Brain circuitry in Major Depressive Disorder:
The critical role of ventral anterior cingulate cortex

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Major Depressive Disorder (MDD) is a mood disorder characterized by a large number and variety of symptoms, including effective/emotional (persistent sadness, anhedonia, anxiety, agitation, guilt feelings, hopelessness, etc.), somatic (tiredness, loss of energy, sleep disturbances, reduced/increased appetite, weight gain/loss etc.) and cognitive symptoms (slowness of thinking, concentration difficulties, etc.). Overall, this suggests the presence of derangements of nerve transmission in different areas/circuits involved in the control of these disturbed brain functions.

The prefrontal cortex (PFC) is deeply involved in higher brain functions, many of which are altered in psychiatric conditions. Lateral areas (e.g., Brodmann area 46), play a central role in cognitive processes, whereas orbital and ventromedial regions are engaged –but not only– in emotional and behavioral control. The ventral anterior cingulate cortex, vACC, (also referred to as ventromedial PFC, subgenual anterior cingulate cortex or subcallosal anterior cingulate cortex), and particularly Brodmann area 25 -Cg25-, plays a key role in emotional processing, being also involved in the pathophysiology of mood and anxiety disorders, due to its connectivity and top-down control of limbic, hypothalamic and reward-linked brain areas (Groenewegen and Uylings, 2000; Alexander et al., 2019). Likewise, these ventromedial areas are also reciprocally connected with the brainstem monoamine cell nuclei (the serotonergic

dorsal and median raphe nuclei -DR/MnR-, the noradrenergic locus coeruleus -LC- and the dopaminergic ventral tegmental area -VTA-) and exert a top-down control of their activity (Figure 1A).

In rodents, the PFC contains four main regions, medial, lateral, ventral and orbital. The medial PFC (mPFC) is a key cortical area in psychiatric research: its function is altered in animal models of mental disorders and it contains the monoamine receptors and transporters targeted by antidepressant and antipsychotic drugs. The cingulate (Cg), prelimbic (PrL) and infralimbic (IL) subdivisions of the mPFC play distinct roles in the processing of cognitive, emotional and behavioral information. In particular, the IL cortex is considered as the rodent equivalent of the primate and human vACC, particularly Cg25, in terms of connectivity and function (Alexander et al., 2019).

Projection pyramidal neurons (excitatory, layer V) in all mPFC subdivisions project densely to DR/MnR, LC and VTA (Gabbott et al., 2005) and control monoamine neuron activity. In the case of DR serotonergic (5-HT) neurons, the electrical stimulation of the mPFC at physiological rates mainly inhibits 5-HT neurons via *i*) self-inhibitory mechanisms (i.e., 5-HT_{1A} autoreceptors) and *ii*) GABA_AR inputs from local interneurons, following initial excitatory inputs onto 5-HT and GABA neurons, respectively (Celada et al., 2001).

Neuroimaging studies revealed the existence of a hyperactive vACC in treatment-resistant MDD patients (Mayberg et al., 2005; Drevets et al., 2008). Given the above anatomical and functional relationships, a hyperactivity of projection pyramidal neurons would translate into a reduced monoaminergic activity (Figure 1B). This view -at least for 5-HT neurons, -the main antidepressant target- is supported by recent rodent data. Using small interfering RNA (siRNA) strategies, we reduced the expression/function of the astroglial glutamate transporters GLAST and GLT-1, that take up >90% of synaptic glutamate, and induced a local glutamatergic hyperactivity in mouse IL. These mice exhibited a robust depressive-like phenotype, accompanied by a reduced activity of 5-HT neurons and by a decreased expression of brain derived neurotrophic factor (BDNF, a prototypical marker of MDD) in cortical and hippocampal areas (see Fullana and Gasull-Camós et al., 2020 and references therein). Remarkably, the same siRNA application in PrL equally reduced local GLAST/GLT-1 expression, but did not evoke a depressive-like phenotype nor reduced 5-HT function, highlighting the relevance of the glutamate/5-HT interplay in IL (but not PrL) in emotional regulation.

