Endocannabinoid System Modulation of Flow States: A Theoretical Model and Review

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The authors are seeking publication of this paper due to a few important and novel elements. First, the relationship between flow states and the endocannabinoid system have been poorly delineated in the literature. Second, the paper includes the novel proposal of a “flow cycle” which has to date not been published in a peer-reviewed manner. Third, much of the research on flow states has been restricted to the domain of psychology so research on its biological mechanism is of critical importance. Finally, this paper looks to better join flow research to the larger bodies of stress and attention literature.

Abstract

The relationship between the endocannabinoid system (ECS) and the optimal state of consciousness known as flow is poorly understood. The ECS is a modulatory biological system implicated in a diverse range of functions including attention and stress. Flow is characterized by focused task-specific attention and neurobiological alterations in normal stress processing. Despite this overlap, there has been little work exploring the relationship between flow and the ECS. This paper surveys the literature to develop the hypothesis that the ECS modulates entrance into flow through well-characterized stress and relaxation pathways, that this system is responsible for key characteristics of the flow experience, and that the ECS aids in the recovery from this energy
intensive state. The four stages of a flow cycle—struggle, release, flow, and recovery—are delineated to explore this relationship. This review supports the central role of the ECS in flow experience and provides avenues for future research.

1 Introduction

The optimal state of consciousness known as flow is intimately bound up with physiological arousal and related stress processes. This relationship helps explain why flow is especially prevalent in high arousal situations such as combat, sports, and social situations, especially those social situations containing evolutionarily primed stimuli such as competition, physical risk, and group belongingness (Jackson, 1996; Harari, 2008; Shehata et al., 2021). Characterizations of the state often focus on the challenge/skill balance wherein challenge moderately exceeding an individual’s skill is both a main characteristic of flow and a trigger for the experience (Csikszentmihalyi, 1997). In other words, there is some level of baseline arousal necessary for entrance into flow and this arousal can be understood through well-characterized stress pathways.

However, it is still unclear as to why some high-stimulation situations are experienced as flow, while others are encoded as stressful or, at their extreme, traumatic. One might therefore hypothesize a high arousal inflection point through which an individual passes from a stress response into flow. This inflection point would consist of the physiological, phenomenological, and biological processes of arousal and stress, including their downregulation. Elsewhere in the literature, this inflection point is referred to as a challenge response (Elliot, 2008), which is distinct from the fight-or-flight response.

Building atop research into the challenge response, this paper hypothesizes a “flow cycle” where flow exists as part of a four stage process of struggle, release, flow, and recovery. The “struggle phase” is predominantly a state of physiological arousal, wherein the resulting stress response produces a state of vigilance. The “release phase” entails a physiological shift away from stress that is subjectively experienced as a sense of “letting go,” and neurobiologically related to a relaxation response. The “flow phase” is an energy-demanding peak state of consciousness. Finally, the “recovery phase” is a refractory period following the flow state that is characterized by learning, greater psychological complexity, and an increased sense of mastery.

The endocannabinoid system (ECS) is a neuromodulatory biological system implicated in a diverse range of functions including—most notably for the flow experience—stress and attention. In relation to flow states, the ECS has been shown to be the primary agent in the exercise-induced flow state known as runner’s high (Sparling et al., 2003; Dietrich and McDaniel, 2004). It also plays key roles in the two main human stress networks: the hypothalamic pituitary adrenal (HPA) axis and the sympathomedullary (SAM) axis. It is implicated in attentional processes including neurotransmitter and hormone expression alongside network activity such as the default mode network (DMN) and bottom-up processes. This paper argues that all of this evidence demonstrates that the ECS is a major contributor to the neurobiological mechanism underpinning the state of flow. Through this lens, in fact, flow can be conceptualized as an adaptive stress response. Conversely, the evidence implicates a poorly functioning ECS as a major contributor to maladaptive stress responses and, as a result, a blocker of flow.

This paper examines the relationship between the ECS and the flow cycle in order to better align the two bodies of knowledge and propose avenues for new research. It first examines a variety of models
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for flow in order to introduce the flow cycle as a fruitful theoretical framework for joining these bodies of research. Second, it reviews the ECS with a focus on endogenous and exogenous cannabinoids, their receptors and enzymes, and the relevant functions of the system. Third, it revisits the flow cycle in light of the ECS in order to more deeply interrogate its underlying biological processes. The paper concludes with avenues for future inquiry.

2 Models for Flow

Flow has been defined as an optimal state of consciousness characterized by absorption in a task without reflective self-consciousness and, paradoxically, with a deep sense of control (Csikszentmihalyi, 1990). Attempts to understand flow’s neurobiology has implicated a wide number of cognitive neuroscience research domains, stretching from stress and attention to motor learning and affective processing, alongside a variety of domain applications such as athletics, creativity, and leadership (Jackson, 1996; Csikszentmihalyi, 2004, 2013). While many seminal studies on the biological processes underpinning flow have been performed or inferred from related research (Peifer and Tan, 2021), the ECS’s influence on flow has been largely unexplored. This section compares models for conceptualizing flow and proposes a four stage “flow cycle” that places stress and attentional processes at its center. Later sections discuss the role of the ECS in each stage of that cycle.

2.1 Theoretical Models for Flow

According to Csikszentmihalyi’s (Csikszentmihalyi, 1997) pioneering research on flow, the state has nine psychological characteristics. Three of these characteristics were later described as flow triggers, that is proximal conditions or preconditions that appear to produce flow (Csikszentmihalyi et al., 1993). The three proximal conditions are:

1. Challenge-Skill Balance: The activity balances the challenge at hand with the participant’s skill
2. Clear Goals: It is clear what the individual seeks to accomplish during a given task
3. Unambiguous Feedback: The environment provides clear feedback on how the individual is progressing towards their goals

Additionally, the following are the remaining six characteristics of flow (Csikszentmihalyi, 1990):

1. Action-Awareness Merging: One moment blends into the next with no clear divide between the action and the awareness of performing that action
2. High Concentration: The individual is deeply focused on the task at hand
3. Sense of control: There is a sense of personal control or agency over the situation
4. Loss of self-consciousness: There is a loss of reflective self-consciousness
5. Transformation of time: Time either seems to be moving faster or slower than normal
6. Autotelic experience: The experience of the activity is autotelic, containing its own meaning and purpose

The value of differentiating flow’s proximal conditions from its core psychological characteristics allows us to track flow over time. The addition of this temporal dimension improves both model quality and the probability of inciting flow via flow’s triggers, for instance in online environments (Chen et al., 1999).

Among flow’s triggers, the challenge-skill balance has received a disproportionate amount of research attention, both as the most potent measure of flow and the easiest to replicate in lab
environments (Klasen et al., 2012; Ulrich et al., 2014; Yoshida et al., 2014; Harmat et al., 2015; Tozman et al., 2015; Tian et al., 2017). This has resulted in many research protocols viewing flow operationally as synonymous with the challenge-skill balance (Katahira et al., 2018).

Graphically, this balance has been represented as a three quadrant model with challenge on the vertical axis, skills on the horizontal axis and flow as the midpoint between boredom (high skills, low challenge) and anxiety (high challenge, low skills) (Csikszentmihalyi, 1990). Later additions include apathy as a low skills and low challenge fourth quadrant (Ellis et al., 2018), and an eight channel model with additional descriptors for the various affective locations within the two dimensional challenge/skills space (Massimini and Carli, 1988). See Fig. 1 below.

