

## TRENDS AND PERSPECTIVE

# 5-HT<sub>2A</sub> Agonists: A Novel Therapy for Functional Neurological Disorders?

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## Abstract

Functional neurological disorders are frequently encountered in clinical practice. They have a poor prognosis and treatment options are limited. Their etiology is unknown, but leading theories propose a disturbance of somatic self-representation: the mind perceives dysfunction of a body region despite intact motor and sensory pathways. Central to this model is the concept of an abnormal top-down cognitive influence upon sensorimotor function. There is growing interest in the use of 5-HT<sub>2A</sub> agonists in the management of neuropsychiatric conditions. Recent studies have shown that these agents induce changes in neural activity that disrupt hierarchical brain dynamics and modulate networks subserving self-related processing. Converging evidence suggests they may hold unique therapeutic potential in functional neurological disorders. This is of importance given the considerable personal and societal burden of this condition and we argue a clinical trial to test this hypothesis is warranted.

**Keywords:** functional neurological disorders, 5HT2a agonists, fMRI, neural dynamics.

## Introduction

Functional neurological disorders (FNDs) are a common condition that exist on the borderland of neurology and psychiatry. They tend to be poorly managed and there are few proven therapeutic options (Carson et al., 2004; Kanaan et al., 2011; Cottencin, 2014; Lehn et al., 2016). Most leading theoretic models implicate an impairment of somatic self-representation in their psychopathology (Brown, 2004; Edwards et al., 2012; Vuilleumier, 2014; Ejareh Dar and Kanaan, 2016; Voon et al., 2016a).

5-HT<sub>2A</sub> agonists have recently emerged as a plausible adjunct therapy for major depression, anxiety, and drug addiction (Grob et al., 2011; Bogenschutz and Johnson, 2016; Carhart-Harris, 2016; Johnson et al., 2016). Use of these agents was first predicated

on observed clinical benefit, and imaging studies have begun to unravel the neural basis of their psychoactive effects (Nichols, 2004; Carhart-Harris et al., 2012, 2016a; Majic et al., 2015; Tagliazucchi et al., 2016). Based on current understanding of FND pathophysiology and the effects of 5-HT<sub>2A</sub> agonists on brain function, we argue there is a convergence of evidence to support their use in the management of this condition.

## FNDs: Clinical Background

FNDs are defined by the appearance of neurological symptoms without underlying structural pathology (American Psychiatric

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## Significance Statement

Functional neurological disorders are a common neuropsychiatric condition. We argue there is converging evidence to suggest a role for 5HT<sub>2A</sub> agonists in their management. This hypothesis is supported by neuroimaging and behavioural findings, and is of significance given the current lack of treatment options.

Association, 2013). These symptoms may take varied forms including hemiparesis, visual impairment, or movement disorders (Stone et al., 2005, 2010b). Their nomenclature has undergone historical change and encompasses terms including hysteria, psychogenic movement disorder, and conversion disorder (American Psychiatric Association, 2013; Crommelinck, 2014). FNDs are distinct from feigning or malingering as they are considered a psychiatric condition and the patient's complaint is not consciously produced. Although psychiatric comorbidity is associated with FNDs it is neither necessary nor sufficient for onset (Stone et al., 2010a; Cottencin, 2014).

Diagnosis of an FND relies on normal neurological investigations and characteristic inconsistencies in the clinical examination (Stone et al., 2005; Carson et al., 2012; Daum et al., 2014). Diverting attention from the affected body part, for example, often leads to symptom improvement. Unfortunately treatment options are limited, prognosis is unfavorable, and clinicians have historically adopted a distrustful attitude toward these patients (Carson et al., 2004; Kanaan et al., 2011; Gelauff et al., 2014). Psychotherapy is typically offered but there is minimal evidence for benefit (Ruddy and House, 2005; Cottencin, 2014). Physiotherapy may assist with recovery of motor manifestations (McCormack et al., 2014). FNDs account for a substantial proportion of patients referred to specialty medical clinics and pose a significant burden on both the individual and healthcare system. Incurred costs and impact on quality of life are comparable with "organic" neurological disease (Nimnuan et al., 2001; Anderson et al., 2007; Stone et al., 2010b; Carson et al., 2011).

