual representation of the evidence that mu-opioid receptor (MOR) activity plays a role in the aetiology of immunophenotypes of mental health disorders.

0. The feedback loop between the immune system and MOR activity means that if one is dysfunctional, the other may well be dysfunctional.
1. 'Sickness' behaviours that are cited as an example of immunophenotypes are the same behaviours as those shown by those who take exogenous mu-opioid substances
   a. The previous proposed link between inflammation and these behaviours
2. Stress can lead to MOR dysfunction via changes to MOR epigenetics as well as via immune response dysregulation.
3. MOR dysfunction also leads to an altered pain response, which is seen in those with depression and schizophrenia and some report it in ASD. This may also explain the co-morbidity between chronic pain and mental health issues.
4. The Lateral Habenula (LHb) functioning is altered by MOR and immune dysfunction, leading to social withdrawal.
5. Pellissier et al. (2018) described how MOR activity, be it excessive or insufficient, plays a role in social dysfunction.
6. Early stages of research on MOR-based pharmaceutical treatments for ASD & depression are promising for a subgroup of those with these diagnoses.

Mental Health's long-term plan to identify more reliable endogenous explanations for a wide variety of mental health disorders (Insel, 2013) speaks to this. The present article seeks to address this plan, as well as building on recent calls to action from researchers across fields (Allsopp et al., 2019; Gassen and Hill, 2019).

Here, we have proposed a possible aetiology for a subtype of various mental health conditions known as immunophenotypes. While we are not the first to highlight the relevance of inflammation as a role in subtypes of specific disorders such as depression (Lamers et al., 2018a,b; Pariante, 2017), schizophrenia (Müller et al., 2015; Lee et al., 2017; Tanaka et al., 2017) and ASD (Meltzer and Van de Water, 2017), this is the first overview of the role of inflammation across multiple disorders where a biochemical explanation for why immunophenotypes might exist across diagnoses is provided. We propose a novel mechanism of how the immune system may be causing 'sickness-type' behaviours (fatigue, appetite change, social withdrawal and inhibited motivation) in those who have these immunophenotypes. We have considered the role of a malfunctioning endogenous opioid system – more specifically, we suggest altered mu-opioid receptor activation as a possible mechanism. Based on this hypothesis, we feel that encouraging new research into the role of opioid abnormalities in mental health issues is of vital importance. Such research may help increase the number of effective treatments that healthcare professionals are able to turn to in order to help their patients as well as allow for a better understanding of the biochemical underpinnings of mental health disorders.

## Declaration of competing interest

The authors of the above article declare that there is no known conflict of interest.

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