HHS Public Access

Author manuscript

Curr Opin Pulm Med. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Curr Opin Pulm Med. 2023 November 01; 29(6): 603–609. doi:10.1097/MCP.0000000000001014.

Neuropsychiatric adverse effects from CFTR modulators deserve a serious research effort

Michael B. VanElzakker[*,1], **Emma M. Tillman**[*,2], **Lael Yonker**[1], **Eva-Maria Ratai**[1], **Anna M. Georgiopoulos**[**,1]

[1]Massachusetts General Hospital

[2]Indiana University School of Medicine

Abstract

Purpose of review—This review highlights the problem of neuropsychiatric adverse events (AEs) associated with elexacaftor/tezacaftor/ivacaftor (ETI), current suboptimal mitigation approaches, a novel testable mechanistic hypothesis, and potential solutions requiring further research.

Recent findings—Studies show that a minority of PwCF initiating CFTR modulators experience neuropsychiatric AEs including worsening mood, cognition, anxiety, sleep, and suicidality. The GABA-A receptor is a ligand-gated chloride channel, and magnetic resonance spectroscopy neuroimaging studies have shown that reduced GABA expression in rostral anterior cingulate cortex is associated with anxiety and depression. Recent research details the impact of peripheral inflammation and the gut-brain axis on central neuroinflammation. Plasma ETI concentrations and sweat chloride have been evaluated in small studies of neuropsychiatric AEs but not validated to guide dose titration or correlated with pharmacogenomic variants or safety/efficacy.

Summary—Although ETI is well-tolerated by most PwCF, some experience debilitating neuropsychiatric AEs. In some cases, these AEs may be driven by modulation of CFTR and chloride transport within the brain. Understanding biological mechanisms is a critical next step in identifying which PwCF are likely to experience AEs, and in developing evidence-based strategies to mitigate them, while retaining modulator efficacy.

Keywords

cystic fibrosis; CFTR modulator; depression; anxiety; adverse event

INTRODUCTION

In recent years, there has been a revolution in cystic fibrosis (CF) treatment. The drug approach called HEMT (highly effective CF transmembrane conductance regulator [CFTR] modulator therapy), including elexacaftor/tezacaftor/ivacaftor (ETI), has proven

**Corresponding author: Anna M. Georgiopoulos, MD, Department of Psychiatry, Yawkey 6900, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, Phone: 617-724-6300, Fax: 617-726-5567, ageorgiopoulos@mgh.harvard.edu.
*These two authors contributed equally to this work

transformative for many persons with CF (PwCF), improving lung function and respiratory symptoms, CF-associated morbidity and mortality, and multidimensional quality of life.[1–3] ETI does not work mechanistically for up to 10% of PwCF in the US, who have 2 nonsense or other rare *CFTR* gene variants that do not produce CFTR protein.[4] However, ETI is also not a feasible option for some genotype-appropriate PwCF. Despite improvements in physical health, a minority of PwCF initiating CFTR modulators have experienced clinically significant neuropsychiatric adverse effects (AEs), including worsening mood, cognition, anxiety, and sleep, and emergent suicidal thoughts or behavior.[5–11] These symptoms can be so profound that some PwCF make the difficult decision to stop using a medication that would reduce their physical suffering and extend their life. In order to develop management strategies for those experiencing biologically-driven neuropsychiatric AEs related to ETI, uncovering underlying mechanisms is an urgent research priority.

In this perspective piece, we first describe the problem of neuropsychiatric AEs associated with ETI and the current suboptimal mitigation approach. Next, we describe a novel testable hypothesis for these ETI-based neuropsychiatric AEs seen in some PwCF, and briefly describe promising scientific approaches to test this hypothesis. Finally, we offer some potential solutions that could result from future research.

