Supplementary material

A three-dimensional model of neural activity and phenomenal-behavioral patterns

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A) Data overview on phenomenal-behavioral patterns and their neural correlates

1) Psychomotor dimension and its neural correlates

a) Psychomotor excitation

1. Psychomotor hyperactivity

Psychomotor hyperactivity is characterized by an increase and acceleration of perceptive states and body movements. Hyperactivity in healthy subjects is closely associated to impulsivity and the cyclothymic temperament, which are related to increased functional connectivity (FC) between subcortical and cortical sensorimotor areas and increased neuronal variability (i.e., temporal variability of BOLD signal fluctuations, an indirect index of neuronal activity) in the sensorimotor network (SMN)[1-2]. Coherently, psychomotor hyperactivity in attention-deficit/hyperactivity disorder is related to increased subcortical-cortical FC within the SMN[3]; moreover, this disorder is associated with increased task-based activation in the SMN[4]. Manic states (including psychomotor hyperactivity as core symptomatology) in bipolar disorder (BD) are related to: increased neuronal variability, global signal representation, and regional homogeneity (ReHo, a measure of local connectivity) in the SMN (with SMN ReHo specifically correlating with hyperactivity), along with increased FC in the motor cortical areas and dorsal attention network[5-9]; increased occurrence of a coactivation pattern (CAP) involving SMN areas (correlating with motor agitation)[10]; increased thalamus-SMN FC[11]; and increased FC between substantia nigra/ventral tegmental area and motor cortex, as well as decreased raphe nuclei-related FC[11-12]. Analogously, psychomotor hyperactivity in schizophrenia (SCZ) is associated with increased thalamus-SMN FC and reduced raphe nuclei-related FC[13].

2. Hyperkinesia

Hyperkinesia is characterized by severe psychomotor hyperactivity with involuntary movements (such as tics, choreoathetosis, dystonia, and dyskinesia). Hyperkinesia in Tourette syndrome is consistently associated with increased cerebral metabolic rate (CMR) and increased task-based activation, along with specific activation before and during tic onset, in the premotor and motor cortices[14-16]. Coherently, hyperkinesia in Huntington's disease is robustly related to increased FC in the SMN (representing the core network involved in the pathophysiology of this disease)[17]. Such hyperkinetic symptoms may stem from abnormal striatopallidal activity, finally leading to disinhibition of the thalamo-cortical projections within the motor system[18].

3. Catatonia (excited)

Catatonia is characterized by extreme psychomotor alterations (i.e., stupor, catalepsy, posturing, echolalia-echopraxia, stereotypy, and agitation). Interestingly, according to an evolutionary interpretation, catatonia could resemble the phenomenon of tonic immobility, a stereotyped defense response of some animals alternating immobility and agitation in situations of extreme danger[19]. Excited catatonia may represent the extreme pole of psychomotor excitation, characterized by fluctuations between agitation with non-goal-directed interaction with the external environment and tonic immobility (with tetanic rigidity). Catatonia in SCZ and other diseases is related to alterations

of cerebral blood flow (CBF), amplitude of low-frequency fluctuations (ALFF, an indirect measure of neuronal activity), task-based activation, and neurotransmitter signaling in motor areas[20]. In particular, catatonia has been associated with increased CBF in the premotor and motor cortex, as well as decreased gabaergic (inhibitory) signaling in the sensorimotor cortex (coherently, gabaergic drugs can alleviate acute catatonia in some cases)[20-23], and this could represent a potential underpinning of excited catatonia (however, the specific correlates of excited and inhibited catatonia need to be further investigated).

