Translation of animal endocannabinoid models of PTSD mechanisms to humans: Where to next?

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Abstract

The endocannabinoid system is known to be involved in mechanisms relevant to PTSD aetiology and maintenance, though this understanding is mostly based on animal models of the disorder. Here we review how human paradigms can successfully translate animal findings to human subjects, with the view that substantially increased insight into the effect of endocannabinoid signalling on stress responding, emotional and intrusive memories, and fear extinction can be gained using modern paradigms and methods for assessing the state of the endocannabinoid system in PTSD.

Keywords: Cannabinoids; endocannabinoids; posttraumatic stress disorder; stress; memory; fear conditioning; PTSD

Introduction

Posttraumatic Stress Disorder

Exposure to a traumatic event can cause long-term psychological problems and mental health disturbances. Posttraumatic stress disorder (PTSD) is a highly debilitating and relatively common mental health disorder that can occur following exposure to one or more common traumatic stressors (e.g., physical or sexual assault, exposure to threatened or actual death, or serious injury). Such events can be experienced directly, witnessed, or experienced vicariously through the experience of a close friend or family member (American Psychiatric Association, 2013). PTSD symptoms can begin to occur immediately following the traumatic experience, but formal diagnosis of PTSD requires at least a one-month separation from the event. For some people, PTSD may only begin after a significant delay following trauma, sometimes even years after the experience (Bryant et al., 2013). Symptoms of PTSD include hyperarousal, avoidance of stimuli or situations associated with the trauma, negative cognitions and mood, and recurrent, distressing memories of the experience (American Psychiatric Association, 2013). PTSD is associated with significant impairments in daily functioning and is highly comorbid with major depression, substance abuse, and suicidal behaviour (Cougle et al., 2009; Rytwinski et al., 2013; Zatzick et al., 1997). Although it is a necessary component, trauma exposure by itself does not guarantee that an individual will go onto develop PTSD. In fact, although approximately 90% of the U.S. population has experienced a traumatic event, only 8.3% report lifetime PTSD (Kilpatrick et al., 2013). Worldwide, lifetime prevalence of PTSD is estimated to be 3.9% (Koenen et al., 2017). It is important to note that there are some conditional risk factors (e.g., sex, proximity, type of trauma) that increase the risk of developing PTSD (Blanco et al., 2018; Breslau et al., 1998; Kessler et al., 2005; Kessler et al., 1995; Scott et al., 2018). It is accepted that PTSD presents a substantial societal burden and significant research is devoted to improving treatments

around the world (American Psychiatric Association, 2013; Calhoun et al., 2002; Nichter et al., 2019). Understanding why some people develop PTSD whereas others do not has led to distinct areas of PTSD research and various theories as to the potential cognitive and neurobiological mechanisms underlying the disorder. Understanding these underlying mechanisms is essential in developing more targeted and effective treatments for PTSD.

Improving PTSD Treatments

PTSD is typically treated using exposure therapy under the cognitive behavioural therapy framework (Bisson et al., 2013; Watts et al., 2013). Exposure therapy operates on the basis that PTSD is a disorder characterised by impaired capacity to extinguish conditioned fear to trauma reminders that no longer present threat, as well as generalisation of this fear towards similar stimuli and situations (Ehlers & Clark, 2000). By gradually exposing patients to these stimuli and situations in a safe environment, the fear memory is slowly decoupled from these stimuli and overridden by safety learning (Bouton, 2004). Pharmacological treatments are also often used in the management of PTSD. Specifically, selective serotonin reuptake inhibitors (SSRIs) are most commonly prescribed in PTSD cases and appear to have the highest efficacy out of available pharmacological therapies (Jonas et al., 2013; Stein et al., 2006). There are currently two FDA approved medications (Sertraline and Paroxetine) for the treatment of PTSD. However, general medications such as SSRIs do not target specific PTSD mechanisms (Rauch et al., 2019), require long-term use, are associated with withdrawal symptoms, and are not efficacious in as many patients as behaviour therapies (Fava et al., 2015; Jonas et al., 2013; Ostacher & Cifu, 2019). For this reason, psychological treatments are recommended by clinical guidelines as the frontline treatments for PTSD (Ostacher & Cifu, 2019). Exposure therapy shows the highest efficacy out of all psychological treatments (Watts et al., 2013), but up to 40% of patients continue to show partial or zero treatment

response (Bisson et al., 2013). Therefore, understanding how to improve treatments for a broader range of patients is a priority.

Given that exposure therapies are designed to reduce anxiety towards trauma reminders by promoting therapeutic safety learning (which is hypothesized to operate via mechanisms of fear extinction learning; Rothbaum & Davis, 2003), preclinical and clinical fear extinction paradigms are widely used as lab-based models of exposure therapy. As such, one lab-based approach ultimately intended to improve PTSD treatment involves examining the effect of various pharmacological and non-pharmacological treatments on fear learning processes, under the assumption that treatments that exhibit efficacy in the lab, may be promising candidates in the clinic (Cisler et al., 2020; Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Adams, et al., 2021; Zoellner et al., 2017). Another way in which research has sought to improve PTSD treatment is by exploring the neurobiology relating to existing mechanisms. By pharmacologically targeting pathways that are involved in PTSD aetiology, it is possible that psychological treatment efficacy can be improved. Several options have currently been explored for this purpose (Amos, et al., 2014). Most notably, hydrocortisone trials in conjunction with exposure therapy have been shown to improve treatment outcomes (Yehuda et al., 2015, but see Golier et al., 2018 and Lehrner et al., 2021), and hydrocortisone in the immediate aftermath of trauma improve PTSD symptom prognosis (Amos et al., 2014), although treating post 9/11 Veterans with dexamethasone the night before virtual reality exposure therapy was associated with a significantly higher dropout rate than placebo (76.9 % vs 28.5 %) (Maples-Keller et al., 2019). Other promising options have been trialled in humans with limited efficacy, including propranolol, oxytocin, gabapentin, and d-cycloserine (Amos et al., 2014; McGuire, et al., 2017).

Hydrocortisone was a particularly appealing agent for clinical trial because of existing knowledge of cortisol dysregulation in PTSD and the intimate relationship between cortisol

and memory and arousal symptoms of PTSD, including fear extinction (de Quervain et al., 2017). Recently, endogenous cannabinoids (endocannabinoids) have been shown in animal models to tightly regulate cortisol reactivity following acute stress (Balsevich et al., 2017; Morena et al., 2016). The endocannabinoid system is composed of native ligands such as arachidonoyl ethanolamide (AEA) (Devane et al., 1992) and 2-arachidonoyl glycerol (2-AG) (Suguira et al., 1995) which affect not only the cannabinoid receptors 1 and 2, but also a wide range of neurobiological targets (Ligresti et al., 2016). The enzymes that degrade these endocannabinoids (e.g. fatty acid amide hydrolase; FAAH as well as monoacylglycerol lipase; MAGL) are considered potentially important targets for future pharmaceuticals across a wide variety of indications. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) – the main two cannabinoids found in cannabis – act largely through the endocannabinoid system, as do the minor cannabinoids found in cannabis (Oultram et al., 2021).

Animal models strongly suggest that endocannabinoids may directly modulate fear extinction and emotional memories in PTSD (Hill et al., 2018; Ney, Matthews, et al., 2018, 2019a). Therefore, one of the next avenues to explore in improving PTSD treatments is by modulating the endocannabinoid system. However, in contrast to the cortisol field, relatively few studies have assessed the role of endocannabinoids in humans during tasks designed to assess PTSD mechanisms. Studies that translate animal models of neurobiological mechanisms to humans are essential in developing effective treatments, since confirmation that the mechanisms involved in animal behavioural regulation also occurs in humans is fundamental to confirmation of a potentially effective treatment. Further, translational research of animal findings for the effect of cannabinoids and endocannabinoids in PTSD is essential, given the increasing legality and acceptance of cannabinoids as pharmacological and recreational options throughout the world.