THE SCOPE OF THE PROBLEM

There is substantial evidence that ETI can drive clinically significant neuropsychiatric AEs in a subset of PwCF. Our team at Massachusetts General Hospital (MGH) has proposed a conceptual framework regarding etiology and management strategies.[9,11] We conducted a retrospective study of symptom trajectories in adults who initiated ETI and subsequently had at least 1 visit with the CF psychiatrist (N=31).[11] Of these, 16 PwCF experienced new or worsening neuropsychiatric symptoms that were unexpected and determined to be probably-related to ETI, according to National Cancer Institute guidelines for AE reporting requirements and conservatively considering standard factors such as temporal relationship, response to ETI discontinuation, dose adjustments and rechallenge, and existence of alternative explanation. This represented an 11% incidence of probable neuropsychiatric AEs in the overall cohort of adults taking ETI (N=148) and 52% of the 31 psychiatrically referred adults.[11]

The literature on ETI effects on depression and anxiety in PwCF evidences a general pattern reflecting increased quality of life for a majority, while a minority has new onset or worsened depression and/or anxiety. Piehler et al. prospectively evaluated CF-related quality of life along with depression and anxiety in 70 adults with CF before and after initiation of ETI.[12] At the level of group statistics, this study showed that ETI improved CF-related quality of life, was associated with a very small but statistically significant improvement in median depression scores, and had no effect on median anxiety scores. The authors did not specify the number of PwCF whose depression and anxiety scores increased, but noted that two increased from the moderate to severe range for depression and three increased from the mild to moderate range for anxiety, with uncertain relationship to ETI.[12] A retrospective review of 100 adults with CF also measured CF-related quality of life along with depression and anxiety and found no significant group statistical difference in scores before and after

starting ETI.[13] However, after starting ETI, 22 persons had initiation, increased dose or change in psychiatric medication due to clinical worsening and 23 had new onset of sleep difficulties; two PwCF discontinued ETI due to depression, anxiety, and insomnia.[13] In contrast, four PwCF were able to reduce or discontinue psychiatric medication. Quality of life, depression, and anxiety scores were significantly worse in the group that required any psychiatric medication adjustment versus those who did not.[13] These results support the MGH study conclusion that a sub-group may be particularly susceptible to mental health side effects.[11]

Another study of 78 adults taking ETI used a simple (non-validated) survey about the effects of ETI and the COVID-19 pandemic on mental health. Among those taking ETI, 33 (40%) felt COVID-19 contributed to a worsening of either anxiety, depression, or both, and 7 (9%) felt ETI contributed to worsening in their anxiety, depression, or both.[7] These results highlight the fact that multiple psychosocial factors can impact mental health. However, studies including the above argue for a unique contribution of ETI in approximately 10%.[6,7,11] In 2023, the European Commission added depression as an adverse event with a special warning to the ETI label in the European Union, recommending monitoring for depressed mood, suicidal thoughts and unusual changes in behavior.[14] We propose that the neuropsychiatric AEs that occur in a minority of PwCF deserve to be a research priority.

MECHANISTIC HYPOTHESIS

To identify which PwCF are at elevated risk to experience neuropsychiatric AEs and develop strategies to mitigate them, it is essential to elucidate the complex underlying biological mechanisms that may be at play.

CFTR expression in human brain

ETI acts by increasing production of the *CFTR* gene protein product CFTR and aiding in its functionality at the epithelial surface, where disruption of its ion channel function is thought to be a central mechanism in the failure of mucociliary clearance seen in CF.[15] ETI's mechanism of action centers on supporting the chloride ion channel function of CFTR by targeting the F508del mutation, and by this measure it is very effective. CFTR is classically studied as a chloride (Cl^-) channel, and was once thought to be exclusively expressed by epithelial cells, with disruption of its ion channel function in the lung and the gastrointestinal system of PwCF.[15] However, more recent research has also found widespread CFTR expression in human brain.[16] We hypothesize that neuropsychiatric AEs in some PwCF, perhaps particularly in those with increased baseline inflammation, are driven by modulation of CFTR and chloride transport within the brain.[17–19] This is likely related to the fact that chloride is an important ion for normal inhibitory neurotransmission, which plays a central role in controlling anxiety and depression.