Accordingly, a reduction of vACC hyperactivity may be seen as a regional mechanistic target in antidepressant drug development (Figure 1C). Thus, pharmacological, molecular or other intervention types aimed at reducing the excitation/inhibition ratio in vACC would help to normalize neuronal activity in MDD-relevant subcortical areas innervated by vACC, leading to symptom reduction. Hence, the deep brain stimulation (DBS) of Cg25 evoked an immediate clinical improvement (Mayberg et al., 2005; Puigdemont et al., 2012) and reduced Cg25 hyperactivity in responding patients (Mayberg et al., 2005). Along these lines, blockade of NMDA-R by ketamine or its S-isomer esketamine may contribute to normalize glutamatergic hyperactivity in vACC and to induce immediate antidepressant effects. In support of this view, ketamine i.v. infusion attenuated a task-driven hyperactivity of vACC in MDD patients (Morris et al., 2020) and its i.p. administration reversed the depressive-like phenotype in mice with a hyperactive IL (Fullana and Gasull-Camós et al., 2020). Likewise, the increases in functional connectivity between lateral PFC and vACC induced by ketamine/esketamine infusion in MDD patients are linked to treatment response (Gartner et al., 2019). It is also tempting to speculate that the rapid antidepressant action of positive allosteric modulators of GABA_A-R such as brexanolone and SAGE-217 might involve, among others, the attenuation of vACC hyperactivity, via an enhancement of GABA neurotransmission.

Finally, 5-HT enhancing antidepressant drugs (SSRI, SNRI, TCAs, etc.) may also normalize vACC hyperactivity, yet with a much slower time course, due to presynaptic adaptive mechanisms limiting the increase of the active 5-HT fraction induced by SERT blockade. In this regard, a “pharmacological” dose of the SSRI citalopram that acutely enhances extracellular 5-HT (10 mg/kg i.p.; much greater than the usual clinical regime of 20 mg/day p.o.; i.e., ~0.3 mg/kg·day p.o.) reversed the depressive-like phenotype in mice with a hyperactive IL (Fullana and Gasull-Camós et al., 2020). This effect may involve a regionally-selective inhibitory action of 5-HT in IL (López-Terrones et al., unpublished observations).

In summary, existing literature supports a critical role of vACC in primates/humans, -and of IL in rodents- in MDD and MDD models, respectively. By virtue of its connectivity with, and top-down control of brainstem monoamine nuclei (and in particular, of raphe 5-HT neurons), a *focal* glutamatergic hyperactivity in vACC may translate into a *global* reduction of monoaminergic activity, giving rise to MDD symptoms. Antidepressant effects may result from the restoration of monoamine function with uptake inhibitors but also, -and in a much faster way- from an attenuation of vACC hyperactivity (e.g., DBS, ketamine/esketamine, GABA_A-R modulators, etc.).

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Figure legend

Figure 1. A) The prefrontal cortex (PFC), including the ventral anterior cingulate cortex (vACC) is reciprocally connected with most subcortical areas*, including the brainstem monoamine cell nuclei as well as limbic, hypothalamic and reward-associated areas, and exerts a top-down control on their activity. In turn, the brainstem monoamine nuclei project extensively to the whole forebrain, including cortical, limbic, hypothalamic and reward-associated areas that are also innervated by the vACC (infralimbic cortex, IL, in rodents). **B)** A genetic- or environmentally-induced *focal* hyperactivity in vACC may translate into a *global* reduction of monoaminergic activity in MDD-relevant areas, by virtue of the connectivity and top-down control exerted by the vACC on monoamine systems, giving rise to MDD symptoms. In support of this possibility, a glutamatergic hyperactivity induced in mouse IL resulted in a depressive-like phenotype, associated to a reduced 5-HT function and to a reduced cortical and hippocampal BDNF expression. Remarkably, the same intervention in PrL did not alter mouse behavior nor 5-HT or BDNF expression/function. **C)** Clinical improvement may result from a restoration of monoaminergic activity (in particular, serotonergic, via 5-HT-enhancing drugs), but also from the attenuation of glutamatergic hyperactivity in vACC, via different fast-acting strategies, an action that would then reduce and excessive top-down inhibitory control from vACC on brainstem monoamine nuclei. . *Abbreviations used:* AMY, amygdala; DLPFC, dorso-lateral prefrontal cortex; DR, dorsal raphe nucleus; HPC, hippocampus; HTL, hypothalamus; MnR median raphe nucleus; NAcc, nucleus accumbens. Black arrows depict glutamatergic pathways and green arrows depict serotonergic pathways Adapted from Artigas *Eur Neuropsychopharmacol* 2015.

*with the exception of the basal ganglia, which receive direct PFC inputs but send nerve information back to PFC via the thalamus (mainly centromedial and mediodorsal nuclei). On the other hand, the hippocampal formation receives most cortical inputs from the entorhinal cortex and projects back to it, but also to PFC.

Declaration of Competing Interest

During the last two years, F.A. has been P.I. of a grant from Lundbeck and has been member of the scientific advisory board of Neurolixis. He is also co-inventor of two patents conjugated RNAi molecules.