Beyond these challenge-skills based models, flow is generally understood to be a spectrum of experiences ranging from micro to macro flow states that varies with the intensity of flow’s core psychological characteristics and the level of complexity in consciousness (Csikszentmihalyi, 1990). While there is no clear phenomenological distinction between micro and macro flow, macro flow experiences appear to have many similarities to other altered or non-ordinary states of consciousness (Dietrich, 2003). While some work has been done on macro flow experiences (Csikszentmihalyi, 1990, 2000; Keller and Landhäußer, 2012) most experimental protocols appear to focus on micro flow, as quantified by psychometric instruments such as the Flow Short Scale (Jackson and Eklund, 2004), and as seen in their choice of experimental task, the level of skill required by that task, and the level of psychological complexity expected of participants.

Additionally, while the nine characteristics of flow are generally agreed upon, work has also been done on the social and economic factors that influence flow (Csikszentmihalyi et al., 1993). Other work has questioned whether the concept of flow has been overly married to the nine characteristics and thereby excluded factors such as confidence, positive mental state, and goal alignment (Swann et al., 2012; Stamatelopoulou et al., 2018).

Research has also been extended to the implicit and explicit motivational components of flow, and used those components to explore how achievement, power, and affiliative-intimacy motives influence the salience of information and the choice between various possible responses to one’s situation (Schiepe-Tiska and Engeser, 2012). Meanwhile, behaviorist models for flow have focused on stimulus-response and neurobiological dynamics including the role of dopamine (DA) (Marr, 2001) and cortisol (CORT) (Peifer, 2012). Key distinctions between inputs (or the requirements for flow), mediating and moderating attentional and motivational mechanisms, and subjective and objective outputs have also been used to distinguish aspects of flow (Șimleșa et al., 2018).

To summarize, many models have been proposed to conceptualize flow. An ideal model differentiates proximal and core conditions; understands flow as a spectrum from micro to macro flow states; separates before, during, and after the state; includes motivation; emphasizes the role of attention; and illuminates the state’s underlying neurobiology. Many of these requirements for modeling flow will be explored below, through the framework of the flow cycle.

2.2 The Flow Cycle
The flow cycle is conceptualized as a four stage process, with each stage having distinct phenomenological and neurobiological characteristics (Kotler, 2014). While the subjective aspects of the flow experience—the third stage in the flow cycle—are well studied, the state’s neurobiology
leaves many open questions (de Manzano et al., 2013). This section introduces the four stages of the cycle. Later sections deepen this framework through an exploration of the influence of the ECS on main neurotransmitter and hormone systems relevant to flow as well as the structural and functional activity of the central nervous system (CNS) and peripheral nervous system (PNS).

The flow cycle is proposed to have the following phases, each explored in greater detail below. The “struggle phase” is characterized by mental and/or physical excitation and the related stress response—resulting in a state of vigilance (Peifer et al., 2014a, 2014b). The “release phase” is a transitional phase, subjectively experienced as a sense of letting go, neurobiologically related to the relaxation responses, and resulting in a state of preparedness (Stefano et al., 2008). The “flow phase” is characterized by the subjective experience of flow and the complex neurobiological responses implicated in immersion and task mastery (Harris et al., 2017; Peifer and Tan, 2021). Finally, the “recovery phase” is a refractory period subjectively characterized by a new normal—that is, a state of greater psychological complexity combined, physiologically, with a second relaxation and pleasure response that reinforces the beneficial behavior adopted in response to stressful stimuli (Demerouti et al., 2011; Debus et al., 2014).

Similar cycles have been used to conceptualize various processes, especially in the domain of creative experiences and problem solving. Comparable models include:

- Struggle -> release -> breakout/peak experience -> new normal (Benson and Proctor, 2004)
- Preparation -> incubation -> illumination -> verification (Wallas, 2014)
- Immersion -> impasse -> diversion -> insight (Kounios et al., 2015)

This multi-stage approach to flow was chosen to satisfy the stipulations from the previous section. It differentiates proximal and core conditions by connecting them to stages in a cycle (i.e. proximal conditions generally appear in the struggle and release phases while other characteristics appear later in the cycle). It differentiates micro and macro experiences through the intensity experienced at different stages in the cycle, and more clearly situates the flow process in time, a point often poorly characterized in the literature.

Additionally, to fully characterize this cycle, we still need to detail the motivational, attentional, and neurobiological aspects of this process. This first requires exploring the endocannabinoid system in some detail, before connecting those details to the stress and attentional mechanisms engaged during the flow cycle.

3 The Endocannabinoid System

The ECS is a neuromodulatory biological system composed of endocannabinoids (eCBs), their receptors, and their synthesizing and degrading enzymes. Present in both vertebrates and invertebrates, the ECS is phylogenetically ancient, and has been found in animals as primitive as sea-squirts (Elphick and Egertova, 2001; Matias et al., 2005). In humans, the ECS begins to develop in the first embryonic stages and continues to form through the pre and postnatal stages (Fride et al., 2009).

The primary eCBs are arachidonylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG). The main receptor sites are the cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) sites, where CB1 is among the most abundant receptors in the mammalian brain (Munro et al.,
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1993; Egertová et al., 1998). The ECS has been known to play a role in many functions including memory, pain, appetite, immune function, stress, and attention (Zou and Kumar, 2018). The focus of this review will be on the ECS role in stress and attention, which are the most relevant to flow.

3.1 Receptor Sites

The actions of the ECS can largely be accounted for by the CB1 and CB2 receptors as they are the primary mechanism of action for endogenous, exogenous, and synthetic cannabinoids. CB1 receptors exist primarily in the CNS and PNS neurons while CB2 receptors are primarily present in immune cells (Howlett et al., 2002). The ECS is rare in its retrograde signaling wherein postsynaptic neurons release eCBs to modulate their presynaptic inputs (Wilson and Nicoll, 2001). The ECS also elicits a so-called “entourage effect” where its action is modulated by a number of non-psychoactive components not readily localizable to individual components (Ben-Shabat et al., 1998). While other receptors have been discovered and have attracted some research attention—especially vanilloid receptor 1 (TRPV1) and G protein-coupled receptor 55 (GPR55)—other, undiscovered receptors and their agonists could help explain the entourage effect (Estrada and Contreras, 2020). Despite these limitations in understanding of the ECS, CB1 and CB2 receptors are the focus of this review given their central role in the functions of the system.

The CB1 receptor site was originally discovered in 1988 (Devane et al., 1988) and was later cloned in 1990 (Matsuda et al., 1990). It is primarily found on the central and peripheral neurons in the presynapse, however CB1 receptors have also been found on glial cells including astrocytes, oligodendrocytes, and microglia (de Almeida and Martins-de-Souza, 2018). CB1 receptors have also been found in brain and muscle mitochondria where they regulate cellular respiration and energy production (Reece and Hulse, 2019; Salehzadeh Niksirat et al., 2019). CB1 receptors are also present in some peripheral organs such as the heart, liver, and testes.

CB1 receptors are among the most common G-protein-coupled receptors in the brain and are expressed most highly in the CNS in regions associated with higher cognitive functions and movement. Brain tissues particularly dominant in CB1 receptors include the cerebral cortex (particularly frontal regions), hippocampus, basal ganglia (particularly the substantia nigra and globus pallidus), cerebellum, hypothalamus, and anterior cingulate cortex (ACC). While CB1 receptor localization studies reveal similarities across species, humans express a greater concentration of CB1 receptors in the amygdala and cingulate cortex. Interestingly, few receptors are found in the human brainstem controlling cardiovascular and respiratory functions, explaining why overdoses with exogenous cannabinoids are generally not seen (Herkenham et al., 1990; Howlett et al., 2002; Burns et al., 2007). In fact, agonization of CB1 by (-)-delta-9-trans-tetrahydrocannabinol (Δ⁹-THC) usually just referred as THC has been shown to increase pregnenolone, a negative allosteric CB1 modulator, by up to 3000% in rats, demonstrating a feedback system for protecting against overactivation (Vallée et al., 2014).