The most important inhibitory neurotransmitter in the brain is GABA (γ-aminobutyric acid), and chloride is so central to its proper function that the GABA-A receptor is commonly categorized as a ligand-gated chloride channel. Upon binding of GABA to its receptor, a synaptic pore opens that allows chloride anions to pass, leading to hyperpolarization or inhibition of the neuron. Just as chloride balance dysfunction is a core mechanism of

CF, proper chloride balance is a core mechanism of normal brain function, particularly regulation of anxiety and depression. For example, the anti-anxiety and anti-depressive actions of benzodiazepines are exerted by binding to the GABA-A receptor and modulating GABA-induced chloride current.[20]

Specific emotion regulation brain circuits and structures are particularly reliant upon GABA – and therefore chloride – function. For example, the rostral anterior cingulate cortex (rACC) is an emotion regulation hub whose function is disrupted in multiple psychiatric conditions, including depression and anxiety (See Figure 1). Neuroimaging studies using magnetic resonance spectroscopy (MRS) have repeatedly shown that reduced GABA concentration in rACC is associated with anxiety and depression symptoms.[21–24] Loss of GABAergic function disinhibits the excitatory neurotransmitter glutamate, which is thought to be a central mechanism of anxiety and depression. Relatedly, inflammation-related activation of glial cells (the resident immune cells of the central nervous system) causes release of proinflammatory and neuroexcitatory mediators, including glutamate. Therefore, loss of GABA function would interact with inflammatory processes, driving neuropsychiatric consequences.

Furthermore, ETI appears to affect 5-HT2 serotonin receptor subtypes.[25] There is high expression of serotonin 2A receptors (5HT-2AR) in the cingulate cortex. This receptor system is intimately related to GABA function both at the neurotransmitter and receptor level.[26,27] While this topic demands further study, given the central role of 5-HT2 receptor subtypes in suicidality[28] there may be a compounding effect of ETI on both GABA and serotonin (5-HT) function in vulnerable individuals.

Peripheral inflammation can affect the brain

Inflammation may be one of the biological vulnerabilities for the development of neuropsychiatric complications of ETI therapy. Peripheral inflammation is itself a risk factor for depression and anxiety.[29] Numerous inflammatory factors are elevated in CF, including IL-1β, TNF-α, IL-6[30–32] and CRP,[33] and even inflammatory cytokine clusters,[34] all of which have been associated with depression, psychosis, and generalized anxiety disorder; increases or decreases in these inflammation-related factors can impact neurocognitive functioning across many disease states.[35,36] These inflammatory factors have their neuropsychiatric effects by activating glia, which is measurable via specialized neuroimaging techniques.[37]

Persistent and dysfunctional inflammation in CF extends beyond cytokine production. Blood neutrophils from PwCF display increased phagocytosis, infection-elicited chemotaxis, and intracellular signaling.[38] Peripheral blood mononuclear cells, including monocytes, display tolerance to LPS,[39] impaired adhesion and trafficking,[40] and overly robust generalized inflammatory responses.[41] In addition to these hyperinflammatory cellular responses, platelets are highly activated to release proinflammatory lipid mediators,[42] all of which can in turn drive inflammation within the subendothelial matrix.[43] While inflammatory response improves in PwCF treated with ETI, restoration of CFTR in immune cells and resolution of inflammatory responses can be variable between individuals and it is possible that shifts in inflammatory signals correlate with neuropsychiatric AEs of ETI.[44,45]

Gut-brain axis in CF

Circulating inflammatory factors are more likely to induce neuroinflammatory consequences if high levels of zonulin, a key regulator of the gut-brain axis,[46] are detected in circulation. Zonulin was initially described as a mediator of gastrointestinal permeability by Fasano et al. and is the precursor for haptaglobin-2 (pre-HP).[47] Zonulin leads to transactivation of EGF receptor via proteinase-activated receptor 2 (PAR2), resulting in loss of tight junctions' competency and increased intestinal permeability.[47–49] Intact tight junctions are critical for regulation of paracellular trafficking and loss of tight junctions have been associated with numerous inflammatory diseases. Beside regulating gut permeability, zonulin has been shown to also regulate the blood brain barrier (BBB)[50] and in a transgenic zonulin mouse model the combined loss of gut and BBB barriers' function led to behavioral changes that were dependent on intestinal microbiota.[51] Gastrointestinal dysbiosis, as seen in celiac disease,[50] inflammatory bowel disease,[52] acute COVID-19,[53] and post-COVID complications,[54] have all been associated with increased zonulin release. While zonulin levels have not been reported in CF, dysbiosis in CF is well established.[55] CFTR−/− murine models display increased evidence of zonulin-mediated intestinal permeability.[56] Importantly, zonulin has been shown to be elevated in numerous mental health conditions,[57] including obsessive-compulsive disorder,[58] bipolar disorder,[59] attention-deficit/hyperactivity disorder,[60] and major depressive disorder.[61,62] Thus, understanding the role of zonulin in CF and in ETI-mediated neuropsychiatric AEs will be highly informative, and variability in peripheral inflammation and dysbiosis in CF could be important regulators of glial activation in the central nervous system.

