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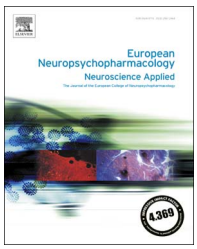

A positron emission tomography study of the serotonergic system in relation to anxiety in depression

Zafer Iscan[a,b,*], Gopalkumar Rakesh[c], Samantha Rossano[d], Jie Yang[e], Mengru Zhang[f], Jeffrey Miller[g], Gregory M. Sullivan[h], Priya Sharma[d], Matthew McClure[d], Maria A. Oquendo[g], J. John Mann[g], Ramin V. Parsey[d,i], Christine DeLorenzo[d,g]

[a]*Centre for Cognition and Decision Making, National Research University, Higher School of Economics, Russian Federation*
[b]*Cognitive Neuroimaging Unit, CEA DRF/Joliot Institute, INSERM, Université Paris-Sud, Université Paris-Saclay, NeuroSpin Center, 91191 Gif-sur-Yvette, France*
[c]*Duke University Health System, Durham, NC, USA*
[d]*Department of Psychiatry, Stony Brook University, Stony Brook, NY, USA*
[e]*Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA*
[f]*Applied Mathematics and Statistics, Stony Brook University, Stony Brook, NY, USA*
[g]*New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, New York, NY, USA*
[h]*Tonix Pharmaceuticals, Inc., 509 Madison Avenue Suite 306, New York, NY, USA*
[i]*Radiology, Stony Brook University, Stony Brook, NY, USA*

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Abstract
Symptoms of anxiety are highly comorbid with major depressive disorder (MDD) and are known to alter the course of the disease. To help elucidate the biological underpinnings of these prevalent disorders, we previously examined the relationship between components of anxiety (somatic, psychic and motoric) and serotonin 1A receptor (5-HT_{1A}) binding in MDD and found that higher psychic and lower somatic anxiety was associated with greater 5-HT_{1A} binding. In this work, we sought to examine the correlation between these anxiety symptom dimensions and 5-HTT binding. Positron emission tomography with [^{11}C]-3-amino-4-(3-dimethylamino-methylphenylsulfanyl)-benzonitrile ([^{11}C]DASB) and a metabolite-corrected arterial input function were used to estimate regional 5-HTT binding in 55 subjects with MDD and anxiety symptoms. Somatic anxiety was negatively correlated with 5-HTT binding in the thalamus ($\beta = -.33$, $p = .025$), amygdala ($\beta = -.31$, $p = .007$) and midbrain ($\beta = -.72$, $p < .001$). Psychic

*Correspondence to: INSERM U992/NeuroSpin/CEA-Saclay, Bât 145, Point Courier 156, 91191 Gif-sur-Yvette cedex, France.
E-mail address: zaferiscan@yahoo.com (Z. Iscan).

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anxiety was positively correlated with 5-HTT binding in midbrain only (β=.46, p=.0025). To relate to our previous study, correlation between 5-HT_{1A} and 5-HTT binding was examined, and none was found. We also examined how much of the variance in anxiety symptom dimensions could be explained by *both* 5-HTT and 5-HT_{1A} binding. The developed model was able to explain 68% (p<.001), 38% (p=.012) and 32% (p=.038) of the total variance in somatic, psychic, and motoric anxiety, respectively. Results indicate the tight coupling between the serotonergic system and anxiety components, which may be confounded when using aggregate anxiety measures. Uncovering serotonin's role in anxiety and depression in this way may give way to a new generation of therapeutics and treatment strategies.
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1. Introduction

Depressive and anxiety disorders have substantial comorbidity, however the shared pathophysiology between the two remains poorly understood. Studies of sequential comorbidity suggest that anxiety disorders are more often preceded by depressive disorders (Moffitt et al., 2007). Patients who are comorbid for both disorders have greater psychosocial disability and a poorer quality of life (Hirschfeld, 2001), and depression with anxious features is associated with worse treatment outcome (Fava et al., 2008).