b) Psychomotor inhibition

1. Psychomotor retardation

Psychomotor retardation is characterized by a reduction and slowing of perceptive states and body movements. Psychomotor retardation in major depressive disorder (MDD) is related to decreased CBF in the motor cortex and striatum[24-26], along with deficits in dopamine signaling in the striatum[27-28]. Moreover, depressive states (including psychomotor retardation as typical symptomatology) in MDD are associated with: consistently decreased ReHo, along with a decrease of ALFF, FC, CMR, and/or CBF, in SMN areas, such as the primary motor, somatosensory, auditory, and visual cortices[29-35]; decreased dominance (dwell time and persistence) of a CAP involving SMN areas[36]; decreased baseline and task-based ALFF in the SMN and dorsal attention network[37]; and decreased FC between supplementary motor area and basal ganglia during motor processing[38]. Coherently, depressive states (including psychomotor retardation) in BD are related to decreased neuronal variability and ALFF, along with a reduction of FC and ReHo, in SMN areas (such as postcentral and precentral gyri)[5-6, 39]; more specifically, psychomotor retardation in bipolar depression is associated with decreased FC between thalamus and SMN, along with reduced substantia nigra-related FC[11]. Accordingly, psychomotor retardation in depression (melancholic depression especially) is supposed to depend on basal ganglia dysfunction driven by deficits in dopamine signaling[40]. Psychomotor retardation in SCZ is related to decreased CBF in the motor cortex[41], along with decreased thalamus-SMN FC and reduced substantia nigra-related FC[13]. Moreover, SCZ (including psychomotor deficit as typical symptomatology) is consistently associated with functional deficits in SMN areas (such as the motor cortex and primary somatosensory, auditory, and, to a lesser extent, visual cortices), mostly detectable since the early stage of illness, including: decreased ALFF and ReHo in the postcentral gyrus, superior temporal gyrus, and occipital cortex[42-43]; decreased FC in the precentral gyrus, postcentral gyrus, fusiform gyrus, and especially the superior temporal gyrus (in the context of widespread network dysconnectivity) often since the early stage (along with increased FC (reduced anti-correlation) of the thalamus with postcentral/precentral gyri and superior/middle/inferior temporal gyri especially during the chronic stage)[44-45]; decreased activation in the basal ganglia and premotor cortex during motor processing[46]; and decreased activation in the superior temporal gyrus (including the primary auditory cortex) during exteroceptive auditory stimulation and verbal processing (especially in auditory hallucinators)[47-49]. Importantly, SCZ has been recently associated with a degradation of the visual-to-somatomotor gradient (secondary connectivity gradient) of cortical organization (involving the somatomotor, somatosensory, auditory, and visual cortices), along with SMN-dominant alterations in the gradient space, including reduced eccentricity of the SMN and shortened network distance of the SMN with the other networks (suggesting a degradation of the functional differentiation of the sensorimotor system and corresponding disorganization of sensory and motor processing)[50]. Psychomotor retardation in SCZ is supposed to depend on inhibition of thalamo-cortical projections within the sensorimotor system driven by deficits in dopamine signaling[51]. Finally, psychomotor retardation can also occur during the (acute) use of substances such as opioids, which is associated with decreased activation and FC in SMN areas (e.g., primary sensory-motor cortex)[52].

2. Hypokinesia
Hypokinesia is characterized by severe psychomotor retardation (bradykinesia or akinesia) with rigidity. Hypokinesia in Parkinson's disease is consistently associated with decreased ALFF and ReHo in the motor cortex and putamen[53-54], along with reduced task-based activation in the supplementary motor area and putamen[55]. Moreover, visual perception deficits frequently occur in this disorder and are associated with a corresponding reduction of FC in the primary visual cortex[56]. Notably, Parkinson's disease arises due to degeneration and cell loss in the substantia nigra and a corresponding loss of dopamine signaling in the striatum[18].

3. Catatonia (inhibited)
Inhibited catatonia may represent the extreme pole of psychomotor inhibition, characterized by stable immobility with no interaction with the external environment. As reported, catatonia in SCZ and other diseases is related to alterations in CBF, ALFF, task-based activation, and neurotransmitter signaling in motor areas[20]. In particular, catatonia has been associated with reduced ALFF and task-based activation in motor, premotor, and prefrontal cortices, along with deficits in dopamine signaling in the basal ganglia (coherently, antidopaminergic drugs can induce rigidity, immobility, and catalepsy)[20, 22, 57-58], and this could represent a potential underpinning of inhibited catatonia (however, the specific correlates of the excited and inhibited catatonia need to be further investigated).

2) Affective dimension and its neural correlates

b) Affective excitation

1. Anxiety
Anxiety is characterized by inner excitation associated with neurovegetative activation. Anxiety and trait anxiety/anxious temperament in healthy subjects are associated with increased FC, increased ALFF, and, more consistently, increased task-based activation (during anxiety induction) in salience network (SN) areas, the insula especially, along with the anterior cingulate cortex, ventral striatum, and/or amygdala[59-66]. Analogously, anxiety in anxiety disorders (including specific phobia and social anxiety disorder, as well as posttraumatic stress disorder) is consistently associated with increased task-based activation mainly in the insula, along with the anterior cingulate cortex and/or amygdala (the brain activation pattern in specific phobia appears the most similar to that observed in anxiety in healthy subjects)[65-66]. Moreover, anxiety-related symptomatology and/or symptom provocation in obsessive-compulsive disorder and anorexia nervosa is consistently associated with increased task-based activation especially in the insula[67-69]. Interestingly, anxiety conditions, such as generalized anxiety disorder, are associated with increased interoceptive sensitivity and increased insula activation during interoception[70-71].