Currently, studying endocannabinoids in humans is not simple, as many of the basic research elements (e.g., analytical method development) have not been achieved to the extent of other endocrine systems (Battista et al., 2014; Fanelli et al., 2012). Further, translating animal literature to humans in pharmacological terms is extremely difficult due to the massive difference in the invasiveness of the allowable procedures. This is compounded by the profuse nature of the endocannabinoid system, as well as the fact that endocannabinoids are synthesised on demand in both central and peripheral tissue, which presents challenges when attempting to relate central nervous system effects using solely peripheral measures (Hillard, 2017). In this review, we detail several of the human paradigms that can be used to translate the relevant animal findings of endocannabinoids for stress responsivity, emotional memories, and fear extinction, with relevance to PTSD. We also discuss several of the new methods that enable assessment of the endocannabinoid system in matrices other than blood, which may assist in building a wider overall picture of the endocannabinoid system in humans. This is especially relevant given that the use of metabolomic and bioinformatic approaches (system biology) is reliant on deep profiling capabilities of the analysis techniques used in metabolic and proteomic analysis.

Given the abundance of reviews on endocannabinoid signalling in stress (Balsevich et al., 2017; Hill & Tasker, 2012; Morena et al., 2016), emotional memories (Atsak, Roozendaal, et al., 2012; Morena & Campolongo, 2014), fear extinction (Ney, Akhurst, et al., 2021; Ruehle et al., 2012), and PTSD (Berardi et al., 2016; Hill et al., 2018; Mayo et al., 2021; Ney, Matthews, et al., 2018; Orsolini et al., 2019), we greatly limit the scope of this review to the topic of translational evidence for endocannabinoid signalling in human laboratory models. Readers who are not aware of the endocannabinoid literature in each of these areas should refer to the listed, or similar, reviews on these topics for further information.

Translation of animal research to human paradigms relevant to PTSD

Understanding stress reactivity is critical to understanding PTSD, since many of the main symptoms of the disorder are derived from maladaptive stress responding to trauma (Pitman et al., 2012). Although not reviewed here, cortisol levels are excessive in the immediate aftermath of trauma and the interactions of endocannabinoids with these stress hormones can predict the strength and valence of emotional memories resulting from the experience (Balsevich et al., 2017; Hill et al., 2018). However, in the long-term PTSD patients tend to show lower cortisol than healthy or trauma-exposed controls (Horn et al., 2014; Morris et al., 2012; Neylan et al., 2005; Norrholm et al., 2016; Yehuda et al., 2005; Yehuda et al., 2002; Yehuda et al., 1995; Yehuda et al., 1990). Therefore, understanding how stress responses occur have implications both in the acute aftermath of trauma, as well as the long-term progression of the disease.

Various animal models have been developed to induce and assess responses to various stressors (Richter-Levin et al., 2019). For example, restraint or immobilisation stress – where an animal has all four limbs restrained for a number of hours – creates an inescapable situation that has long-term effects on behaviour and neuroendocrine responding that appears to be valid in the context of PTSD trauma (Armario et al., 2008). Similarly, inescapable foot-shocks can be used to induce acute stress and is associated with long-term behavioural and neuroendocrine alterations to animals that simulate trauma (Van Dijken et al., 1992). Using models such as these, the role of endocannabinoids in regulating the stress response has been elicited and is reviewed elsewhere (Balsevich et al., 2017; Hill & Tasker, 2012; Morena et al., 2016). Briefly, immediate reduction in AEA concentrations upon stress induction in several key areas of the brain is essential for hypothalamic-pituitary adrenal axis (HPA) initiation and subsequent cortisol release (Bluett et al., 2014; Gray et al., 2015; Patel et al., 2005; Wang et

al., 2012), whereas 2-AG undergoes a delayed increase that coincides with the termination of the stress response (Evanson et al., 2010; Hill et al., 2011; Wang et al., 2012). These findings imply that treatment for PTSD using cannabinoids as modulators of the endocannabinoid system at the level of stress reactivity is possible.

Translation of findings of animal stress paradigms can be achieved using a variety of stress tasks. The Trier Social Stress Test (TSST; Kirschbaum et al., 1993) has been validated over several decades as a robust tool for inducing physiological and endocrine stress responses (Dickerson & Kemeny, 2004; Kudielka et al., 2007). The TSST is a psychosocial stress task where participants must prepare and deliver a brief speech to a panel of critical experts. It has been used extensively in psychological research to study the endocrine responses to stress and, by extension, in memory literature (Kudielka et al., 2007). By contrast, the cold-pressor task induces stress through a physiological manipulation (cold-stress), where participants are required to place their hand in a freezing temperature (e.g. a bucket of ice) (Lovallo, 1975). Despite the cold-pressor task being a classical and widely validated tool for inducing behavioural and endocrine stress responses, recent variations to the task have seen psychosocial stress components added that have increased the robustness of the observed stress responses. For example, the Maastricht Acute Stress Task (MAST; Smeets et al., 2012) alternates the cold-pressor task with a complicated mental arithmetic test where participants are (a) informed that they are being videotaped with their responses recorded and (b) negatively reinforced on their responses, regardless of individual accuracy or speed. Smeets and colleagues (2012) showed that the MAST resulted in significantly higher cortisol responses compared to the cold-pressor task and two other variations to the cold-pressor that involved social-evaluative components. Stress induction paradigms such as these can be used to investigate the effect of acute stress on a range of biological and cognitive markers relevant to disease (Kirschbaum et al., 1999; Linz et al., 2019; Ney,

Felmingham, Nichols, et al., 2020; Shields et al., 2016; Shilton et al., 2017). However, animal models of stress described above are inescapable stressors and induce learned helplessness, which is not directly translated in the human stress paradigms that have been used due to the relationship between PTSD and the unpredictability of an aversive outcome (Foa et al., 1989; Hiroto & Seligman, 1975).

Translation of evidence of endocannabinoid responsivity to acute stress

Despite a substantial preclinical literature examining the effects of stress on endocannabinoid signalling, and vice-versa, there is currently sparse translational evidence of these relationships in humans. One possible explanation involves the lack of invasive techniques that would permit direct translation of animal models in humans. Fortunately, as discussed later in this review, techniques for measuring endocannabinoid reactivity in various human systems is continuously improving.

Endocannabinoids in human blood samples have been reported to show stress reactivity in several studies, however the methods for inducing stress have varied substantially (Chouker et al., 2010; Crombie et al., 2019; Dlugos et al., 2012; Mangieri et al., 2009; Mayo, Asratian, Linde, et al., 2020; Ney, Stone, et al., 2021; Spagnolo et al., 2016). Dlugos and colleagues (2012) examined serum endocannabinoid and cortisol concentrations of healthy participants before and after the TSST. It was found that AEA level was significantly increased immediately following stress induction (Dlugos et al., 2012). More recently, Mayo and colleagues (2020) used the MAST to also find that AEA serum levels were increased immediately following stress induction and this was again replicated among men and women with and without PTSD (Crombie et al., 2019) using the TSST. Crombie and colleagues also showed a significant increase in circulating concentrations of 2-AG, following psychosocial stress (TSST) in healthy non-clinical participants, but not for those

with a diagnosis of PTSD (Crombie et al., 2019). Paradigms using alcohol-related stress imagery scripts have found that alcoholic participants with PTSD who have minor alleles on the *FAAH* C385A polymorphism have decreased subjective stress responses compared to intact C385C carriers (Spagnolo et al., 2016). Similarly, compared to alcoholics who had no increase in AEA, social drinkers had significantly increased AEA blood levels following an alcohol imagery cueing task (Mangieri et al., 2009). These findings suggest that endocannabinoids are acutely sensitive to a wide range of stressors that roughly translate findings from the animal literature.