## FNDs: Pathophysiology

Some insight into the neuropathology of FNDs has been gained through functional magnetic resonance imaging (fMRI) and behavioral studies (Boeckle et al., 2016; Ejareh Dar and Kanaan, 2016; Voon et al., 2016). Findings related to motor agency, self-monitoring, and self-representation are of particular relevance to theoretic models.

Patients with functional motor symptoms experience a loss of volitional control, or agency, over a body part (Voon et al., 2010; Edwards et al., 2011b). The perception of motor agency is thought to emerge from an internal matching of task prediction to task outcome and involves recruitment of the right temporo-parietal junction (Spence et al., 2000; Hallett, 2016; Voon et al., 2016). Reduced activation of this region in patients with FNDs, and normal activation in subjects who feign weakness, suggests a discrepancy between movement intention and realization (Voon et al., 2010; van Beilen et al., 2011; Aybek et al., 2014; Burke et al., 2014; Hallett, 2016). An impairment of motor conceptualization or initiation appears present, perhaps due to other disruptive cognitive processes (de Lange et al., 2007; Voon et al., 2011).

Both patients and individuals at high risk for developing FNDs show a tendency to divert attentional resources onto the self (Roelofs et al., 2003; Brown et al., 2010a, 2010b). Behavioural studies in these groups demonstrate heightened body vigilance,

an inclination to experience perceptually ambiguous sensory stimuli, and a preoccupation with somatic symptoms (Kumru et al., 2007; van Poppelen et al., 2011). Neuroimaging findings support this observation, with increased fMRI activity observed within the ventromedial prefrontal cortex, precuneus and insula (de Lange et al., 2007, 2008, 2010; Cojan et al., 2009). These regions comprise nodes of the brain's default mode network (DMN) and subserve introspective cognitive functions including somatic self-representation and the retrieval of self-imagery (Raichle et al., 2001; Brown, 2004; Vuilleumier, 2014).

## FNDs: Theoretic Models

These findings lay experimental grounding for a leading neurobiological model of FNDs. This model contends that aberrant somatic self-representation, perhaps induced through heightened self-monitoring, exerts excessive influence over normal motor function (Brown, 2004; Edwards et al., 2013; Vuilleumier, 2014; Voon et al., 2016). Abnormal DMN and supplementary motor cortex activity may reflect neural correlates of these psychological changes (Cojan et al., 2009). A mismatch between intended and realized motor function accounts for a perceived loss of self-agency and the observed changes in temporo-parietal junction activation. Traditionally the mechanism of dissociation, defined as a disruption of normally integrated psychological functions including body representation and motor control, has been thought to underlie FNDs (American Psychiatric Association, 2013). This model argues for a discrete loss of integrated somatoform function and is consistent with the notion of dissociation (Voon et al., 2016; Carson et al., 2012). The precipitating reasons for developing an FND remain unclear, although personality factors and maladaptive processing of traumatic life events may play a role (Aybek et al., 2014; Nicholson et al., 2016).

The neurobiological model is also compatible with a Bayesian formulation of FNDs (Edwards et al., 2012). This computational theory asserts that the brain generates our experience of reality through predictive representations of the self and environment (priors), which are compared and updated against somatic and exteroceptive sensory input, forming posteriors (Friston, 2005). Emergence of an excessively precise prior may generate a fixed representation that manifests as a functional symptom (Edwards et al., 2012). This theory accounts for the worsening of symptoms when patients attend to their affected body part: the abnormal prior is strengthened through attentional focus (Edwards et al., 2013). It also provides explanatory basis for a "jumping to conclusions" bias found during probabilistic reasoning and a susceptibility to the placebo effect (Kenney et al., 2007; Edwards et al., 2011a; Parees et al., 2012). Both phenomena reflect a tendency to favor internal priors over conflicting external evidence.