2. Dysphoria and euphoria
Dysphoria is characterized by increased pain-related affects. Dysphoria and pain-related states in healthy subjects, as it manifests in pain and sadness and the related depressive and irritable temperaments, are associated with increased ALFF and, more consistently, increased task-based activation in SN areas, the insula especially, along with anterior cingulate cortex and other related subcortical-cortical areas (prioritizing interoceptive information processing)[61, 72-75]. Coherently, depressive states (including dysphoria as core symptomatology) in MDD are associated with: increased ALFF, ReHo, FC, and CBF in the insula[31-32, 34, 75-76]; increased dominance (dwell time and persistence) of a CAP involving the insula (along with default-mode areas)[36]; and increased task-based activation in the insula especially (along with the anterior cingulate cortex) during affective processing[77-79]. However, conflicting results have been found in MDD, such as reduced

CBF, ReHo, and task-based activation in the insula[29, 80-81], potentially due to the heterogeneity of the MDD construct, which includes both dysphoric/anxious and anhedonic symptomatology with plausible opposite underpinnings in SN activity. Analogously, depressive states in BD are associated with increased ALFF in the insula[39]. Irritability in healthy subjects and various psychiatric disorders is associated with increased baseline activity and task-based activation mainly in the insula, anterior cingulate cortex, striatum, and amygdala[82]. Coherently, irritability in manic states of BD is associated with increased occurrence of a CAP involving SN areas[10]. Moreover, irritability (along with euphoria) in Alzheimer's disease is related to increased FC in the SN, involving insula and anterior cingulate cortex[83].
On the other hand, euphoria is characterized by increased pleasure-related affects. Euphoria and pleasure-related states in healthy subjects, as it manifests in states elicited by sexual and food-related stimuli, love, and happiness, are consistently associated with increased activation in SN areas, the insula especially, along with the anterior cingulate cortex, ventral striatum, and ventral tegmental area (as well as the orbitofrontal cortex, possibly involved in the processing of more abstract pleasure-related stimuli)[73, 84-87]. Coherently, manic states (including euphoria/irritability as core symptomatology) are associated with increased CMR/CBF mainly in the supragenual anterior cingulate cortex[88] and increased FC mainly between insula, striatum, and orbitofrontal cortex[89-92], along with increased task-based activation in related areas, such as the amygdala (especially) and insula, during affective processing[93-94]. Interestingly, a post-lesional manic state has been associated with increased CBF in the insula and inferolateral prefrontal cortex[95]. Euphoria and related states (e.g., rush/high) induced by substance administration (e.g., opioids, cannabis, alcohol, GHB, nicotine, or cocaine) in healthy subjects or addictive disorders are associated with increased activation, CMR, CBF, ALFF, FC, and/or time spent in SN areas, such as the insula, anterior cingulate cortex, and/or ventral striatum[52, 96-106]. Moreover, euphoria and related states induced by exposure to substance-related stimuli in addictive disorders (e.g., alcohol, nicotine, cocaine, heroin, or cannabis addiction) are associated with increased activation in the insula (especially), anterior cingulate cortex, frontal cortex, and basal ganglia, along with associative areas (e.g., posterior cingulate cortex and dorsolateral prefrontal cortex)[86-87, 107]. Interestingly, ecstatic seizures in epilepsy have been related to increased CBF (along with increased EEG activity) in the anterior insula[108].

3. Panic
Panic may represent the extreme pole of affective excitation, characterized by an anxiety attack of overwhelming intensity with increased body feelings and neurovegetative hyperactivation. Panic could represent a stereotyped response to cope with hazardous situations, such as suffocation[109]. Panic in panic disorder and other anxiety disorders is associated with increased CBF and activation (during provocative stimuli) in the insula (especially), anterior cingulate cortex, amygdala, and brainstem, as well as reduced gabaergic (inhibitory) transmission mainly in the insula (and other frontotemporal areas) and increased interoceptive sensitivity[110-112]. Interestingly, the occurrence of spontaneous panic attacks has been related to increased activation in the insula and amygdala especially[110-111, 113].