Clinically, major depressive disorder (MDD) and generalized anxiety disorder share common core symptoms, which may reflect overlap in etiology. For example, the serotonergic (5-HT) system has been implicated in both the pathophysiology of MDD (Drevets et al., 1999), as well as modulation of anxiety symptoms (Olivier et al., 2013). Specifically, the serotonin transporter (5-HTT) is an important target for treatment of both depression and anxiety (Owens et al., 1997; Reimold et al., 2008; Tatsumi et al., 1997); selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for both unipolar depression and anxiety disorders (Denys and de Geus, 2005; Feighner and Cohn, 1989; Olivier et al., 2013; Reimold et al., 2008).

The 5-HTT anxiety relationship has been explored in humans, and an association is reported between anxiety and polymorphisms of the 5-HTT (Cerasa et al., 2014; Liu et al., 2013; Pietrzak et al., 2013). Further, human PET imaging studies have consistently reported an inverse correlation between 5-HTT binding and the severity of depressive or anxiety symptoms; however, this relationship may be affected by the inclusion of heterogeneous MDD cohorts (Spies et al., 2015), particularly those with anxiety. In PTSD, lower 5-HTT binding in the midbrain and thalamus was associated with greater anxiety (Reimold et al., 2008). Similarly, an inverse correlation was found between 5-HTT expression and symptom severity in patients with PTSD (Frick et al., 2015b) But a study completed in patients with social anxiety disorder by the same group showed higher 5-HTT binding in this disorder compared to healthy control subjects (Frick et al., 2015a).

In some studies, patients with MDD exhibit lower 5-HTT binding in the amygdala (Murrough et al., 2011), midbrain (Malison et al., 1998; Parsey et al., 2006a) medial temporal lobe, and basal ganglia (Newberg et al., 2012) compared with healthy volunteers. However, using the ligand [^{11}C]-3-amino-4-(3-dimethylamino-methylphenylsulfanyl)-benzonitrile ([^{11}C]DASB), we previously found no differences in 5-HTT binding between MDD and healthy controls (Miller et al., 2013).

One of the challenges associated with relating neurobiology to anxiety is that the forms of anxiety co-occurring with MDD, whether subsyndromal or due to syndromal comorbid conditions (panic disorder, generalized anxiety disorder, social phobia), are heterogeneous in presentation. Therefore, breaking anxiety down into clinically distinguishable components may aid in defining its neurobiological underpinnings. This refined approach may also lead to treatments that can target specific anxiety symptoms. In a previous PET study, we used radioligand [^{11}C]WAY-100635 [N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridil) cyclohexanecarboxyamide] to relate 5-HT_{1A} binding to three components of anxiety derived from a large sample of MDD patients: somatic (hypochondriasis, sweating, cardiovascular, respiratory, gastrointestinal and urination symptoms), psychic (anxiousness and irritability), and motoric (agitation) components. In that study, the severity of somatic and psychic anxiety correlated with 5-HT_{1A} binding in anterior cingulate (negatively and positively, respectively), body of cingulate, orbital prefrontal and medial prefrontal cortices, along with temporal, parietal, and occipital cortices in patients with MDD (Sullivan et al., 2005). These regional relationships may explain why buspirone, a 5-HT_{1A} partial agonist, can improve psychic anxiety more rapidly than somatic anxiety (Feighner and Cohn, 1989).

In this present study, we estimate regional brain 5-HTT binding in MDD subjects using [^{11}C]DASB and relate this binding to anxiety symptom dimensions. This overcomes the limitations of previous studies by specifically examining anxiety components within MDD, instead of confounding MDD group differences. To relate this analysis to our previous work examining 5-HT_{1A} binding, we examined the correlation between 5-HTT and 5-HT_{1A} in the regions implicated in the previous study with non-negligible levels of [^{11}C]DASB binding (anterior cingulate cortex, amygdala, midbrain). To further conceptualize the relationship between the serotonergic system and anxiety, we developed a model in which both 5-HT_{1A} and 5-HTT were used to predict anxiety components. This will provide a more comprehensive view of serotonergic function in major

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