CB1 receptors elicit complex effects on neurotransmission [see for review (Howlett et al., 2002)]. eCBs (especially 2-AG) act as fast retrograde synaptic messengers to regulate neurotransmission (Wilson and Nicoll, 2001). The most commonly cited mechanism of CB1 neurotransmission is the inhibition of the brain’s most abundant excitatory neurotransmitter glutamate, alongside its primary inhibitory neurotransmitter γ-aminobutyric acid (GABA). Acetylcholine (ACh), DA, norepinephrine (NE)/epinephrine, serotonin (5-HT), and opioids have also been shown to be at least indirectly modulated by presynaptic CB1 receptors (Howlett et al., 2002; Kurrasch-Orbaugh et al., 2003; Kano
et al., 2009; Akirav, 2011). For instance, DA release in the nucleus accumbens (NAc) is elevated by eCB agonists, likely caused by the inhibition of GABA release (Gardner, 2005)—a detail that will become important in later sections on the flow cycle.

Beyond its role in the CNS, CB1 receptors are also distributed through parts of the PNS. While it is clear that the ECS plays a major role in peripheral functionality (Maccarrone et al., 2015), less is known about PNS activity when compared to its role in the CNS. Fewer cross-species similarities are seen in the PNS than CNS. CB1 receptors have been found in lower concentrations than in the CNS in adrenal, heart, lung, prostate, and other tissues (Galiègue et al., 1995). The CB1 receptor has been implicated in a variety of nociceptive, analgesic, digestive, cardiovascular, and metabolic functions (Clapper et al., 2010; Maccarrone et al., 2015).

In the autonomic nervous system (ANS), CB1 is most prominently expressed on postganglionic sympathetic nerve terminals reducing sympathetic tone and inhibiting the release of NE (Ishac et al., 1996). CB1 receptors in these cells affect processes such as bone formation and stress (Tam et al., 2008). The ECS is known to play a role in crosstalk between the CNS and PNS including regulating behavior and metabolism (Quarta et al., 2010; Lutz et al., 2015). Additional associations between the ECS and autonomic activity are more correlatory in nature such as the ECS and autonomic activity being implicated in both fear extinction and vagal tone (Schmid et al., 2010). It is believed that the vagus nerve is at least in part responsible for the ECS influence on appetite (Woods, 2007; DiPatrizio, 2016).

CB1 and CB2 receptors show high amino acid similarity (Cabral and Griffin-Thomas, 2009). The CB2 receptor site was originally cloned in 1993 (Munro et al., 1993). CB2 is predominantly found in immune cells. However, they have also been found in lower concentrations than CB1 cells in the CNS microglial cells, and possibly only in response to injury (Núñez et al., 2004; van Sickle et al., 2005; Onaivi et al., 2008). While CB1 receptor agonists are associated with psychoactive effects, CB2 agonists are non-psychoactive, making them a strong candidate for novel drug development. It has been proposed that the function of CB2 receptors is a general protective system aimed at non-protein attacks (Pacher and Mechoulam, 2011).

In summary, action on the CB1 and CB2 receptor sites encompass the primary (though not the full) mechanism of the ECS. This action is neuromodulatory in nature affecting a wide variety of processes primarily through direct modulation of glutamate and GABA receptors and, at minimum, the indirect modulation of other neurotransmitter pathways such as DA, NE, and 5-HT. As explored below, these points make the ECS a strong candidate in understanding the biology of flow experience.

3.2 Cannabinoids

There are three classes of cannabinoids: eCBs that naturally occur in animals, exogenous phytocannabinoids found in plants like cannabis, and synthetic analogs of phytocannabinoids. The focus of this review is on the eCB lipids AEA and 2-AG that together comprise the primary and most studied action of the ECS. Enzymes and exogenous cannabinoids are also discussed. This review of the ECS will focus on components of the system most relevant to flow, with deeper examination of the selected functions of the stress, relaxation, and attentional processes that underpin the state.

3.2.1 Endocannabinoids
2-AG is a full agonist of both CB1 and CB2 receptors. The connection between 2-AG and its affinity for cannabinoid receptors was discovered in 1995 (Mechoulam et al., 1995; Sugiura et al., 1995). It is the primary eCB in brain tissue with its expression approximately 170 times more abundant than AEA (Stella et al., 1997). It is believed that 2-AG mediates plasticity and homeostasis by functioning as a fast, phasic signaling molecule triggered by neuronal depolarization (Katona and Freund, 2012). While broadly expressed, its specific action is highly localized.

In contrast to 2-AG’s action as a full agonist, AEA is a partial agonist on both CB1 and CB2 receptors, as well as a full agonist on TRPV1 (Smart et al., 2000; Ross et al., 2001; di Marzo et al., 2002). AEA was discovered in 1992 and named after the Sanskrit term for bliss or extreme joy (Devane et al., 1992). AEA is activated with physiological stress (Hill et al., 2010), and is believed to regulate tonic basal synaptic transmission, making it the slower analogue to 2-AG’s phasic signaling (Katona and Freund, 2012). CB1 agonists have known biphasic effects where lower doses can have inverse effects when compared with higher doses such as anxiolytic effects at low doses but anxiogenic effects at higher doses (Sulcova et al., 1998).

The main function of AEA and 2-AG is neuromodulatory in nature. Each of these compounds reduces the release of both inhibitory and excitatory neurotransmitters, particularly GABA and glutamate. Both compounds are synthesized on demand when and where they are needed, and—unlike most other neurotransmitters—act primarily on the presynapse. This retrograde signaling allows a mechanism for postsynaptic neurons to communicate backwards to modulate their inputs (Wilson and Nicoll, 2001). As we will see below, this neuromodulation contributes to each phase of the flow cycle.

3.2.2 Enzymes
The primary synthesizing and degrading enzymes for both 2-AG and AEA could account for individual differences in flow experience and pose novel drug discovery candidates for treatments of post-traumatic stress disorder (PTSD), depression, nausea, and epilepsy. 2-AG is synthesized from diacylglycerol (DAG) and is moderated by diacylglycerol lipase (DAGL) isotopes (Katona et al., 2006). 2-AG is degraded primarily by monoacylglycerol lipase (MAGL) (Dinh et al., 2004; Blankman et al., 2007). AEA is primarily synthesized from N-acyltransferase (NAT) and N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) (di Marzo et al., 1994; Jin et al., 2007). AEA is degraded by fatty acid amylase hydrolase (FAAH), which is ubiquitously expressed throughout the brain (Tsou et al., 1998).

3.2.3 Exogenous Cannabinoids
Given that much of the ECS literature focuses on exogenous cannabinoids, this section reviews those compounds that illuminate functions of the system relevant to flow. Over five hundred different compounds have been identified in the cannabis plant including over a hundred different cannabinoids (Pertwee, 2014). THC was first isolated in 1964 and is essentially the only psychoactive component of the cannabis plant (Gaoni and Mechoulam, 1964). To date a total of 104 phytocannabinoids have been isolated and divided into 11 classes such as Δ⁹-THC, cannabidiol (CBD), and cannabigerol (CBG) (Pertwee, 2014). Terpenes and flavonoids also mediate the effects of cannabinoids, though they are out of the scope of this review.

Δ⁹-THC is a partial agonist for both CB1 and CB2 receptors (Pertwee, 1997, 2008) and targets a wide variety of other receptors and ion channels (Cascio and Pertwee, 2014). The effects of THC vary...
widely from euphoria to anxiety, and affect emotional regulation, learning, memory, reward, appetite, pain, and other processes [see for review (Parker, 2008)]. The effects of $\Delta^9$-THC on anxiety are biphasic: low doses of the compound are anxiolytic while higher doses are anxiogenic [see for review (Akirav, 2011; Raymundi et al., 2020)]. Genetic deletion of CB1 receptors result in anxiogenic and depressive phenotypes in mice (Viveros et al., 2005).