b) Affective inhibition

1. Anhedonia and analgesia
Anhedonia is characterized by a decreased experience of pleasure (often part of the loss of capacity to experience feelings and affective blunting). Subclinical anhedonia in healthy subjects is associated with decreased task-based activation in the insula, orbitofrontal cortex, and nucleus accumbens, as well as decreased task-based FC between these regions and the ventral tegmental area[114]. Anhedonia in MDD is associated with: decreased CMR in the insula and ventral striatum[115]; decreased FC between insula and fronto-parietal cortex, along with reduced FC between nucleus

accumbens, orbitofrontal cortex, and insula[116-118] (however, increased FC between nucleus accumbens and insula has been also detected[119]); decreased task-based FC between subgenual cingulate cortex, insula, orbitofrontal cortex, nucleus accumbens, and ventral tegmental area[120]; and, more consistently, decreased task-based activation mainly in the ventral striatum, insula, and anterior cingulate cortex (particularly for consummatory anhedonia)[121-124]. Interestingly, depressive states (notably when excluding anxious symptomatology) are related to reduced interoceptive sensitivity[70], and MDD has been associated with decreased insula activation during interoception (as well as increased resting-state FC of the insula with orbitofrontal cortex, amygdala, and default-mode areas)[125]. Coherently, depressive states (including anhedonia as core symptomatology) in MDD are associated with reduced CBF and ReHo in the insula[29, 80], along with reduced task-based activation in the ventral striatum during reward processing[126] and reduced activation in the insula and anterior cingulate cortex during affective and/or cognitive processing[81]. Similarly, anhedonia (specifically consummatory anhedonia) in SCZ is associated with decreased task-based activation mainly in the striatum and insula (albeit less robustly)[122, 124]. Anhedonia and related functional brain changes (mainly associated with depressive states) are supposed to depend on deficits in opioid and/or dopamine (ventral tegmental area-related) signaling (especially in the ventral striatum, insula, and/or orbitofrontal cortex)[123-124, 127-129].
On the other hand, analgesia is characterized by a decreased experience of pain. Analgesia is consistently associated with decreased activation in SN areas, the insula especially[130]. Moreover, analgesic effects (together with anxiolytic effects) can be induced by the use of substances like opioids (at high doses) or alcohol, which is associated with decreased activation and/or FC in SN areas, such as the insula, anterior cingulate cortex, and/or ventral striatum[52, 106, 131-134].

2. Apathy
Apathy is characterized by a severe decrease/lack of affects with loss of drive. Subclinical apathy in healthy subjects is associated with decreased task-based activation in the ventral striatum[135-136]. Apathy in SCZ is associated with decreased task-based activation in the ventral striatum, insula, and anterior cingulate cortex, as well as decreased FC between ventral tegmental area and insula[135-137]. Coherently, SCZ (including apathy as core symptomatology) is associated with reduced FC within the SN[45], as well as reduced task-based activation in the ventral striatum during reward processing[138-139] and reduced activation in the anterior cingulate cortex and insula (along with the striatum and amygdala/hippocampus) during affective processing[140-142]. However, conflicting results have been found in SCZ, such as increased ReHo and decreased/increased ALFF in the insula and/or anterior cingulate cortex (especially in the chronic stage)[42-43], as well as decreased/increased task-based activation in the striatum and amygdala/hippocampus and increased activation in the insula (especially in response to neutral stimuli)[143-144]. This inconsistency is potentially due to the heterogeneity of the SCZ construct (including negative and positive symptomatology) and differentiated alterations across its different stages. Apathy and related functional brain changes in SCZ are supposed to depend on deficits in dopamine (ventral tegmental area-related) signaling[135]. Moreover, the affective and behavioral deficits in frontotemporal dementia, including apathy and interoceptive deficit, are coherently and specifically associated with decreased CMR, FC, and ALFF in SN areas (especially the fronto-insular cortex)[145-148]. Coherently, deficits in interoception and affective processing, as well as a reduction in addictive behaviors and anergia, have been reported in subjects with focal lesions in the insula[149-151].

3. *Depersonalization*
Depersonalization (and related derealization) may represent the extreme pole of affective inhibition, characterized by the loss of body feeling and autonomic blunting with a related sense of disembodiment and detachment from reality[152]. Interestingly, depersonalization can be triggered in threatening situations and could represent an adaptive mechanism allowing the interaction with the dangerous external environment without the interference of overwhelming affects[153].