In addition to psychosocial stress (e.g., TSST), physical stress (i.e., moderate-intensity aerobic exercise) is another manipulation shown to increase circulating concentrations of endocannabinoids in adults with PTSD (Crombie et al., 2018; Crombie, Cisler, et al., 2021; Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Adams, et al., 2021; Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Almassi, et al., 2021), although adults with PTSD appear to exhibit a lesser magnitude of exercise-induced increases in 2-AG, which is consistent with the hypothesis that 2-AG/CB1 receptor signalling is hypoactive in adults with PTSD (Crombie et al., 2019; Hill et al., 2018). Finally, Chouker et al (2010) implemented a parabolic flight-maneuver procedure as a stressor in order to assess motion sickness, cortisol, and endocannabinoid levels in healthy adults prior to and following stress exposure. It was reported that participants with motion sickness had lower AEA levels 10 minutes following take-off compared to those without motion sickness. Further, higher 2-AG and lower cortisol levels at the conclusion of the task were observed in participants without motion sickness compared to those with motion sickness (Chouker et al., 2010). While the Chouker et al finding was the most similar to the model reported in the animal literature, it was not consistent with the finding reported by others that blood AEA levels increase immediately following stress induction in humans. This is likely to be due to the differences

in the stress paradigms used between the studies, with Chouker et al using a manipulation not typically used in psychological stress research. In addition to the significant variability in the stress paradigms used in the human literature, studies have also differed substantially in the timing of sample collection following stress induction and the food intake restrictions imposed prior to the stress task, which is known to affect endocannabinoid blood levels (Hillard, 2017). Importantly though, the findings from the Chouker et al investigation are consistent with the overall theme resulting from these studies, which suggests that circulating concentrations of eCBs in response to a stressor (or at the time of stressor induction) appear to play a vital and protective, stress-buffering role.

All of these protocols measured endocannabinoid reactivity in either serum or whole blood samples. Recently, we had healthy participants undergo the MAST and measured both salivary and plasma endocannabinoid reactivity before and after the task. We found that salivary 2-AG increased immediately, but not 30- or 45-minutes after stress induction (Ney, Stone, et al., 2021). As predicted, salivary cortisol was increased at both 30- and 45-minute intervals following stress. AEA did not show any stress reactivity. Further, plasma endocannabinoids did not show significant stress reactivity and were not correlated with saliva endocannabinoid levels at any time point, which, despite being similarly powered to the earlier studies, suggests that plasma endocannabinoids may show different responsivity to serum endocannabinoids. To our knowledge the reason for this difference is unknown, but there are many differences between serum and plasma content that could explain the discrepancy. For instance, brain-derived neurotrophic factor plasma levels more closely correlate to central nervous system concentrations due to platelet-based generation of BDNF in serum (Fernandes et al., 2015; Gejl et al., 2019; Ney, Felmingham, Nichols, et al., 2020; Rasmussen et al., 2009).

Translation of evidence of endocannabinoid signalling in fear extinction

Impaired fear extinction is theoretically the basis for impaired safety learning, and ultimately fear-related symptomology, in PTSD (Zuj et al., 2016). It is also the basis for exposure therapy, which is the best available known treatment for PTSD (Furini et al., 2014; Graham et al., 2014; Zuj & Norrholm, 2019). The direct translation of fear extinction paradigms is paramount to understanding the relationship between animal research and human experience of PTSD and recovery from PTSD (Graham et al., 2014; Zuj & Norrholm, 2019). Fear conditioning studies in animals present aversive electric shocks (i.e., unconditioned stimuli) to the animal subjects and pair these shocks with a particular stimulus (i.e., conditioned stimulus such as a tone), context, or environment. During this acquisition phase, the pairing of conditioned stimuli with the unconditioned stimuli ultimately results in a conditioned response (e.g., freezing) following the presentation of the conditioned stimuli (e.g., tone) in absence of the administration of the unconditioned stimuli (e.g., footshock). During the extinction learning phase, the outcome measure is typically the rate of freezing behaviours observed in the animals upon presentation of this conditioned stimulus in absence of the aversive stimulus (often times in a context/environment that is different from the acquisition context), and interventions through pharmacological or behavioural means can be compared by contrasting freezing rates during this "extinction learning stage", which mirrors the extinction learning that occurs during exposure therapy. Similarly, human studies administer aversive stimuli (e.g. electric shock or loud noise) in combination with stimuli, contexts, or environments to produce conditioned responses. The rate of learning (i.e., dependent variable) that occurs throughout a fear conditioning paradigm (i.e., fear acquisition, fear extinction, fear extinction recall phases) is typically measured via physiological (e.g., skin conductance responses) and cognitive (e.g., threat expectancy ratings) measures. Importantly, as in animal models, the extinction learning phase is intended

to mirror safety learning in exposure therapy. In this way, findings from animal research can be translated to human fear extinction paradigms (Milad & Quirk, 2012; Milad et al., 2014) in an attempt to assess neurobiological and endocrine effects of extinction learning (Felmingham et al., 2021; Fullana et al., 2016; Merz et al., 2018; Merz et al., 2014; Milad et al., 2013; Milad et al., 2014; Schenker et al., 2021; Shvil et al., 2014). Using modern techniques of neuroimaging and other biological assessments, the invasive measurements conducted in animal fear extinction experiments can be translated with relative confidence to humans.

The role of endocannabinoids in fear extinction has been elicited in animal research. Cannabinoid receptor 1 (CB1) antagonism has been repeatedly shown to impair fear extinction recall and this effect is replicated in animals exposed to CB1 knockout (Bitencourt et al., 2008; Chhatwal et al., 2005; Marsicano et al., 2002). Conversely, inhibition of endocannabinoid hydrolysis through inhibition of the FAAH enzyme (resulting in elevated AEA levels) improves fear extinction learning and fear extinction recall (Bitencourt et al., 2008; Chhatwal et al., 2005; Gunduz-Cinar et al., 2013) and this effect is impaired by CB1 antagonism (Aisenberg et al., 2017; Segev et al., 2014; Zubedat & Akirav, 2017). These findings showed very clearly that the endocannabinoid system, through direct activation of CB1, is crucial to fear extinction learning and recall in animals (Hill et al., 2018; Morena et al., 2016; Ney, Matthews, et al., 2018, 2019a).

There is an increasing amount of human fear extinction research attempting to translate these findings in animals to human paradigms. Among the human studies conducted to date, the majority of studies have either examined the influence of genetic variation within the endocannabinoid system (Dincheva et al., 2015; Heitland et al., 2012; Mayo, Asratian, Lindé, et al., 2020; Sporhs et al., 2021; Zabik et al., 2021) or the influence of a pharmacological (Das et al., 2013; Hammoud et al., 2019; Klumpers et al., 2012; Mayo,

Asratian, Lindé, et al., 2020; Rabinak et al., 2014; Rabinak et al., 2013; Rabinak et al., 2020; Rabinak et al., 2018) or behavioural (Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Almassi, et al., 2021) manipulations on fear extinction outcomes. Although the majority of studies have examined non-clinical populations, two investigations have examined a clinical sample of adults with PTSD (Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Almassi, et al., 2021; Ney, Matthews, et al., 2021).