CBD is the primary non-psychoactive cannabinoid in cannabis accounting for the majority of its extract and was first isolated in 1941 (Adams, 1942). CBD has antianxiety, antipsychotic, anticonvulsive, antinausea, and antiinflammatory properties [see for review of therapeutic targets (107)]. It also has neuroprotective qualities and has been shown to improve the adverse attentional, learning, and memory effects of THC (Solowij et al., 2018). Other cannabis compounds such as CBN also display similar neuroprotective potential, for example, in the treatment of amyotrophic lateral sclerosis (Weydt et al., 2005).

While many effects of CBD are well understood, its mechanism for action has not been fully clarified. CBD has a low affinity and partially antagonistic effect on CB1 and CB2 receptors (Pertwee, 2008). There is evidence pointing to its inhibition of AEA reuptake through fatty acid-binding proteins that transport AEA to FAAH for hydrolysis (Leweke et al., 2012; Elmes et al., 2015). CBD also inhibits FAAH (Bisogno et al., 2001; Petrocellis et al., 2011). AEA is a full, weak agonist on the vanilloid receptor TRPV1 (also known as the capsaicin receptor) and CBD has been shown to activate TRPV1, and to have similar molecular structure to capsaicin (Bisogno et al., 2001). CBD is also active in various 5-HT pathways including acting as a 5-HT1A receptor agonist (Campos and Guimarães, 2008; Zanelati et al., 2009; Gomes et al., 2010). The action of CBD and the entourage effect could also be explained by yet undiscovered receptor(s) or antioxidant properties (Onaivi et al., 2002; Mecha et al., 2012).

3.3 Selected Functions of the ECS
The function of the ECS is diverse and complex. As one of the primary neuromodulatory systems, it is responsible for general autoregulatory actions throughout the nervous system. The focus of this review is on the selected functions of the ECS most closely related to flow: stress, relaxation, and attention.

3.3.1 Stress
The stress response is mediated by both 2-AG and AEA through actions in the amygdala, hypothalamus and prefrontal cortex (PFC), where 2-AG modulates the tonic stress response and AEA the basal response. The ECS has been proposed to prevent cell damage and death due to stress-related excitotoxicity and neuroinflammation (Wang et al., 2012). A poor functioning ECS is implicated in PTSD, anxiety, depression, and schizophrenia [see for review (Parolaro et al., 2010; Akirav, 2011; Chadwick et al., 2020)]. Chronic stress can reduce the number of CB1 receptors (Hillard, 2014). The ECS modulates fear conditioning, helping decondition responses to fear-inducing stimuli. There are two primary stress response pathways, which LeDoux (Ledoux, 1988) refers to as the “low road” and “high road”. The low road involves both a fast response through the amygdala on the order of tens to hundreds of milliseconds (the SAM axis) as well as the slower, hormonal HPA axis response on the order of minutes. The high road also starts in the amygdala and continues through the medial prefrontal cortex (MPFC), though it produces responses that are several milliseconds longer than the SAM axis. There are five total distinct fear response pathways that characterize these high and low
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roads (Silverstein and Ingvar, 2015). Together, these pathways work in concert to produce a state of preparedness, with the ECS playing a central role in each.

Low road activation of the HPA axis begins with information received from the senses through the thalamus and amygdala, particularly the basal lateral amygdala (BLA). Upon the detection of a threat to homeostasis, the paraventricular nucleus (PVN) of the hypothalamus secretes corticotropin-releasing hormone (CRH). This is the main control mechanism of the HPA axis. When CRH binds to receptors in the anterior pituitary gland, it releases adrenocorticotropic hormone (ACTH)—though CRH is not the only possible precursor for ACTH release. ACTH is also released into the general circulatory system and binds to receptors on the adrenal cortex resulting in the release of glucocorticoids such as CORT, a primary human stress hormone. Glucocorticoids negatively regulate the release of CRH and ACTH, and serve as one potential termination of the HPA axis stress response via a classic feedback mechanism (Hauger and Dautzenberg, 2000; Tsigos and Chrousos, 2002).

In relation to the stress response, CB1 receptors are located in the BLA, PVN (Herkenham et al., 1991), pituitary corticotropic cells (Pagotto et al., 2006), NAc, and in the adrenal glands (Galiègue et al., 1995). Stress causes a decrease in AEA in the BLA and an increase in 2-AG that together results in the suppression of inhibitory inputs to principal neurons (Campolongo et al., 2009; Di et al., 2016). There are temporal considerations as well. Restraint stress decreases AEA immediately and it returns to control level within 30 minutes, allowing for a temporary increase in HPA axis activity. PVN 2-AG immediately increases in response to restraint stress and remains elevated for longer than AEA (Wang et al., 2012). Finally, AEA inhibits glutamatergic inputs to principal neurons, resulting in the suppression of CRH secreting neurons and therefore the habituation response. In the PVN, stress stimulates the synthesis of AEA and 2-AG which suppresses excitatory glutamate inputs to CRH neurons in this region. In the PFC, glucocorticoids increase 2-AG to alter GABA tone thereby allowing the termination of the HPA axis (Lee and Gorzalka, 2015). For a complete review see Morena et al., 2015.

The low road SAM pathway also begins with the thalamus, amygdala, hypothalamus, and NAc. The hypothalamus activates autonomic nerves and promotes epinephrine and NE release. These two pathways are linked, as stimulation of the HPA axis increases autonomic, SAM axis activity through the reduction of parasympathetic vagal tone. However, the HPA axis does not increase sympathetic tone as sympathetic activity does not affect HPA axis expression (Agorastos et al., 2019). When sympathetic projections release NE, the ECS helps inhibit its release through CB1 receptors from postganglionic sympathetic neurons that decrease both sympathetic tone and blood pressure (Niederhoffer and Szabo, 1999; Niederhoffer et al., 2003; Di et al., 2016).

The high road pathway connects the thalamus to the PFC through the hippocampus and ACC, a structure where affective and cognitive information converge (Bush et al., 2000; Paus, 2001). CRH from the amygdala and PVN also targets the locus coeruleus (LC), the sole source of NE in the mammalian forebrain, which innervates many regions including the MPFC (Wyrofsky et al., 2019). CB1 receptors have been found in the LC including on both the glutamatergic and GABAergic presynaptic axon terminals involved in NE signaling (Scavone et al., 2010). CB1 mediation of NE firing in this region is biphasic, wherein too much or too little activity increases firing. These biphasic effects provide a central mechanism for protection against neuronal death by preventing neuronal over-firing. Furthermore, the MPFC and hippocampus are able to inhibit, organize, and
modulate the faster stress response and dampen amygdala output (Likhtik et al., 2005; Hübner et al., 2014; Hartmann et al., 2019). The impact of the ECS on the high road is only partially understood. Conflicting findings have shown differing effects of cannabis on increases and decreases in volume, blood flow, activation, and connectivity in both the ACC and MPFC (Kowal et al., 2013; Bloomfield et al., 2019). CBD has also been shown to modulate DNA methylation in stress and depression-exposed mice, pointing at an additional mechanism through which the ECS moderates stress adaptation (Sales et al., 2019). Finally, CBD has also been shown to modulate synaptogenesis in the PFC resulting in antidepressant-like effects (Sales et al., 2020).