Depersonalization in depersonalization disorder is associated with reduced task-based activation in the anterior insula especially (and amygdala), as well as decreased ability to identify feelings and flattening of autonomic responses, during the processing of affective stimuli[152, 154-155].

3) Thought dimension and its neural correlates

a) Thought excitation

1. Mind-wandering

Mind-wandering is characterized by an increase of stimulus-independent ideas with changing contents (associated with a relative detachment from the current environment). Mind-wandering and related spontaneous thought processing, such as remembering and future thinking (along with reduced engagement in the current environment and increased behavioral stability), in healthy subjects are consistently associated with increased activation and increased FC (including dynamic FC variability) in default-mode network (DMN) areas, such as the perigenual anterior cingulate cortex/medial prefrontal cortex, posterior cingulate cortex/precuneus, temporoparietal junction/middle temporal gyrus, and parahippocampal gyrus[156-163]. More specifically, mind-wandering concerning mental time travel (thinking about past or future events) or future thinking is related to increased FC (coupling) between the medial prefrontal cortex/dorsal-medial prefrontal DMN subsystem and hippocampus/medial-temporal DMN subsystem[162-163]. Moreover, mind-wandering concerning future thinking (including planning and goal-directed thinking) is associated with additional activation in central executive network (CEN) areas, such as the dorsolateral prefrontal cortex[156-157]. Notably, mind-wandering is related to additional activation in sensory areas (possibly concerning specific thought contents), such as the insula (interoceptive contents), somatosensory cortex (exteroceptive somatic contents), and visual cortex (exteroceptive visual contents)[156], in turn showing increased FC with the DMN[161]. Mind-wandering is increased and associated with negative affects and anhedonia in MDD or anxiety disorders, correlating with increased FC between DMN and insula[164]. Mind-wandering is also increased and related to positive symptoms in SCZ, in turn associated with increased FC within the DMN (along with decreased FC within the SN and decreased FC between SN and DMN)[165]. Moreover, mind-wandering is increased in Parkinson's disease with hallucinations, correlating with increased FC between DMN and the visual cortex[166].

2. Repetitive thinking

Repetitive thinking is characterized by an increase of intrusive ideas with restricted and repetitive contents (associated with a substantial detachment from the current environment), as can occur in depressive rumination, worry and obsession, or craving. Repetitive thinking manifesting as depressive rumination (mainly repetitive thoughts on invariant contents, focused on past events, and usually associated with negative affects, along with a reduced affective response to environmental stimuli) in healthy subjects is consistently associated with increased task-based activation and altered FC of DMN areas, such as the perigenual anterior cingulate cortex/medial prefrontal cortex, posterior cingulate cortex/precuneus, temporoparietal junction/middle temporal gyrus, and parahippocampal gyrus[167-172]. More specifically, depressive rumination is associated with: activation in the DMN, especially the core subsystem (mainly comprising the medial prefrontal cortex, posterior cingulate cortex, and temporoparietal junction) and dorsal-medial prefrontal subsystem (mainly comprising the dorsomedial prefrontal cortex and temporal pole/middle temporal gyrus), rather than the medial-temporal subsystem (mainly comprising the retrosplenial cingulate cortex and parahippocampal areas)[168]; increased FC between core DMN areas (i.e., increased FC between the posterior cingulate cortex and perigenual anterior cingulate cortex), increased efficiency/node strength in the dorsal-medial prefrontal cortex within the DMN, increased