In regard to non-clinical human studies investigating genetic variation within the endocannabinoid system, Dincheva et al. (2015) were the first to report that mutation of the FAAH gene (specifically C385A allele carriers of rs324420), presumably resulting in higher AEA levels, was associated with accelerated extinction learning in a human fear extinction paradigm. Similarly, Mayo, Asratian, Linde, et al. (2020) reported that C385A allele carriers exhibited significantly greater AEA levels, and presence of the mutation was also associated with enhanced fear extinction learning and recall. Similar to this, lower reactivity in the amygdala was observed by Zabik et al. (2021) during fear extinction recall in C385A allele carriers, but no genotype effects were observed in physiological or behavioural measures. In contrast, Spohrs et al. (2021) reported no differences between AC and CC rs324420 groups during extinction learning, but they did observe that task-related changes in AEA concentrations were associated with neural activity during extinction (Spohrs et al., 2021). Notably, this study only recruited male participants, despite evidence that endocannabinoids are both expressed and involved in stress and fear extinction differently between the sexes (Morena et al., 2021; Ney, Matthews, et al., 2018). Further, Mayo, Asratian, Linde, et al. found no difference in fear extinction between AC and CC carriers, but did report a significant difference between performance in these groups and the AA group. Finally, one other study among non-clinical adults found that a polymorphism in the CB1 gene

(rs1049353, but not rs2180619), was associated with poorer fear extinction in healthy humans (Heitland et al., 2012).

In contrast to non-clinical investigations, only one study has assessed the effects of genetic variation within the endocannabinoid system in humans with PTSD who underwent a fear extinction paradigm. We recruited healthy and PTSD participants in a standard fear extinction study where they completed habituation, fear conditioning, and extinction learning phases (Ney, Matthews, et al., 2021). All participants provided saliva samples for DNA genotyping of rs324420 (*FAAH* gene single nucleotide polymorphism), rs1049353 (*CNR1* gene single nucleotide polymorphism), and rs2180619 (*CNR1* gene single nucleotide polymorphism) and a subsample of participants provided blood samples before and after the extinction tasks. In contrast to the existing literature, we found that A allele carriers of rs324420 had generalisation of fearful reactions during extinction learning towards the safety signal, but only if they had PTSD. This effect did not occur in healthy participants. We also found that A-allele carriers of rs1049353 who had PTSD had higher responses to the conditioned stimulus compared to the safety stimulus during extinction learning, suggesting that lower CB1 abundance reduced extinction learning in PTSD participants. In further support of this, our sub-analysis revealed that plasma AEA level moderated the effect of rs324420 on fear extinction, such that lower AEA was associated with poorer extinction in A-allele carriers, but higher AEA was associated with better extinction in these participants. This effect was not replicated when OEA or 2-AG was substituted for AEA. This means that the effect of rs324420 mutation on extinction is driven by AEA and not other endocannabinoids. Critically, OEA and AEA are structurally similar and share most of the same molecular targets, except for CB1 receptors (Ligresti et al., 2016). Therefore, this finding supports the earlier genetic findings, such that direct agonists of the CB1 receptor enhance extinction learning in humans. Overall, future studies should expand on candidate

loci studies of endocannabinoid polymorphisms in human fear extinction studies to further elicit the translational potential of cannabinoids for human treatments of PTSD.

In addition to studies assessing genetic variation within the endocannabinoid system, a few investigations have examined the effect of pharmacological (i.e., FAAH inhibitor, CB1 agonist) and behavioural (i.e., aerobic exercise) manipulations to the endocannabinoid system on fear extinction outcomes. Among pharmacological manipulation studies, Rabinak and colleagues (2014) as well as Klumpers et al. (2012) did not find physiological (skin conductance) evidence of enhanced extinction learning among non-clinical adults following an acute dose of a CB1 receptor agonist (dronabinol), although greater ventromedial prefrontal cortex and hippocampus activation (i.e., regions implicated in enhanced extinction learning) during a fear extinction recall test was reported (Rabinak et al., 2014). Additionally, Das et al. (2013) reported trends towards significantly improved extinction as measured with skin conductance responses following CBD dosing. In contrast, Rabinak et al. (2013) and Hammoud et al. (2019) found that THC improved physiologically-measured indices of fear extinction learning. Additionally, Mayo, Asratian, Lindé, et al. (2020) provided the first evidence of enhanced extinction recall in non-clinical adults following 10-day administration of a FAAH inhibitor (PF-04457845), which resulted in a 10-fold increase in circulating concentrations of AEA. Finally, Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Almassi, et al. (2021) recently reported that moderate-intensity aerobic exercise delivered after fear extinction learning occurred, resulted in enhanced consolidation of fear extinction learning and extinction recall (i.e., reduced threat expectancy following reinstatement) among adult women with PTSD. Importantly, exercise-induced increases in circulating concentrations of AEA were found to mediate the relationship between aerobic exercise and cognitive indices (i.e., threat expectancy ratings) of extinction recall (Crombie,

Cisler, et al., 2021; Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Adams, et al., 2021).

In addition to Crombie et al.'s (2021) investigation that implemented a behavioural approach (i.e., aerobic exercise) to examine the effect of endocannabinoid system enhancement on fear extinction learning, to our knowledge there is only one other clinical mechanistic trial that included PTSD patients Rabinak et al. (2020). However, Rabinak and colleagues (2020) design was slightly different as they did not administer a fear extinction paradigm, but rather assessed reactivity in corticolimbic brain regions using fMRI during a commonly administered threat imagery task. Results from this study revealed that acute THC administration reduced amygdala activation and increased mPFC activation to threat. It is worth noting that a few other investigations with non-clinical populations (Gee et al., 2016; Gunduz-Cinar et al., 2013; Hariri et al., 2009) have been conducted examining the influence of genetic variation and pharmacological manipulations on various other fear, anxiety, and stress related processes– however, given that these studies did not administer traditional fear conditioning paradigms, discussion of these findings is beyond the scope of this review. Collectively, although in its infancy, there is building evidence to suggest that targeting the endocannabinoid system may be a promising method for improving extinction learning and enhancing extinction recall, which may have implications for improving the efficacy of exposure-based therapies. Clearly, more research (examining genetic influences and pharmacological/behavioural manipulations) is needed in clinical mental health populations such as PTSD.

There are multiple reasons why these studies have not always produced the same results as other human studies and as those predicted in animal models. Firstly, animal studies have less ethical constraints and are able to selectively dose brain regions that are more likely to improve extinction processes, such as injecting potent, synthetic CB1 agonists directly to

the mPFC. Similarly, animal studies are able to induce far stronger levels of trauma to their subjects, whereas the aversive stimuli imposed on human participants is often merely an inconvenience that is not perceived as life-threatening. This means that animals typically experience stronger fear learning and consequently steeper fear extinction that is more likely to be affected by interventions. Thirdly, animal studies typically use only male subjects. Significant research shows that the endocannabinoid system is sexually dimorphic and responds differently following stress depending on sexual hormonal conditions (Atkinson et al., 2010; Craft et al., 2013; El-Talatini et al., 2010; Ney, Matthews, et al., 2018, 2019b; Watts et al., 2020; Wyrofsky et al., 2018; Zer-Aviv & Akirav, 2016). Similarly, exogenous cannabinoids are metabolised differently between males and females, and the physiological effects are also different (Cuttler et al., 2016; Rubino & Parolaro, 2011; Struik et al., 2018). This means that the human studies, which typically include both males and females, may have contrasting findings to the animal literature due to the introduction of a wider range of sex hormones. This possibility is especially important given increasing evidence of sex- and sex-hormone influence on stress reactivity, PTSD, and fear extinction, as well as many other psychiatric disorders (Gogos et al., 2019; Graham & Milad, 2013; Laird et al., 2019; Lebron-Milad et al., 2012; Li & Graham, 2017; Milad et al., 2010; Ney, Gogos, et al., 2019).