Activated glia drive neuroexcitation, the opposite of GABA signaling. If ETI disrupts GABA function, this could predispose some individuals to a double-hit of reduced GABA function (less inhibition) from the drug and intensified glutamate signaling (more excitation) from the inflammation. This effect may potentially be exacerbated in individuals with reduced ability to metabolize ETI, including due to genetic variants.

Pharmacogenomic variation

Decreased drug metabolism may be a factor in driving CNS effects of ETI, particularly given that its components appear capable of crossing the blood-brain barrier. Pharmacogenomic variants in *CYP3A4*, *CYP3A5* (primary metabolism), and additionally, *ABCG2*, *SLOC1B1/1B3*, *ABCB1* may have a minor role in ETI plasma concentrations.[63,64] Ivacaftor also inhibits *CYP3A4*.[65,66] Inflammation has also been shown to inhibit CYP3A.[67] PwCF have chronic lung infections associated with chronic inflammation. Inhibition of *CYP3A4* by either drug-drug interaction or inflammation results in decreased *CYP3A4* metabolism and increased plasma ETI concentrations, which could increase risk of AEs. Therefore, dose reduction is recommended when concomitant use of CYP3A4 inhibitors is necessary. Hepatic injury, cataracts, and hypersensitivity reactions were cited in the product labeling as significant AEs, yet it is unclear which or of these are ETI concentration dependent. The relationship between ETI plasma concentrations and neuropsychiatric AEs has yet to be determined. Additionally, degree of CF liver or kidney disease may have an additive impact on metabolism which was not accounted for in ETI metabolism studies in healthy subjects.[66,68,69]

CURRENT APPROACHES TO MANAGEMENT

One current approach to mitigating neuropsychiatric AEs of ETI in PwCF is off-label ETI dose reduction. This is suboptimal because there is minimal data informing the approach to dose reduction, and while dose reduction can help mitigate neuropsychiatric symptoms for some, it comes at the cost of an uncertain risk of short- or long-term reduced effectiveness against CF symptoms. PwCF, family caregivers and CF care teams may thus be reluctant to employ this strategy or differ in opinion about its risk/benefit ratio. Additionally, in some cases neuropsychiatric AEs continue unless ETI is discontinued or psychopharmacologic therapies are employed.[6,11,70]

In a study of 266 adults with CF taking ETI, 19 (7%) reported neuropsychiatric AEs including anxiety, low mood, insomnia, brain fog, and reduced concentration.[6] Of these, 13 attempted ETI dose reduction, of whom all also received psychological intervention and six received antidepressants; all maintained clinical efficacy and sweat chlorides in the normal to borderline range. Ten of 13 had improvement or resolution of neuropsychiatric AEs, with post-dose reduction sweat chlorides in the normal or borderline range; two required discontinuation and one switched back to ivacaftor.[6] The authors hypothesized that neuropsychiatric AEs were attributable to psychiatric vulnerability, differences in elexacaftor metabolism, and increased systemic CFTR expression.[6]

In a case series of ten PwCF with new neuropsychiatric symptoms after ETI initiation, including anxiety, irritability, sleep disturbance and/or mental slowness, one discontinued ETI and resumed ivacaftor therapy. Nine underwent dose reduction, using a standardized protocol with serial sweat chloride measurement.[70] Mean sweat chlorides were similar on the standard dose (33.4 mmol/L) and the reduced dose (34 mmol/L). While six of the nine had complete resolution of symptoms with dose reduction, three had only partial resolution.[70]

Sweat chloride concentrations decrease with ETI treatment, and data show a direct relationship between improved pulmonary function and sweat chloride concentrations,[71] but to our knowledge neither ETI concentrations nor sweat chloride concentrations have been associated with the occurrence of AEs.[72] Additionally, when an AE is associated with ETI, there is not a standard approach to monitoring the balance of safety (avoidance of AEs) and efficacy (pulmonary function, exacerbations, etc.). Plasma concentrations of ETI and sweat chloride concentrations have been evaluated in small studies but are not clinically validated to guide dose titration and are not correlated with safety or efficacy.[73–75]