Central to both the neurobiological and Bayesian models is a disturbance of the normal cognitive hierarchy: lower-order sensori-motor function is disrupted by higher-order cognitive processes (Brown, 2004; Carson et al., 2012; Edwards et al., 2012, 2013; Voon et al., 2016). One may speculate, therefore, that

an intervention capable of disrupting both hierarchical brain dynamics and self-representation could confer a therapeutic benefit. 5-HT<sub>2A</sub> agonists appear to impact both processes and emerge as a plausible candidate. We shall first consider the effect of these agents on neural activity at a cellular and network level and, based on these findings, argue for their potential use in FNDs.

### The 5-HT<sub>2A</sub> Receptor: Single Neurons and Neural Circuits

Serotonin (5-hydroxytryptamine or 5-HT) modulates cortical function via widely projecting axons acting on a diversity of receptor subtypes (Puig et al., 2005; Celada et al., 2013). The 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors exert the greatest influence over cortical function. The 5-HT<sub>2A</sub> receptor is largely responsible for the psychoactive effect of psychedelic compounds such as psilocybin (Glennon et al., 1984; Nichols, 2004).

Activation of the 5-HT<sub>2A</sub> receptor promotes neuron excitability through membrane depolarization and increased action potential probability (Araneda and Andrade, 1991; Andrade, 1998; Celada et al., 2013). There is strong expression of this receptor on excitatory pyramidal cells across most cortical layers, and it has a subcellular distribution favoring proximal apical dendrites, perhaps conferring a role to enhance synaptic input (Andrade, 1998; Zhang and Arsenault, 2005; Celada et al., 2013; Santana et al., 2004; Halberstadt, 2015). Expression is weaker in GABAergic interneurons, with the notable exception of parvalbumin-positive subtypes (Willins et al., 1997; Santana et al., 2004; Puig and Gullledge, 2011b). The 5-HT<sub>2A</sub> receptor is found across most macroscopic cortical regions; however, greatest densities have been observed within the prefrontal cortex and association areas (Santana et al., 2004; Saulin et al., 2012).

The impact of 5-HT<sub>2A</sub> agonists on network function within cortical circuits is incompletely understood (Puig and Gullledge, 2011a). Increased firing rates and spontaneous excitatory postsynaptic potentials have been observed in slice recordings of pyramidal cells (Puig et al., 2003; Zhang and Arsenault, 2005; Halberstadt, 2015). These neurons form long range cortico-cortical and cortico-thalamo-cortical projections mediating neural information flow between brain regions (Theyel et al., 2010; Ueta et al., 2014; Ramaswamy and Markram, 2015). 5-HT<sub>2A</sub> agonists may also enhance the power of gamma-frequency local field potential recordings, possibly due to enhanced synchrony within populations of parvalbumin-positive interneurons (Puig et al., 2010; Buzsaki and Wang, 2012). This frequency band is thought to promote the dynamic binding of neural activity between brain regions (Buzsaki, 2011). Neuroimaging and electroencephalogram (EEG) studies provide support for a role in enhancing long-range information flow and provide a glimpse into the macroscopic dynamics induced by these agents.

### 5-HT<sub>2A</sub> Agonists: Neuroimaging and EEG Studies

Subjects receiving 5-HT<sub>2A</sub> agonists report a range of experiential phenomena. Most common are hallucinations, synesthesia, and ego dissolution: the experience of a diminished sense of self; (Nour et al., 2016; Tagliazucchi et al., 2016). The neural correlates of these psychoactive effects have been explored with fMRI and EEG.

Under resting conditions, macroscopic functional brain networks display a modular and hierarchical topography.

Connectivity within a distinct network tends to be dense, forming a module, whereas connectivity between modules is sparse (Bullmore and Sporns, 2009). 5-HT<sub>2A</sub> agonists induce a reduction in fMRI activity and functional connectivity within higher-order modules including the DMN. The magnitude of these changes correlates with the intensity of ego dissolution, consistent with the role of these regions in sustaining self-related cognition (Carhart-Harris et al., 2012; Tagliazucchi et al., 2016).