Finally, there is also growing evidence that these fear extinction paradigms may have issues with clinical validity and statistical robustness, as described by multiple research groups including our own (Bach et al., 2018; Bach & Melinscak, 2020; Beckers et al., 2013; Lonsdorf et al., 2019; Ney, Laing, et al., 2020; Ney, Wade, et al., 2018; Pöhlchen et al., 2020). These are broad issues with fear extinction paradigms that are not specific to the endocannabinoid field. Specifically, fear extinction studies that use physiological outcomes are typically underpowered, with conservative estimates of required sample size at least 70 per group for skin conductance to detect moderate effects (Bach & Melinscak, 2020; Khemka

et al., 2017). No studies in the above literature achieved this sample size, though it should be noted that the issue of underpowered research is pervasive in the fear conditioning and behavioural psychology literature. It is possible that lack of replicability in fear conditioning studies is foremost an issue of study power; alternatively, Khemka et al. (2017) may have overestimated the required sample sizes. The findings of this study should be independently verified; however, it is well known that psychophysiological measures require larger samples due to the inherent variability in measurements (Boucsein, 2012) and the true sample requirements are likely to be larger than is conventionally collected, even if 70 per sample is an overestimation. Recently it has also been shown that fear extinction paradigms may not adequately model learning deficits in PTSD, with no difference in extinction or extinction recall in one recent study (Pöhlchen et al., 2020), and minimal differences in extinction learning as demonstrated in meta-analysis (Duits et al., 2015). Finally, it has been demonstrated by our research group, as well as others, that variability in statistical methods between fear extinction studies significantly reduces the replicability of reported findings (Lonsdorf et al., 2019; Ney, Laing, et al., 2020). Future research should work towards improving the replicability of this mode of investigation by improving the quality of statistical analyses and rigorously assessing the validity and relevance of the studied mechanisms to those of clinical populations.

Translation of evidence of endocannabinoid signalling in emotional and intrusive memories

The hallmark of PTSD symptomology are repeating, spontaneous, and distressing intrusive memories that are related to trauma (American Psychiatric Association, 2013). Given the importance of emotional memory symptoms to PTSD aetiology, various animal models have been developed that attempt to simulate the types of memory processes that

underlie the genesis and maintenance of these symptoms. One commonly used animal model is the inhibitory avoidance paradigm, where animals receive a foot-shock in a certain context. During a follow-up session, the animals' latency of re-entering this context is measured as an index of emotional memory recall (Gold, 1986). Another way of testing memory in animals is the Morris Water Maze, where animals are placed in a pool of water that is designed to impede their scent and vision. In this task, they are required to internalise external cues of the maze that allow them to escape from the water. Control animals (usually rats) will display an increasing speed of escape, and the change in this speed can be experimentally altered by pharmacological, genetic or behavioural manipulations (Morris, 1984). Both of these paradigms are very commonly utilised in basic memory and emotional memory research.

A large body of animal and clinical literature has firmly established a causal role of glucocorticoids (such as cortisol) in emotional memory strength and subsequent intrusive memories (McGaugh & Roozendaal, 2002; Pitman, 1989; Pitman et al., 2012; Roozendaal & McGaugh, 2011). Glucocorticoids are released during an emotional event and inhibit GABAergic signals in the basolateral amygdala (BLA), which results in emotional salience assigned to the experience that determines its biological significance (Roozendaal et al., 2009; Roozendaal & McGaugh, 2011). This was shown in inhibitory avoidance studies where administration of a glucocorticoid receptor agonist into the BLA, but not the adjacently positioned central nucleus of the amygdala, enhanced memory retention in rats, whereas glucocorticoid antagonism of the BLA but not the central nucleus impaired memory retention (Roozendaal & McGaugh, 1997). Similarly, antagonism of the amygdala GABAergic system in rats improved memory retention of an inhibitory avoidance task, whereas GABAergic receptor enhancement reduced memory retention (Brioni et al., 1989). Excessive activation of glucocorticoids during intense trauma consolidates these negative experiences to the point where they become fragmented and do not consolidate correctly to autobiographical memory.

The result are intrusive memories, which are fragmented, spontaneous, and often visceral or sensory rather than explicit (Brewin et al., 2010; Pitman, 1989; Pitman & Delahanty, 2005; Pitman et al., 2012). Understanding how memory traces can be restored to normal is imperative to most therapies for PTSD.

Animal research has demonstrated that endocannabinoids affect emotional memory processing, though the direction of the effect is highly dependent on contextual factors (Morena & Campolongo, 2014). CB1 agonists appear to impair acquisition (Campolongo et al., 2012; Lichtman et al., 1995) and retrieval of memory (Atsak et al., 2015; Atsak, Hauer, et al., 2012; Niyuhire et al., 2007; Segev et al., 2018). However, these findings are dependent on stress levels of the animals through modulation of glucocorticoid release. Specifically, under higher stress load high endocannabinoid levels are associated with memory improvement, whereas under low stress load decreased endocannabinoid levels are associated with the prototypical reduction in memory found in heavy marijuana users (Campolongo et al., 2013; Morena & Campolongo, 2014; Morena et al., 2015; Morena et al., 2014). Therefore, current evidence suggests that cannabinoids have divergent effects on memory processes that is dependent on stress levels. This has particular implications for PTSD, since PTSD is marked by memory consolidation under stress, and PTSD patients are thought to display dysregulated glucocorticoid and endocannabinoid profiles (Hauer et al., 2013; Hill et al., 2013; Hill et al., 2018; Yehuda et al., 2015; Yehuda et al., 1995).

Findings in animal memory literature can be translated to humans using emotional memory paradigms (Holmes et al., 2004). Emotional memory paradigms pair exposure to emotionally salient images or films on the first testing session and return to the laboratory at a follow-up session for a deliberate recall task that is conducted unexpectedly to prevent rehearsal effects (Iyadurai et al., 2019). The paradigm is well-suited for testing factors associated with both the consolidation and retrieval of emotional memories. Inclusion of an

intrusive memory diary is also possible in this study design. The intrusive memory diary was first developed by Holmes et al. (2004) as a way of assessing the self-reported intrusive memories that participants experienced of each image over the time period since testing. Clearly, images with low valence are not expected to produce intrusive memories; but intrusions can become quite frequent with higher image valence – particularly of traumatic or emotionally salient content (Clark & Mackay, 2015; Clark et al., 2015). Paradigms measuring intrusive memories of film clips or pictures have been validated over the past two decades as a valid and reliable way of measuring learning and memory mechanisms that are relevant to PTSD (Iyadurai et al., 2019; James et al., 2016).

Emotional memory paradigms can pair exposure of emotionally salient stimuli with neurobiological assessments, and in doing so test the relationship between biological phenotypes of interest and memory of the stimuli. For example, our group has shown that poor quality rapid-eye movement sleep is associated with heightened intrusive memories of emotional pictures in PTSD participants (Ney, Hsu, et al., 2020), that there are sex differences in the number of intrusive memories following exposure to emotional images (Hsu et al., 2018), and that cortisol and salivary alpha amylase interact to predict the number of intrusive memories reported by healthy and PTSD participants (Nicholson et al., 2014). Moreover, our group, as well as others, have found that progesterone and estradiol levels in saliva are associated with increased explicit and intrusive memories of negative imagery (Andreano & Cahill, 2010; Cheung et al., 2013; Ertman et al., 2011; Felmingham et al., 2012; Ferree et al., 2011; Ney, Felmingham, & Nichols, 2020; Nielsen, Ahmed, et al., 2013; Nielsen et al., 2014; Nielsen, Segal, et al., 2013; Soni et al., 2013; Wassell et al., 2015; Wegerer et al., 2014). Therefore, it is clear that this paradigm is useful for identifying neurobiological and endocrine markers relevant to memory consolidation and retrieval

(Holmes et al., 2004), which are processes that are critically important to PTSD aetiology and maintenance (Brewin, 2011, 2014; Pitman et al., 2012).