Behavior and perceptual effects are also observed in ECS-mediated stress responses (Estrada and Contreras, 2020). Genetic and pharmacological inhibition of FAAH results in greater AEA and less stress, and is mediated by CB1 receptors (Moreira et al., 2008). Inhibition of ECS signaling increases stress and anxiety, while moderate increases of signaling decrease stress and anxiety, which together account for the biphasic action of the ECS [see for review (Lutz et al., 2015)]. The biphasic response is mediated by action on GABA and glutamate neurotransmission (Rey et al., 2012). TRPV1 is also a candidate for the ECS-mediated stress response (Rubino et al., 2008).

The ECS-modulated fear response affects both short and long-term fear expression and fear extinction. As the fear extinction response is believed to be mediated by associative safety learning, mice knockout studies showed that a process similar to habituation influences fear extinction (Kamprath et al., 2006). This effect has been linked to eCBs in the BLA where eCBs facilitate the extinction of adverse memories through their inhibitory effects on GABA neurons (Marsicano et al., 2002). An additional process for fear extinction has been proposed through an ECS-mediated impairment of fear memory by blocking reconsolidation (Lin et al., 2006).

These findings implicate ECS function as having a central role in both adaptive and maladaptive stress responses. Its role can be traced through the HPA and SAM axis and to the PFC’s inhibition of these processes, pointing toward the ECS playing a central role in the adaptive response to stress that is experienced in flow.

3.3.2 Relaxation
The relaxation response was first proposed as an opposing force to the stress response (Benson et al., 1974; Benson and Klipper, 1976). Building off of the work of Walter Hess, who termed the phenomena the “trophotropic response” (Hess and Hughes, 1958), Herbert Benson and colleagues extended this research through the study of the physiology of the relaxation response in the contexts of meditation, yoga, and prayer (Benson et al., 1974). Benson’s research, which has been reconfirmed elsewhere, found that the gaseous signaling molecule nitric oxide (NO) mediates the relaxation response (Stefano et al., 2001). The NO response is, in turn, coupled to ECS expression as both AEA and 2-AG stimulate NO release (Fimiani et al., 1999a).

NO has been implicated as a primary actor in the relaxation response, responsible for reduced heart rate, vasodilation, decrease of brain activity, decreased metabolism, analgesia, reduced blood pressure, and reduced breathing rate (Wallace et al., 1971; Stefano et al., 2001). NO is created through the process of nitric oxide synthase (NOS) and has three isoforms. Neuronal NOS (nNOS) is primarily found in high concentrations in neuronal tissues. Inducible NOS (iNOS) is primarily found in macrophages. Endothelial NOS (eNOS) is only found in endothelial tissues. Collectively, nNOS and eNOS are referred to as constitutive NOS (cNOS), which is regulated by the ECS.
cNOS is found in many regions in both the CNS and PNS (Stefano et al., 2006). Similar to eCBs, NO acts as a retrograde signaling molecule (O’Dell et al., 1991; Stefano et al., 2003). NO is a fast-acting molecule with a short half-life of approximately 200 milliseconds in brain cells (Laranjinha et al., 2012), 0.05 to 1.8 milliseconds in blood (Borland, 1991; Liu et al., 1998), and between 0.5 and 5 seconds in living tissue (Wood and Garthwaite, 1994; Bryan and Grisham, 2007). It is highly diffusible and can elicit effects relatively far from its site of production (Davis et al., 2001). There is some contention around whether a nitroxidergic nerve close to the adrenergic sympathetic nerve bundle releases NO (Stefano et al., 2001) or if NO acts as a local, non-synaptic, and diffusion-controlled signaling molecule (Freudenberg et al., 2015).

ECS expression is primarily tied to cNOS-derived NO release (Lipina and Hundal, 2017). In humans, AEA can cause NO release from immune cells, neural tissues, and vascular endothelial cells (Stefano et al., 1996, 1997, 1998, 2000; Deutsch et al., 1997; Fimiani et al., 1999b; Carney et al., 2009). In vitro assessment shows that AEA inhibits NE release in renal sympathetic nerves, while stimulating NO release in renal endothelial cells (Deutsch et al., 1997). CB1 receptors also coexist on, at least, a third of nNOS-expressing neurons (Azad et al., 2001; Fusco et al., 2004). In short, the ECS regulates much of the NO-mediated relaxation response.

In addition to the ECS-mediated stress modulation pathways explored in the previous section, the modulation of stress is also related to an ECS-mediated NO process. Sympathetic activation causes NE release from sympathetic nerves and an AEA-mediated NO response downregulates this activation. This initial signal of activation (i.e. an anticipatory stress response) appears to have a screening function resulting in the scanning of the environment for possible threats before either relaxation or focused attention can occur (Stefano et al., 2003; Bouret and Sara, 2005). As explored in greater detail below, this paper hypothesizes that it is this NO-mediated downregulation of the stress response that governs the onset of flow.

3.3.3 Attention
The ECS has a known role in attentional processes. While many of the relevant studies have been performed on cannabis users (Martín-Santos et al., 2009), the effects of cannabis use on brain function are contentious and there are numerous problems with experimental designs. One notable challenge is that exogenous cannabinoids only partially replicate endogenous processes. Despite these issues, ECS modulation through cannabis has been shown to have direct effects on bottom-up attentional processes, DMN activation, and various other aspects of cognition.

On cognitive tasks, chronic high-THC cannabis users show less reliance on top-down attentional control than non-users and do not show overall performance deficits (Nusbaum et al., 2017). Another fMRI study of chronic cannabis users found greater functional connectivity between the PFC and the occipito-parietal cortex, showing the compensatory role top-down attentional networks play when tasked with exerting greater cognitive control (Harding et al., 2012). Cannabis also impacts binocular depth inversion, a visual phenomena associated with bottom-up processing. Cannabis affects the direction and switching of attention, an effect highly correlated to frequency and length of cannabis use (Leweke et al., 2000). Additional findings on ADHD determined that ADHD is causal of lifetime cannabis use (Soler Artigas et al., 2020) and that attention deficit may be more closely associated with cannabis use than ADHD symptomatology (Wallace et al., 2019).
Attention appears to be influenced not only by the activation of attentional structures but also by inhibition of DMN activity. THC has been associated with reduced deactivation in the DMN, including key structures such as the posterior cingulate cortex and angular gyrus (Bossong et al., 2013). CBD and THC have also been shown to have inverse effects on the functional connectivity of the PFC, striatum, and hippocampus—the principle structures of the salience network involved in orienting attention towards meaningful or important stimuli (Bhattacharyya et al., 2014).

Monitoring circulating levels of plasma AEA and 2-AG in humans during attention tasks revealed a negative correlation between 2-AG and cognitive flexibility performance, a positive correlation between AEA and cognitive flexibility and decision making performance, and no significant correlation between either 2-AG or AEA and an inhibition response (Fagundo et al., 2013). Acute reductions in selective attention quantified using visual tasks while recording event-related potentials showed a decrease in performance and P300 amplitude with THC exposure (Böcker et al., 2010). THC also has known effects on time overestimation and underproduction, although chronic users do not show these effects. This has been hypothesized to be caused by ECS-modulated DA activity (Kitamura and Kumar, 1983; Murillo-Rodriguez et al., 2014), and could help explain time dilation experienced in flow.

In summary, ECS-related changes to attentional processing have been established. DMN and salience network activity as well as cognitive flexibility, task performance, and time dilation are all influenced by the ECS. Cannabis users are more dependent on bottom-up processes. These attentional changes are closely related to those experienced in flow, as will be explored below.

4 The ECS Role in Flow Experience

The role of the ECS in flow has largely been explored in relation to the exercise-induced flow state known as “runner’s high.” However, this paper hypothesizes that the ECS plays a critical role in stress experienced as a precursor to flow, the reduction of stress before transitioning into flow, various attentional processes experienced throughout the flow cycle, and recovery from the state. This section further explores the biology of the flow cycle and integrates the central role of the ECS in this process.