MECHANISTIC RESEARCH TO IMPROVE UNDERSTANDING OF NEUROPSYCHIATRIC EFFECTS OF ETI

Research to discover measurable markers that correlate with ETI efficacy and AEs is key to AE mitigation. It is important to investigate the impact of pharmacogenes including *ABCG2*, *SLOC1B1/1B3*, *ABCB1*, *CYP3A4*, and *CYP3A5* variants on ETI concentrations in PwCF to determine if these differences in drug metabolism contribute to AEs. If so, pharmacogenomic testing and measurement of ETI concentrations could be incorporated

into routine clinical care to predict risk for AEs and guide protocols for individualized ETI dose adjustment and monitoring. Additional efforts are also needed to define dysbiosis and the inflammatory profiles in individuals who develop complications from ETI, and determine the role of the gut-brain axis.[76]

Measures of drug function and metabolism can be combined with measures of inflammation and central nervous system GABA function. Magnetic resonance spectroscopy (MRS) is a noninvasive neuroimaging technique that uses MRI (magnetic resonance imaging) scanners; it is capable of detecting the concentration of certain chemical metabolites in brain tissue without the use of injections or radiation. Although GABA is only present at millimolar levels in the human brain, its concentration can be measured with tailored MRS sequences, making MRS an effective technique for noninvasively measuring both GABA and neuroinflammation[37,77] and therefore a potentially fruitful technique to test the hypothesis that GABA alterations and inflammation are central to neuropsychiatric side effects in some PwCF taking ETI. MRS studies have repeatedly shown that reduced GABA expression in rACC is associated with anxiety and depression symptoms,[21–24] providing evidence that similar mechanisms may be occurring – and measurable – in PwCF experiencing neuropsychiatric AEs. This line of work may ultimately elucidate factors contributing to the elevated prevalence of psychiatric conditions such as depression, anxiety and attention-deficit hyperactivity disorder in PwCF,[78] predating the availability of CFTR modulators. Further, improved mechanistic understanding will lay the foundation to determine whether psychopharmacologic treatments employing specific mechanisms of action (including novel agents targeting GABA)[79] are preferential for managing various neuropsychiatric AEs related to ETI.[11]

CONCLUSION

Although ETI is well-tolerated by most PwCF, some experience debilitating neuropsychiatric AEs. Understanding biological mechanisms is a critical next step in identifying which PwCF are likely to experience AEs, and in developing evidence-based, efficient strategies to mitigate them, while retaining modulator efficacy.

Acknowledgements:

We thank Alessio Fasano for his comments on this manuscript.

Financial support and sponsorship:

Cystic Fibrosis Foundation (GEORGI23Y3; 004760Y122—Tillman; YONKER20A0-KB); National Heart, Lung, and Blood Institute (5K08HL143183; Yonker); PolyBio Research Foundation (VanElzakker)

Conflicts of interest:

MBV reports grants from the National Institutes of Health; and service on the board of directors of PolyBio Research Foundation. EMT reports grants and travel reimbursement from the Cystic Fibrosis Foundation; grants from the National Institutes of Health; and personal fees from Snow Companies. LY reports grants from the Cystic Fibrosis Foundation and grants from the National Heart, Lung, and Blood Institute. EMR reports personal fees from Columbia University for a talk in 2022; personal fees from Imaging Endpoints; grants and travel reimbursement from the National Institutes of Health; grants from the National Science Foundation; and service on the advisory board of Brain Spec. AMG reports personal fees from the Belgian Cystic Fibrosis Foundation/King Baudouin Foundation; grants, personal fees, and travel reimbursement from Cystic Fibrosis Foundation; grants

from the Dutch Cystic Fibrosis Foundation; travel reimbursement from the European Cystic Fibrosis Society; travel reimbursement from the French Cystic Fibrosis Society; personal fees from the Italian Cystic Fibrosis Research Foundation; grants from the National Heart, Lung, and Blood Institute; personal fees from Saudi Pediatric Pulmonology Association; grants and personal fees from Vertex Pharmaceuticals; and personal fees from Virginia Commonwealth University.