We are only aware of one human study that has tested the relationship between endocannabinoids and emotional memories (Wirz et al., 2018). Healthy participants who were genotyped for CB1 rs1049353 underwent the TSST or control condition before completing an emotional memory task using emotional pictures. They also had neural correlates of image processing assessed using fMRI. It was reported that A-allele carriers had stronger ventromedial prefrontal cortex activity when viewing images of negative valence after stress compared to the GG homozygotes. Further, neural amygdala and hippocampus activity was associated with memory recall in the A allele carriers under stress, but not the GG homozygotes (Wirz et al., 2018). These findings were interpreted to support a protective role of the A allele of rs1049353 in emotional memory consolidation under stress, but are somewhat inconsistent with the clinical literature where it was reported that A carriers had higher PTSD symptomology if they had experienced higher childhood abuse (Mota et al., 2015). Regardless, the exact functional consequence of variation of the rs1049353 polymorphism is unknown and it is therefore hard to surmise what effect should be expected in a memory paradigm. Further, intrusive memories were not measured in this study.

We recently attempted to replicate and extend this study, but we also genotyped the CB1 polymorphism rs2180619 in addition to rs1049353, as well as the FAAH polymorphism rs324420 (Ney et al., Unpublished data). Our participants included PTSD patients and healthy controls, and a sub-sample of participants provided blood samples for plasma endocannabinoid analysis. We found that negative intrusive memories were more likely to be experienced by PTSD G-allele carriers of rs2180619. This finding is important because rs2180619 G allele is associated with lower expression of the CB1 receptor, higher anxiety levels, and lower working memory performance (Lazary et al., 2009; Ruiz-Contreras et al.,

2014). We also found that heightened plasma AEA and mutation of the rs324420 polymorphism were associated with reduced explicit recall of negative pictures. This finding was consistent with the animal literature such that our participants were not under a high stress load during the task as shown by stable cortisol levels before and 20 minutes following task completion (Ney et al., Unpublished data). These results therefore provide strong translational evidence from animal to human and suggest that PTSD memory symptoms may be affected by the endocannabinoid system, however more research is needed both in understanding the consequences of mutation of these polymorphisms as well in emotional memory paradigms more generally. No study has examined endocannabinoid markers in humans using an intrusive or emotional memory trauma film paradigm.

Improving methods for measuring endocannabinoid reactivity in humans

Endocannabinoids are quantifiable and responsive to exercise in saliva

Examination of the endocannabinoid system (including endocannabinoids) is a relatively new field of research (Mechoulam & Parker, 2013). Analytical methods for quantification of endocannabinoids in various human matrices, such as plasma, serum, urine, and milk have been achieved (Battista et al., 2014). However, even in more common research matrices, such as plasma, quantifying endocannabinoids presents numerous challenges such as isomerisation of 2-AG, low levels of AEA, and lack of consistent reference intervals between laboratories (Fanelli et al., 2012). Further, limited research has been conducted in quantification of endocannabinoids in saliva and little is known about their properties, if they are present in this matrix (Battista et al., 2014; Matias et al., 2012). Development of methods for quantifying other salivary analytes, such as cortisol or salivary alpha amylase, has provided significant insight and research technologies to investigate psychological phenomena (Kirschbaum & Hellhammer, 1989; Kirschbaum & Hellhammer, 1994; Nater &

Rohleder, 2009). For this reason, investigation of the presence and role of endocannabinoids in saliva is a pertinent topic to psychological and health research.

Despite several previous studies reporting no presence of endocannabinoids in saliva (Battista et al., 2014; Lam et al., 2010), we were able to detect and reliably quantify AEA, 2-AG and OEA at low levels (Ney, Felmingham, Matthews, et al., 2020) with a method that was similar to that reported by Matias and colleagues (2012). Our method is linear with low percentage variation across samples spiked at the same concentration. Further, using our method, 2- and 1-AG isomers were chromatographically separable, and OEA was abundantly expressed. Salivary endocannabinoids showed the same ex vivo generative properties of brain and plasma endocannabinoids, which has previously been reported as an important factor in sample storage (Fanelli et al., 2012; Wood et al., 2008). We also showed that all three of these endocannabinoids increase in response to 20-minutes of moderate intensity exercise and return to basal levels 20-minutes following exercise cessation (Ney, Felmingham, Matthews, et al., 2020). Immediate increases in salivary 2-AG concentration in response to acute stress were also observed in our psychosocial stress study (Ney, Stone, et al., 2021).

Salivary cortisol is not protein-bound (Kirschbaum & Hellhammer, 1989), which means that it is desirable to collect over plasma cortisol, since protein-bound cortisol is not biologically active. Similar to this, circulating endocannabinoids are unlikely to be protein-bound (Hillard, 2017) and there is therefore a strong possibility that endocannabinoids detectable in saliva may originate from plasma. If this were the case, then measurement of saliva endocannabinoids levels could be used as a proxy for blood levels. However, in our study, the lack of correlation between plasma and saliva endocannabinoid levels suggests that these do not share a common source (Ney, Stone, et al., 2021). Further, we found that endocannabinoids rapidly increased following both stress and exercise, which is typically the timing of an autonomic nervous system response. Saliva excretion is also controlled by the

autonomic nervous system (Beata et al., 2017; Proctor & Carpenter, 2007) and it has previously been reported that activation of cannabinoid receptors in the saliva glands of rats by AEA results in inhibition of saliva secretion (Prestifilippo et al., 2006; Prestifilippo et al., 2009; Prestifilippo et al., 2013). This suggests that endocannabinoids that are detectable in saliva are synthesised locally as part of the autonomic nervous system response since the salivary glands are innervated by the autonomic nervous system and control salivary excretion under stress (Beata et al., 2017; Nater & Rohleder, 2009; van Stegeren et al., 2008).

Our Ney, Stone, et al. (2021) study was limited by a relatively large proportion of saliva AEA levels falling below the limit of quantification. Confirmation of the relationship between blood and saliva endocannabinoids therefore requires improved method and instrument sensitivity available from recent advances in mass spectrometry systems (i.e., our measurement device in Ney, Stone, et al., (2021) was 10 years old and less sensitive compared to newer models). Finally, our application of this chemical method supports a biological role for endocannabinoids in human saliva during exercise (Ney, Felmingham, Matthews, et al., 2020); however, the study was only conducted in a single participant over 30 exercise sessions and therefore needs replication. Additional research should be conducted before the relationship between saliva and blood endocannabinoids can be concluded.

Endocannabinoids can be quantified in hair using simplified tandem mass spectrometry methods

Methods for quantifying endocannabinoids in hair are also becoming published more frequently (Gao et al., 2020; Krumbholz et al., 2013; Mwanza et al., 2016; Voegel et al., 2021) but have been applied only sparingly (Croissant et al., 2020; Koenig et al., 2018; Wilker et al., 2016; Wingenfeld et al., 2018). Applications of hair methods have shown great potential to explain the long-term effects of disorders on endocannabinoid concentrations,

and vice versa, with reports of altered endocannabinoid profiles in unaccompanied child refugees (Croissant et al., 2020), in war veterans with PTSD (Wilker et al., 2016), in borderline personality disorder patients (Wigenfeld et al., 2018) and in mothers with childhood maltreatment (Koenig et al., 2018). It is likely that the advent of methods for quantifying retrospective endocannabinoids (i.e., in hair) will result in greater number of discoveries using this methodology in coming years.