4.1 The Struggle Phase

Struggle is a phase characterized by physiological arousal with the related stress response resulting in a state of vigilance. Struggle correlates to flow most notably in pre-performance anxiety and the related concept of psychic entropy. Much of the literature on the challenge/skills balance emphasizes the anxiety that is experienced with too much challenge, however this experience of struggle is not often conceptualized as a necessary precursor to flow. This paper hypothesizes that pre-performance anxiety—that is, an increase in psychic entropy experienced before performance situations—is a necessary precursor to flow.

Csikszentmihalyi (Csikszentmihalyi, 1990) hypothesized that the opposite of flow is “psychic entropy,” or a state of disorder in consciousness as new information is evaluated relative to current goals. Flow, therefore, entails a heightened congruence between goals and incoming information that frees up “psychic energy,” which Csikszentmihalyi defines as synonymous with attention (Csikszentmihalyi, 1990). Other work, especially with professional athletes, emphasizes pre-performance anxiety as having a significant impact on flow (Jackson and Csikszentmihalyi, 1999; Swann et al., 2012). This paper hypothesizes that pre-performance anxiety—that is, an increase in psychic entropy experienced before performance situations—is a necessary precursor to flow.
Stated otherwise, increased challenge and other psychosocial pressures produce an entropy loading phase, before psychic energy can be freed through goal alignment and various other flow precursors. This psychic energy can then be made use of in flow.

This phenomenon has been termed the “anticipatory stress response,” wherein a stress signal precedes the relaxation response, possibly increasing vigilance and environmental scanning before relaxation is deemed safe (Stefano et al., 2008). Anticipatory stress in response to an increase in psychic entropy is likely a necessary aspect of all flow experiences, though it is more clearly connected to achievement situations. This could also account for why high perceived risk activities such as action sports (Allison et al., 2012; Hardie-Bick and Bonner, 2016), illegal activities such as graffiti (Rheinberg and Manig, 2006), and public speaking (Bassett et al., 1987) are associated with high flow. Finally, this anticipatory response can be assessed by an increase in plasma NE levels and increased sympathetic nervous system activity (Hoffman et al., 1982).

The flow experience has been linked to valence and arousal, autonomic activation, and HPA axis activity. In the two-dimensional affective space of valence (degree of pleasantness) and arousal (activation level) proposed by Lang (Lang, 1995), flow is hypothesized to represent a high valence and high arousal state. This has been confirmed in multiple psychophysiology studies (de Manzano et al., 2010; Nacke and Lindley, 2010) linking arousal and sympathetic activation. Additional research has established an inverted U-shape relationship between flow and both sympathetic arousal and HPA axis activity, with one study also showing a linear and positive relationship between flow and parasympathetic expression, suggesting that the co-activation of both ANS branches characterizes the flow experience (Peifer et al., 2014b). Salivary CORT has also been positively correlated to flow (Keller et al., 2011; Peifer et al., 2014b; Tozman et al., 2016), while high exogenous CORT has been shown to block flow (Peifer et al., 2014a). All of this implies that the ECS modulates the overactivation of stress pathways.

While CORT has been the primary hormone examined in relationship to flow, additional research suggests that other arousal hormones and neurotransmitters are active in the struggle phase, including DA, NE, ACh, and dehydroepiandrosterone (DHEA). PET imaging has revealed that DA D2 receptor availability in the dorsal striatum is correlated with flow proneness (de Manzano et al., 2013), which has also been correlated to gray matter volume in the DA system (Salehzadeh Niksirat et al., 2019). CB1 receptors have been shown to co-express with both DA and 5-HT (Hermann et al., 2002). As explored above, NE and ACh are also involved. Finally, research shows that part of the difference between a fight-or-flight and a challenge response can be attributed to the ratio between CORT and DHEA (Morgan et al., 2004; Cicchetti and Rogosch, 2009; Wemm et al., 2010). Evidence suggests that DHEA is itself an eCB with affinity to CB1 and CB2 receptors that is also degraded by FAAH (Brown et al., 2010).

In summary, the struggle phase is essentially a stress response incited by psychic entropy. It is characterized by general arousal and related energy mobilization, as well as activity in both the HPA and SAM axes. One possible new research avenue would entail more thorough analysis of the ratio between CORT and DHEA as a predictor of flow experience. Given the ECS’ fundamental role in these stress responses, it is very likely that flow’s struggle phase is modulated by the ECS.
The flow experience can be conceptualized as a high valence, high arousal state, which allows it to be interpreted in relation to a larger body of psychophysiology research. Elsewhere, cognitive appraisal of a situation has been viewed as the transitional mechanism that moves subjects from the struggle phase into flow (Blascovich and Tomaka, 1996; Tomaka et al., 1997). Yet little work has connected this transition to underlying biological processes. This section explores cognitive appraisal and the ECS and NO-mediated relaxation response as the transitional processes between the struggle phase and the flow state. This release phase is characterized as a shift from sympathetic dominance to the coactivation of the sympathetic and parasympathetic branches of the ANS.

Transcutaneous vagus nerve stimulation, which increases arousal through LC activation and NE release, has been shown to have a causal role in blocking flow (Colzato et al., 2018). This finding supports the hypothesis that while NE plays a crucial role in scanning the environment for the most salient object of attention and for general arousal, flow will not occur without a method for transitioning from vigilance to focused attention. It therefore follows that the struggle phase entails sympathetic dominance and other stress processes, while the release and flow phases counteracts these processes with parasympathetic engagement.

The interaction between the sympathetic and parasympathetic branches of the ANS can be reciprocal, positively related (i.e. co-activation or co-inhibition), or uncoupled (Berntson et al., 1991). ECS expression correlates to these measures as well (Stefano et al., 2003; Zuurman, 2008; Schmid et al., 2010). Flow has generally been correlated to coactivation of the sympathetic and parasympathetic branches of the ANS through cardiac, respiratory, facial muscle, electrodermal, and hormone metrics. Findings also support flow as a high arousal and high valence state. See Table 1 for an overview of these findings in psychophysiological studies of flow.

Studies on the psychophysiology of flow have generally confirmed a positive correlation between flow and both sympathetic and parasympathetic expression, although there have been varied results in regards to the parasympathetic activity. Increases in HR, LF-HRV, RR, CORT, SC, and facial EMG correlate the flow experience with a degree of arousal, sometimes conceptualized as an inverted-U (rather than a linear) relationship (de Manzano et al., 2010; Nacke and Lindley, 2010; Mauri et al., 2011; Peifer et al., 2014b; Tozman et al., 2015; Bian et al., 2016; Tian et al., 2017; Knierim et al., 2018). Additional studies have linked flow to parasympathetic expression using HF-HRV, RD, and LF/HF ratio (de Manzano et al., 2010; Peifer et al., 2014b; Harmat et al., 2015; Tozman et al., 2015; Bian et al., 2016; Tian et al., 2017; Knierim et al., 2018; Chin and Kales, 2019) while others still have found no correlation (Kivikangas, 2006). These differences could be caused by variance in experimental protocols and lack of specificity in some of the metrics used. One study found that parasympathetic expression is a predictor of flow only in higher arousal and challenge conditions, while lower arousal situations showed no correlation (Tozman et al., 2015). Another study found that flow and executive function were both maximized with approximately 90% sympathetic dominance (Chin and Kales, 2019).