Concurrently, 5-HT<sub>2A</sub> agonists increase global brain connectivity by increasing functional connectivity between lower and higher-order modules (Carhart-Harris et al., 2016a; Tagliazucchi et al., 2016). This produces a flattening of the brain's hierarchical topography (Petri et al., 2014). Lower-order sensori-motor and association cortex, in particular, develop robust functional connectivity with higher-order modules (Kometer et al., 2013; Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2016a; Tagliazucchi et al., 2016).

Information theoretic analyses performed on EEG recordings have revealed specific changes in neural dynamics that extend these fMRI findings. Neural activity recorded from higher-order frontal brain regions appears to exert less constraint over activity within lower-order centro-posterior regions (Alonso et al., 2015). Conversely, activity within lower-order regions has greater influence over higher-order areas. This represents a reversal of normal hierarchical brain dynamics. It may also provide a mechanistic explanation for intrusive sensory experiences and feelings of loss of separation from the environment: sensory information is allowed to seep across functional boundaries (Alonso et al., 2015; Tagliazucchi et al., 2016).

### 5-HT<sub>2A</sub> Agonists: A Novel Therapy for Functional Neurological Disorders?

These findings have a compelling application to FNDs. 5-HT<sub>2A</sub> agonists appear to modulate the two processes of central importance to theoretic models: self-representation and the influence of higher-order cognitive processes upon lower-order sensori-motor function (Brown, 2004; Edwards et al., 2012; Vuilleumier, 2014; Voon et al., 2016).

Firstly, these agents diminish fMRI activity and functional connectivity within networks subserving self-related cognitive processing. The experience of ego dissolution, a measure of integrated self-representation, substantiates this neuroimaging finding (Nour et al., 2016). This would be anticipated to weaken an abnormal somatic representation underlying functional symptoms.

5-HT<sub>2A</sub> agonists also enhance functional connectivity between hierarchical brain networks, and the influence of neural activity from lower-order upon higher-order regions. In effect, higher-order constraints are removed, and unregulated neural activity within sensori-motor and association cortex is observed (Muthukumaraswamy et al., 2013; Alonso et al., 2015; Carhart-Harris et al., 2016). Synesthetic and intrusive sensory experiences support this empirical finding. More importantly, it may resolve a pathological influence of the mind over the body, leading to an improvement of symptoms.

A benefit is also apparent when considering FNDs from a Bayesian perspective. In this framework, the brain generates experiences of reality through a balance of top-down and bottom-up input. 5-HT<sub>2A</sub> agonists suppress the former by diminishing the influence of higher-order brain regions, and enhance the latter by promoting connectivity and neural information flow originating from lower-order regions. According to the Bayesian

model, this would be expected to weaken abnormally precise higher-order representations and increase the salience of sensory input. A functional symptom may therefore be alleviated.

## Summary and Future Directions

There is strong interest in the therapeutic potential of 5-HT<sub>2A</sub> agonists in mood disorders and drug addiction (Johnson et al., 2014; Carhart-Harris et al., 2016b; Rucker et al., 2016). The use of these agents was first predicated on promising case reports; however, clinical and experimental evidence to support their use is now accumulating (Nichols, 2004; Ripoll et al., 2005, 2006; Majic et al., 2015; Carhart-Harris et al., 2016b; Rucker et al., 2016). Based on the known impact of these agents on brain activity and our current understanding of FND neuropathology, these agents appear particularly suited for the management of this condition. This may be of considerable importance given the current lack of treatment options available.

Studies utilizing 5-HT<sub>2A</sub> agonists raise legitimate ethical and safety concerns due to risks associated with their hallucinogenic properties. These may be mitigated in a controlled environment (Carbonaro et al., 2016; Rucker et al., 2016). We see a need for a study examining a carefully selected and homogeneous patient cohort, such as refractory functional hemiparesis in the absence of psychiatric comorbidity, in conjunction with best-practice treatment including physiotherapy and psychotherapy. Intermittent dosing schedules similar to existing trials in depression could be employed (Carhart-Harris et al., 2016b). The study hypothesis would be that use of 5-HT<sub>2A</sub> agonists to transiently perturb brain network activity would enhance symptom recovery relative to a non-drug patient control group.

## Statement of Interest

T.N. serves as an advisor for Lundbeck Australia.

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