Our laboratory also developed a method with similar limits of detection to previous reports using greatly simplified sample preparation, which is favourable for studies requiring large sample sizes (Ney, Felmingham, et al., 2021). Specifically, AEA, 2-AG, and OEA were quantifiable at low concentrations with high accuracy, precision, and linearity. In contrast with previous methods, our sample preparation consisted of only one step, which was the extraction step that is common to all methods. Previous methods have reported necessity of following steps involving on- and off-line solid phase extraction (Gao et al., 2020; Krumbholz et al., 2013; Mwanza et al., 2016), as well as supported liquid extraction (Voegel et al., 2021). Our method uses chloroform as a redissolution solvent, since much of the endocannabinoid analyte appeared to be bound to water-insoluble material that was removed during solid phase extraction. In this paper, we found that hair AEA levels were negatively correlated with salivary cortisol and OEA in a small group of healthy participants. Further, we identified that whereas cortisol and progesterone were extracted at approximately 75% efficiency after a single extraction step, endocannabinoids AEA and 2-AG were extracted at 100% efficiency after a single extraction. This suggests that our method is able to be conducted with extremely high efficiency, despite its rapid nature (Ney, Felmingham, et al., 2021). Future studies should measure hair endocannabinoids to answer further clinical questions, or during analogue tasks measuring outcomes such as fear extinction or emotional memories.

Imaging the endocannabinoid system using positron emission tomography

Over the past two and a half decades, positron emission tomography (PET) imaging techniques have been developed that allow the cannabinoid receptors in the human brain to be visualised (Hamilton et al., 2021). Beginning in 1998, radioligands that can selectively bind to CB1 (Gatley et al., 1998; Horti et al., 2006; Horti & Laere, 2008) and CB2 (Ling et al., 2015; Moldovan et al., 2016; Ni et al., 2019; Spinelli et al., 2018) have been developed, which allows the availability of cannabinoid receptors in the live human brain (i.e. as indexed by how many receptors the experimental ligand can bind to) to be imaged both at rest and during a limited number of PTSD-relevant laboratory tasks. For example, it has been shown that there are gender differences in CB1 availability (Normandin et al., 2015) and that cannabis abuse is associated with significantly lower CB1 availability in cannabis dependent participants compared to controls, but not after two days of withdrawal (D'Souza et al., 2016). In PTSD, it has previously been reported that increased CB1 availability in the human brain is associated with incidence of PTSD in a small group of participants (Neumeister et al., 2013). In combination with low observed AEA peripheral levels in PTSD participants of this study, this result was interpreted as being indicative of CB1 upregulation to compensate for deficient AEA (Neumeister et al., 2013). Based on studies such as this, it is clear that human imaging techniques could provide high translational value, but to our knowledge this is the only study that has tested for differences between PTSD and healthy populations using either CB1 or CB2 imaging techniques.

PET methods for imaging FAAH content in the brain have also been developed (Rusjan et al., 2018; Rusjan et al., 2013; Wilson et al., 2011). Using these methods, it has been shown that reduced FAAH content is associated with violent offending in participants with antisocial personality disorder (Kolla et al., 2021), with cannabis use in young

participants (Jacobson et al., 2021), with greater positive psychosis symptoms amongst schizophrenic patients (Watts et al., 2020), and in treatment-seeking patients with alcohol use disorder (Best et al., 2020), but is elevated in the prefrontal cortices of patients with borderline personality disorder (Kolla et al., 2020). Using PET imaging, it was also identified that FAAH content was negatively related to amygdala connectivity with the ventromedial prefrontal cortex and dorsal anterior cingulate cortex of healthy participants (Green et al., 2021), all of which are targets involved in fear extinction and PTSD (Bouton et al., 2020; LeDoux, 2014). A recent study also produced the first steps in developing a PET imaging technique for MAGL protein (Chen et al., 2021), though this technique is currently irreversible and requires further development prior to use in humans. Future studies should also consider examining the relationship between cannabinoid receptor availability, FAAH, and other endocannabinoid targets during the fear extinction or intrusive memory paradigm as these techniques appear to be highly sensitive to clinical differences between patient groups.

Trial and Development of Cannabinoid-based Therapies

The consensus from a largely animal literature is that cannabinoid agents (or manipulations that enhance eCB signalling) should prove to be promising treatments for improving several mental health outcomes among PTSD patients. However, relatively few studies have directly tested this hypothesis. In humans, there have been several clinical trials and retrospective studies, most of which suggest strong potential for cannabinoids to improve PTSD symptomology. Several studies found that nabilone (or similar) improved nightmares, sleep quality, and some waking symptoms in PTSD patients (Cameron et al., 2014; Fraser, 2009; Jetly et al., 2015). However, of these studies the only trial was Jetly et al (2015), and this study was not a randomised clinical trial. There have been several reports of case studies

where cannabinoids have improved both sleep quality and waking symptoms of PTSD and patients with anxiety (Elms et al., 2019; Passie et al., 2012; Shannon et al., 2019; Shannon & Opila-Lehman, 2016), but no direct clinical trials in conjunction with therapy have been conducted to date. Most recently, Bonn-Miller et al. (2021) randomly assigned participants with PTSD to three weeks of either active treatment (three varying dose combinations of cannabis) or placebo. They reported that no significant changes in PTSD symptomology was observed between the treatment groups, though noted that higher powered studies were required (Bonn-Miller et al., 2021).

Significant limitations exist when inferring the results of Bonn-Miller et al. (2021) and translational, mechanistic cannabinoid research in humans using the fear conditioning paradigm. The fear conditioning paradigm (where findings have seemed to reflect potential efficacy of cannabinoids in PTSD) has been dosed acutely with the intention of improving performance on the laboratory tasks. The clinical implication for this type of research differs from the study design of Bonn-Miller and colleagues by assuming that cannabinoids would need to be dosed acutely during therapy rather than chronically over a designated time period. It is also critical to consider effective dose and formulation control when developing pharmaceutical options for PTSD. Studies in both the clinical and laboratory literature have not only used varying doses and formulations but have not in any study measured the pharmacokinetic association between plasma cannabinoid level and task or clinical performance. Given that cannabinoids are metabolised significantly differently between individuals (Huestis, 2007), it is essential that metabolite levels are examined with reference to study outcomes. In addition, as with any plant-based medicine, exact knowledge of pharmaceutical formulation is critical to understanding which components are effective between indications. In Bonn-Miller et al. the study drug was described as “four concentrations of cannabis”, implying that although the THC and CBD levels were controlled

for, entourage effects from other components of the plant were not measured. Finally, cannabinoid purity has not been factored for in any of these studies to our knowledge, as there is significant room for industrial growth and manufacturing capabilities in the international cannabinoid sector that would produce high purity active pharmaceutical ingredients (Oultram et al., 2021). More research is needed to assess under what conditions cannabinoid therapy will be most effective for treating PTSD.

Most population-based cross-sectional data suggests that cannabis use is associated with reduced symptom severity, comorbid depression, and suicidality in PTSD patients (Bonn-Miller et al., 2020; Greer et al., 2014; Lake et al., 2019). However, some cross-sectional data suggests the opposite, with reports that increased cannabis use amongst PTSD patients is associated with worse symptoms (Gradus et al., 2010; Loflin et al., 2017), though the direction for these effects are not clear due to the nature of the study design. Regardless, it is clear that PTSD patients use cannabis far more often than the general population, suggesting that it provides some measure of symptom relief (Cougle et al., 2009). Several studies have also found that PTSD is associated with altered peripheral endocannabinoid concentrations (Hauer et al., 2013; Hill et al., 2013; Neumeister et al., 2013; Wilker et al., 2016), though the direction for these differences to the general population is inconsistent between studies.