One well-regarded way to view the relationship between flow and stress is the “transactional stress model,” which claims that stress results from the transactions between a person and their environment and postulates a process of cognitive appraisal wherein a given situation is evaluated in relation to one’s goals and whether it represents a threat, loss, or challenge (Lazarus et al., 1980). In this model, the difference between boredom, flow, or an overloaded state is a function of the environment and a person’s assessment of whether they have necessary skills, energy, social support,
and other resources to meet the demand. This cognitive appraisal theory helps balance psychophysiological results with related subjective experience.

An additional dimension of the release phase specific to social flow situations was demonstrated in a study of group singing that correlated decreased ACTH to both flow and oxytocin release (Keeler et al., 2015). In the future, this research could be extended to additional social neuropeptides including endorphins, vasopressin, DA, 5-HT, and testosterone, which have been associated with different dimensions of human sociality (Pearce et al., 2017). Finally, specific neural correlates for group flow have also been explored implicating alternative activation patterns in the regions explored above (Shehata et al., 2021). This represents a social dimension of cognitive appraisal that provides the social support to confirm one’s psychosocial safety to meet the demands of challenging environments.

Finally, cognitive appraisal theory differentiates challenge from threat with each of these states having a distinct yet related physiological activation (Tomaka et al., 1997). Additionally, a number of studies correlate flow to self-efficacy, or one’s belief in their ability to succeed, including experiments where the manipulation of the self-efficacy showed a possible causal relationship with the state (Salanova et al., 2006, 2014; Rodríguez-Sánchez et al., 2014; Peifer et al., 2020). Beyond the aforementioned NO processes, work on mindset and stress has pointed to the ratio of DHEA to CORT as the difference between adaptive and maladaptive beliefs about stress, providing additional nuance to the biology of cognitive appraisal (Crum et al., 2017). DHEA also has an influence on endothelial NO, further implicating it in stress and release effects (Simoncini et al., 2003; Meijerink et al., 2011).

In summary, the transition from the struggle phase into the flow phase entails the transition from sympathetic dominance of the struggle phase to the coactivation of the primary branches of the ANS seen in the release and flow phases. This effect has elsewhere been characterized through cognitive appraisal, reflecting the phenomenology of the state. As explored in previous sections, the stress response is largely regulated by the ECS. Additionally, the relaxation response also implicates the ECS-modulated release of NO. Taken together, the evidence supports the ECS as a major regulator of the transition from a state of struggle into the state of flow.

4.3 The Flow Phase
While much more research needs to be done on the flow phase itself, ECS involvement with the state has been confirmed in the experience of runner’s high. Neuroimaging studies of flow have also illuminated enough of the structure and function of the state to link it with ECS activity. Finally, the DA system in conjunction with bottom-up information processing are additional correlates to flow, and both have strong ECS connections. These along with other research avenues are discussed in this section.

The euphoric state of runner’s high is a flow state experienced during prolonged exercise. Originally, runner’s high was attributed to epinephrine and NE (Howley, 1976). Later, the “endorphin hypothesis” (Morgan, 1985) pointed to the opioid system’s activation for pain management as the likely cause. While endorphins are associated with the euphoria of runner’s high (Boecker et al., 2008), it has been demonstrated that the ECS is largely responsible for the effect (Sparling et al., 2003; Dietrich and McDaniel, 2004). AEA engenders the release of brain-derived neurotrophic factor (BDNF), regulates HPA axis overexpression, and promotes analgesic effects (Heijnen et al., 2016).
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This relationship has been demonstrated in humans, dogs, mice (Fuss et al., 2015), and ferrets (Raichlen et al., 2012). Chemically blocking mu-opioid receptors to block endorphin effects during exercise still resulted in euphoria and ECS activation (Fuss et al., 2015; Crombie et al., 2018; Siebers et al., 2021), while opioid activation has been shown in high intensity interval training but not with lower intensity or endurance exercise (Saanijoki et al., 2017). While these findings don’t rule out the role of the opioid system in flow, they do implicate the ECS in the euphoric effects of exercise, as a main actor in pain management, and influencing exercise-induced neurogenesis through the release of BDNF.

DA has also been demonstrated to be a correlate of flow (Marr, 2001). Flow proneness is correlated with both DA D2 receptor availability (de Manzano et al., 2013) and gray matter volume in the dorsal striatum (Salehzadeh Niksirat et al., 2019). DA and flow has also been associated with the nigrostriatal DA system (Ulrich et al., 2014, 2015) and the right caudate (Salehzadeh Niksirat et al., 2019). DA projections from the dorsal raphe nucleus have been shown to have a causal role in downregulating the MPFC in flow, possibly explaining the sense of selflessness (Ulrich et al., 2016) and implicating serotonergic pathways in flow.

THC has been correlated to increased DA in the striatum and dorsal putamen (Bossong et al., 2008, 2015). CBD’s antipsychotic property is thought to function through the striatal DA D2 receptor blockade, the target of many antipsychotic medications (O’Neill et al., 2020), as well as through glutamate and 5-HT signaling (Pretzsch et al., 2019). AEA inhibits DA transport function, blocking DA reuptake (Oz et al., 2010) and, in rats, increasing DA levels in the NAc shell (Solinas et al., 2006). Cannabis has also been linked to DA transmission through mu1 opioid receptors, though the connection between flow and the opioid system is understudied (Tanda et al., 1997). Finally, crosstalk between the ECS and both the DA and 5-HT systems have been demonstrated through the co-expression of these receptors, though this relationship varies in different brain regions (Hermann et al., 2002).

Beyond these neuromodulatory effects, another influential notion in the biology of flow has been the transient hypofrontality hypothesis, which theorizes that flow states, like other altered states, are characterized by temporary PFC deregulation (Dietrich, 2003). fMRI recordings from jazz musicians helped confirm this idea (Limb and Braun, 2008) although other work has shown mixed results, for instance two fNIRS studies with similar experimental designs found different activation patterns in this region (Yoshida et al., 2014; Ulrich et al., 2015). Yet current research and theories still support the general idea of transient hypofrontality and, more specifically, that flow entails a transition from conscious, top-down processing to more automated, bottom-up processing similar to that seen in cannabis users.

Beyond the downregulation of the PFC, flow has also been correlated to a variety of deeper brain regions, a great many of which are impacted by the ECS system. Many of these effects appear as non-linear, U-shaped relationships where higher activation correlates to flow until a critical threshold is reached, then the relationship inverts. This inverted U-shaped effect has been observed in the thalamus, basal ganglia, and midbrain, while a U-shaped relationship has been seen in the MPFC and amygdala (Ulrich et al., 2014, 2015, 2016). Interestingly, functional connectivity between the ventral MPFC and amygdala is increased through mindfulness-based stress reduction, which also points at the importance of this pathway for emotional regulation and attention (Kral et al., 2018).
Many of the brain structures implicated in transient hypofrontality and required for bottom-up processing are modulated by the ECS, and this is especially true for the basal ganglia (Morera-Herreras et al., 2016) and amygdala, which both have a high density of CB1 receptor sites. This supports the idea that flow requires the activation of lower brain structures involved in automation of behavior through an ECS-mediated process. Another idea in the biology of flow conceptualizes that state as the cognitive synchronization of the attentional and reward networks, both of which are modulated by the ECS (Weber et al., 2009; Zona et al., 2017).

The biological mechanisms beneath the flow phase appear to be the DA system, bottom-up processing, and a variety of brain regions known to either coexpress with CB1 receptors, or to be directly modulated by the ECS system itself. Additionally, runner’s high is largely influenced by ECS expression. This evidence supports the role of the ECS in the flow phase of the flow cycle.