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KEY POINTS

- A minority of PwCF initiating CFTR modulators such as elexacaftor/tezacaftor/ivacaftor (ETI) experience new or worsening mood/anxiety disorders, cognitive impairment, sleep disturbance, or suicidality.
- Chloride balance dysfunction is a core mechanism of both cystic fibrosis and psychiatric disorders including anxiety and depression.
- Multiple biological factors may contribute to ETI-related neuropsychiatric adverse events, including inflammation, gut dysbiosis, and individual differences in drug metabolism impacting plasma ETI concentrations.
- Understanding these biological mechanisms is key to identifying risk for neuropsychiatric adverse events and management strategies that optimize modulator tolerability and efficacy.

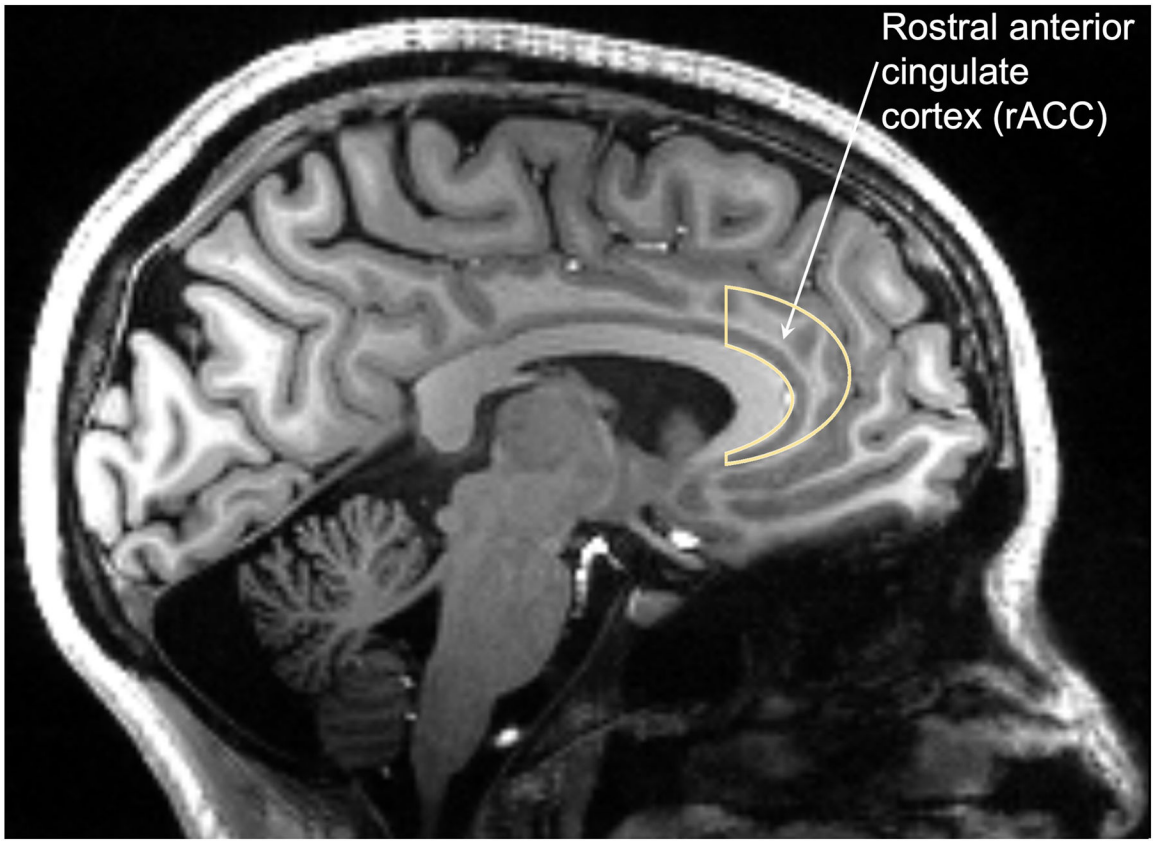

Figure 1.

The rostral anterior cingulate cortex (rACC) is an important structure in emotion regulation neurocircuitry. Several studies have shown that decreased GABA concentration in rACC is associated with neuropsychiatric symptoms such as anxiety and depression. ETI drug therapy may affect GABA function via chloride. Furthermore, rACC is dense with serotonin 2A receptors (5HT-2Ar), which are also involved in emotion regulation and directly modulated by ETI.