It is also worthwhile considering that the endocannabinoid system shows prevalent interactions with multiple other molecular signalling systems. For example, increasing evidence shows that endocannabinoids mediate dopaminergic release and signalling (Covey et al., 2017; Mateo et al., 2017) and this interaction is likely to affect outcomes in PTSD (Ney, Akhurst, et al., 2021). In fact, the most recent and largest GWAS study in PTSD revealed that the PARK2 gene – a dopamine gene – was one of the only predictors of PTSD (Nievergelt et al., 2019). Similarly, endocannabinoids interact with serotonin, TRPV1

channels, brain-derived neurotrophic factor pathways, and others (Ney, Matthews, et al., 2019a). Importantly, the exact molecular effects of CBD, and even to some extent THC, are not fully characterised and the complexities of their synergistic effects remains to be understood (Ligresti et al., 2016; McPartland et al., 2015). Specifically, studies have begun to reveal that CBD and THC can produce therapeutic effects when combined at sub-threshold doses, but the mechanism for this is not yet understood (Casey et al., 2017; Mitchell et al., 2021). Research examining the effect of exogenous cannabinoid through multiple signalling pathways, particularly those that are likely to be relevant to PTSD, is possibly a way towards efficacious product development.

Conclusion

The development of precision medicine relies on strong knowledge of role of a target molecular system in a disease state (Adams & Petersen, 2016). Development begins with systematic preclinical research, where mechanisms of molecular influence can be determined with high specificity. However, at some stage animal findings must be translated to human subjects: molecular influences that are evidenced in animal models must be replicated in humans. This is first achieved through cost-effective associative studies (such as the fear extinction paradigm) and then in clinical trials for new drugs. Research that has linked the endocannabinoid system to fear extinction, emotional memories, stress responding, and PTSD has been almost entirely conducted in animals and yet, clinical trials of cannabinoids for PTSD are progressing rapidly.

The work of several research groups has provided initial translational, associative, and mechanistic evidence of the effect of endocannabinoid signalling in stress responding, emotional memories, fear extinction, and PTSD. These findings have several implications for the endocannabinoid literature and in many cases overlap with the animal literature. For the

first time, it has now been shown that blood levels of endocannabinoids in humans show associations with complex behavioural responses consistent with those reported in preclinical literature. The implication of these findings is that many of the animal findings that show efficacy of cannabinoid-based treatments for improving aversive memory symptomology may have the same effect in humans. This has implications for the initiation and continuation of clinical trials of cannabinoids for PTSD, particularly in conjunction with exposure therapies where safety learning is fostered. There are currently ongoing randomised, placebo-controlled clinical trials in PTSD using THC (NCT04080427) and FAAH inhibition (EudraCT 2020-001965-36), which will provide high quality evidence as to whether cannabinoids can treat PTSD effectively. Multiple lines of evidence across these studies point towards a strong contribution of the CB1 receptor in human fear extinction and emotional memory, particularly in patients with PTSD.

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Alignment and misalignment of translational PTSD mechanism and endocannabinoid studies with animal models

Studies	**Manipulation**	**Measures**	**Outcomes**	**Alignment**	**Misalignment**
Stress Reactivity					
Chouker et al., (2010)	Airflight manoeuvres	Whole blood	Endocannabinoid level	Stress reactivity successfully induced. Findings align with animal models	Stress task not representative of trauma or animal models. No receptor manipulations possible.
Crombie et al., (2019)	TSST, PTSD vs control	Serum	Endocannabinoid level	Stress reactivity successfully induced. Demonstrated differentiation between PTSD and controls. Task may reflect animal models.	Findings do not strictly align with animal models. Stressor is escapable. No receptor manipulations possible.
Dlugos et al., (2012);	TSST	Serum	Endocannabinoid level	Stress reactivity successfully induced. Task may reflect animal models.	Findings do not strictly align with animal models. Stressor is escapable. No receptor manipulations possible.
Mayo, Asratian, Linde et al., (2020)	MAST	Serum	Endocannabinoid level	Stress reactivity successfully induced. Task may reflect animal models.	Findings do not strictly align with animal models. Stressor is escapable. No receptor manipulations possible.
Ney, Stone, et al., (2021)	MAST	Plasma, saliva	Endocannabinoid level	Stress reactivity successfully induced. Task may reflect animal models. 2-AG showed on-demand responsivity in saliva	Findings do not align with animal models. Stressor is escapable. No receptor manipulations possible.
Emotional Memories					

Ney et al., (Unpublished)	IAPS images, PTSD vs control	Plasma, genetics	Intrusive memories, explicit memories	Some ecological validity as stimuli are perceptive-based. Findings align with animal models.	Task valence relatively low. Uses imagery rather than spatial and inhibitory models used in animals.
Wirz et al., (2018)	IAPS images	Genetics	Explicit memories	Some ecological validity as stimuli are perceptive-based. Findings may reflect animal models.	Task valence relatively low. Uses imagery rather than spatial and inhibitory models used in animals.
Fear Conditioning					
Crombie, Sartin-Tarm, Sellnow, Ahrenholtz, Lee, Matalamaki, Almassi, et al., (2021)	PTSD vs control	Serum	US expectancy	Findings align with animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently.
Das et al., (2013)	32mg CBD, inhaled, single dose	-	Skin conductance, US expectancy	Findings may reflect animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently. Drug is not CB1-selective.
Dincheva et al., (2015)	Correlative study	Genetics, MRI	Skin conductance	Findings reflect animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently.
Hammoud et al., (2020)	7.5mg THC, oral, single dose	fMRI	Skin conductance	Findings align with animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently. Drug is not CB1-selective.

Heitland et al., (2012)	Correlative study	Genetics	Fear potentiated startle	Findings may align with animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently.
Klumpers et al., (2012)	10mg THC, oral, single dose	-	Skin conductance, US expectancy	Task may reflect animal models.	Findings do not align with animal models. Stressor is escapable and of lower valence. Testing sessions are spaced differently. Drug is not CB1-selective.
Mayo, Asratian, Lindé, et al., (2020)	4mg FAAH inhibitor, oral, daily for 10 days	Serum, genetics	Fear potentiated startle	Findings align with animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently.
Ney et al., (2021)	PTSD vs control	Plasma, genetics	Skin conductance	Findings mostly align with animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently.
Rabinak et al., (2013)	7.5mg THC, oral, single dose	-	Skin conductance, US expectancy	Findings align with animal models. Task may reflect animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently. Drug is not CB1-selective.
Rabinak et al., (2014)	7.5mg THC, oral, single dose	fMRI	Skin conductance, US expectancy	Task may reflect animal models. fMRI measures aligned with animal models.	Physiological measures did not align with animal models. Stressor is escapable and of lower valence. Testing sessions are spaced differently. Drug is not CB1-selective.

Rabinak et al., (2018)	7.5mg THC, oral, single dose	fMRI	Skin conductance, US expectancy	Task may reflect animal models. Findings align with animal models.	Stressor is escapable and of lower valence. Testing sessions are spaced differently. Drug is not CB1-selective.
Sporhs et al., (2021)	Correlative study	Plasma, genetics, fMRI	Fear ratings	fMRI data align with animal models. Task may reflect animal models.	No physiological measures. Fear ratings did not align with animal models. Stressor is escapable and of lower valence. Testing sessions are spaced differently.
Zabik et al., (2021)	Correlative study (virtual reality)	Genetics, fMRI	Skin conductance, US expectancy, distress	fMRI data align with animal models.	Most data did not align with animal models. Virtual reality exposure different to animal models. Stressor is escapable and of lower valence. Testing sessions are spaced differently.

TSST = Trier Social Stress Task; MAST = Maastricht Acute Stress Test; CBD = Cannabidiol; THC = delta-9-tetrahydrocannabinol; FAAH = fatty acid amide hydrolase;

PTSD = posttraumatic stress disorder; IAPS = International Affective Pictures System; fMRI = functional magnetic resonance imaging