4.4 The Recovery Phase and a New Normal

The final stage of the flow cycle is a recovery phase, an allostatic process by which reward, relaxation, learning, pain management, and physical recovery reinforce beneficial behaviors in response to stress. This results in a “new normal,” a state of increased psychological complexity. The biology of the recovery phase likely varies across activities, where recovery from an exercise-induced flow state has a different profile (e.g. higher opioid system activation) than the recovery that follows a flow state induced by cognitive tasks (cognitive flow), for instance. However, all flow experiences are high energy states that demand a recovery process. While little work has been done on the post-flow recovery phase, this is not true for the recovery requirements of sustained attentional focus and exercise. This section reviews this work with a focus on opioids, endorphins, and NO, along with their connection to the ECS.

The extent to which flow demands significant energy resources has been confirmed by an fMRI study showing a similarity between flow and an attentional overload condition and a dissimilarity between flow and a boredom condition (de Sampaio Barros et al., 2018). Recovery has also been demonstrated to be a predictor of the flow experience, and generally maps to circadian rhythms, which further underscores the idea that recovering from cognitive flow requires replenishing the energy depleted by the state (Demerouti et al., 2011; Debus et al., 2014). Additionally, in athletics, the recovery period has been well-studied, and consistently demonstrates the high energy demands of flow and the necessity of a post-flow recovery period (Swann, 2016).

While there is much more work to be done, the findings on runner’s high explored in the previous section support the ECS role in post-flow euphoria, although this is only one aspect of the recovery process. Elsewhere it has been hypothesized that opioids, NO, 5-HT, and catecholamines could all be activated in the modulation of pain perception, mood, and other post-exercise effects [e.g. (Santos and Galdino, 2018)]. This cascade of different post-exercise neurotransmitters and hormones have complex interaction effects on limbic pleasure and reward pathways such as the coupling of AEA, morphine, and NO (Fimiani et al., 1999b).

The full biological recovery process after a flow experience is not fully known. Yet recovery from exercise and/or cognitively demanding tasks offers some conclusions and it is clear that the ECS is implicated in recovery from both physical and psychological stress. The ECS is likely implicated in recovery from other flow experiences given the ECS role in stress adaptation in energy intensive
states. Additionally, the ECS role in fear extinction and neuroplasticity also offer additional research avenues for this post-flow experience refractory period.

5 Future Research
Based upon the central role of the ECS in all aspects of the flow cycle, a number of new research avenues are possible. Among the most practical research avenues are those that provide tools to improve access to flow by managing the entrance into the state, and recovery from the state. This section summarizes these possibilities in the behavioral and personality domains, and highlights research opportunities primarily in the struggle, release, and recovery phases.

There are many behavioral and personality links between flow and the ECS. Flow proneness has been associated with OCEAN personality traits, most notably a positive correlation between flow and openness to experience (Ullén et al., 2016; Marty-Dugas and Smilek, 2019). Similar findings have also been found among cannabis users (Terracciano et al., 2008; Fridberg et al., 2011; LaFrance and Cuttler, 2017; Petrucci et al., 2020; Schwarzbold et al., 2020). Emotional stability is also correlated to flow proneness and this personality trait has been linked to the CNR1 gene regulating CB1 receptor expression (Juhasz et al., 2009). ECS-linked exploratory and novelty-seeking behavior (Lafenêtre et al., 2009; Häring et al., 2011) could also relate to the desire to seek out flow experiences so the CNR1 gene could be predictive of flow proneness.

The combination of this personality and behavior research, alongside all the other neurophysiological work reviewed in this paper, shows that ECS expression is a prerequisite for flow. This also means that modulation of the ECS poses novel drug targets—most notably FAAH—for increasing the probability of experiencing flow. The ratio of CORT and DHEA could also be a major predictor of flow experience, and exogenous modulation of the eCB DHEA could influence experience of the state. Additionally, little is currently known about the relationship between flow and the opioid system, especially in the recovery phase of the cycle, and this demands further scrutiny. The influence of 5HT and parasympathetic engagement are also understudied in post-flow recovery. The ECS has a major role in fear extinction, neuroplasticity, and motivation that could illuminate post-flow learning, long-term stress adaptation, and reward-seeking behavior (Zona et al., 2017). Finally, aspects of the shared biological mechanism of mindfulness and flow are clear such as in MPFC activation, however these two domains are poorly delineated, as are their clinical relevance and the role of the ECS in this pathway.

6 Discussion
This paper explored the relationship between the endocannabinoid system and the state of flow. In humans, the ECS is a primary neuromodulatory system and plays a central role in functions ranging from inflammation and memory to affective processes and appetite. The focus of this review has been on the ECS’s role in flow-relevant attentional and stress processes as well as the relaxation response. Flow was further conceptualized as an adaptive stress response. Then a temporal dimension was added to flow modeling, and the four stage flow cycle was introduced. Finally, the ECS’s crucial role in all four phases of the flow cycle—struggle, release, flow, recovery—was explored, alongside new avenues for research.

In total, these findings support the hypothesis that the ECS plays an important role in flow, that a well-functioning ECS is a vital prerequisite for flow, and a poorly-functioning ECS can limit flow
experience. In other words, the ECS modulates entrance into flow through well-characterized stress and relaxation pathways, is responsible for some of the state’s key psychological characteristics, and aids in the recovery from this energy-intensive experience.

7 Conflict of Interest

Conor Murphy is employed by Flow Research Collective and owns shares in Ojai Energetics. Steven Kotler is employed by Flow Research Collective and owns shares in Ojai Energetics. Will Kleidon is the founder of Ojai Energetics. Michael Mannino is employed by Flow Research Collective. Taylor Kuhn has no conflict of interest. Rian Doris is employed by Flow Research Collective. Adolfo Caballero is employed by Flow Research Collective.

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Methodology: CBM, SK, WK
Investigation: CBM, ADC
Visualization:
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12 Figure Captions

**Fig. 1. Flow Channel Model (A) and Experience Fluctuation Model (B).** These are dominant alternative models to the flow cycle. Adapted Flow Channel Model (Csikszentmihalyi, 2000). Adapted Experience Fluctuation Model (Fave et al., 2003).

13 Tables

**Table 1. Correlations between flow and autonomic arousal.** HRV: heart rate variability; LF-HRV: low frequency band of HRV corresponding to sympathetic activity; HF-HRV: high frequency band of HRV corresponding to parasympathetic activity; LF/HF: ratio of low frequency to high frequency HRV; HR: heart rate; RSA: respiratory sinus arrhythmia, or the synchronicity of HR and respiration; RR: respiratory rate; RD: respiratory depth; SC: skin conductance, CS: the corrugator supercilii muscle or “frown muscle;” ZM: the zygomaticus major muscle or the “smile muscle”; and OO: the orbicularis oculi muscle or the “blinking muscle”.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cardiac</th>
<th>Respiratory</th>
<th>Facial EMG</th>
<th>Electrodermal</th>
<th>Glucocorticoids</th>
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<thead>
<tr>
<th>Study</th>
<th>Effect and Correlation</th>
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<tr>
<td>(Kivikanga, 2006)</td>
<td>Decrease of CS</td>
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<td>No correlation to ZM or OO</td>
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<td>(Nacke and Lindley, 2010)</td>
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<td>(Peifer et al., 2010)</td>
<td>Increase in CORT</td>
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<td>(Peifer et al., 2011)</td>
<td>Inverted U-shape in CORT</td>
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<tr>
<td>(Keller et al., 2011)</td>
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<td>(Mauri et al., 2011)</td>
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<td>(Peifer et al., 2014b)</td>
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<td>(Tozman et al., 2015)</td>
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<td>(Bian et al., 2016)</td>
<td>Increase in HR</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
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<td>Decrease in IBI</td>
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<td>Inverted U-shape in HRV, LF-HRV, and HF-HRV</td>
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<td>Inverted U-shape in HRV and no correlation to LF-HRV</td>
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<td>(Chin and Kales, 2019)</td>
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