FC (coupling) between the core subsystem and medial-temporal subsystem of DMN, and decreased FC (decoupling) between the core subsystem and dorsal-medial prefrontal subsystem of DMN[169, 171-172]. Moreover, thought rumination is associated with additional activation in CEN areas, as well as the subgenual anterior cingulate cortex and insula (possibly concerning interoceptive contents/visceral responses) or visual cortex (possibly concerning exteroceptive contents)[167-168, 170]. Finally, thought rumination is related to increased FC between DMN and CEN[173], as well as increased dominance and occurrence of CAPs involving DMN areas and insula[36, 174]. Analogously, thought rumination (especially brooding) in MDD is associated with: altered/increased task-based activation in DMN areas, such as the medial prefrontal cortex, posterior cingulate cortex, middle temporal gyrus/temporoparietal junction, and parahippocampal gyrus (along with the subgenual anterior cingulate and dorsolateral prefrontal cortices)[167, 175]; altered/increased FC between core DMN areas (e.g., increased FC of the posterior cingulate cortex with the perigenual anterior cingulate cortex and temporoparietal junction, but decreased FC in the precuneus), increased FC in the medial prefrontal cortex/dorsal-medial prefrontal subsystem of DMN, and increased FC between the dorsal-medial prefrontal subsystem and medial-temporal subsystem of DMN[167, 172, 176-179]; increased dominance of the DMN over the CEN, as well as increased FC between DMN and CEN[173, 180]; and increased dynamic FC between DMN (medial prefrontal cortex) and insula, as well as increased dominance and occurrence of CAPs involving DMN areas and insula[36, 174, 181]. Coherently, depressive states (including thought rumination as typical symptomatology) in MDD may be associated with: increased CMR, CBF, ReHo, ALFF, and/or FC in DMN areas, converging in the medial prefrontal cortex/perigenual anterior cingulate cortex[29-31, 33-34, 182-183]; increased FC within the DMN, especially between medial prefrontal cortex, middle temporal gyrus, and hippocampal areas[184]; decreased dynamic FC (i.e., increased stable positive FC) within DMN areas (i.e., medial prefrontal cortex and parahippocampal areas)[181]; and increased dominance, transition, duration, and occurrence of CAPs involving DMN areas[36, 174, 185]. However, conflicting results have been found in MDD, such as the absence of changes, or decreased activity and/or FC within the DMN (especially in the early stage), possibly pointing toward the heterogeneity of the MDD construct again[186-189]. Analogously, depressive states in BD are related to an increase in neuronal variability, ALFF, global signal representation, ReHo, degree of centrality (DC), and FC within DMN regions, as well as increased occurrence and duration of a CAP involving DMN areas[5-7, 10, 39, 174, 190-191]. Repetitive thinking manifesting as worry in healthy subjects and various pathological conditions, including anxiety disorders (e.g., generalized anxiety disorder), is associated with increased/altered task-based activation in DMN and SN areas, including the prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, and insula, as well as altered FC within DMN areas (such as the perigenual anterior cingulate and posterior cingulate cortices)[64, 167]. Coherently, perseverative thinking and related obsessive symptomatology is associated with increased ReHo in DMN areas (subgenual/pregenual anterior cingulate cortex and middle temporal gyrus/temporal pole) and reduced ReHo in SMN areas[192], as well as increased task-based activation in DMN areas (perigenual anterior cingulate cortex/medial frontal cortex, posterior cingulate cortex/precuneus, and middle temporal gyrus) and SN areas[67-68]. Moreover, worry and related symptomatology in anorexia nervosa is associated with increased FC between DMN and SN areas (such as the posterior cingulate/precuneus and anterior cingulate cortex or insula)[193-194]. Repetitive thinking manifesting as craving in addictive disorders (e.g., alcohol, nicotine, cocaine, heroin, or cannabis addiction) is consistently associated with increased activation in DMN areas, such as the medial prefrontal cortex, posterior cingulate cortex, and middle temporal gyrus/temporoparietal junction (along with the dorsolateral prefrontal cortex, orbitofrontal cortex, and SN areas, such as the insula, anterior cingulate cortex, and ventral striatum), during exposure to substance-related stimuli[86-87, 195-198].

3. Psychosis

Psychosis may represent the extreme pole of thought excitation since it can be defined as an extreme dissociation of thought from the environment, as occurring in hallucinations and delusions.

Hallucinations are phenomenal experiences with high sensorial intensity (and considered real) occurring without corresponding environmental stimulation of the relevant sensory system (false perceptions). The experience of hallucinations in SCZ is associated (in state studies) with transient activation (modality specific) of the sensory cortices[47-48, 199-206]. In particular, the experience of auditory hallucinations is consistently associated with increased activation in the superior temporal gyrus (including the auditory cortex) especially, along with the postcentral/precentral gyrus, middle temporal gyrus, inferior parietal lobule/temporoparietal junction, inferior frontal gyrus, insula, anterior cingulate cortex, and hippocampus/parahippocampal gyrus[47-48, 199-206]. On the other hand, the experience of visual hallucinations is associated with increased activation in the occipito-temporo-parietal cortex, such as the cuneus, lingual/fusiform gyri, and precuneus (including the visual cortex)[201, 203]. Importantly, an activation in DMN areas (including the ventromedial prefrontal cortex), as well as a positive correlation between DMN and hallucination-related areas, has been detected during the period preceding the hallucinatory experience[203-204, 206]. Complementarily, proneness to hallucinations in SCZ is associated (in trait studies) mainly with increased connectivity (modality specific) of the sensory cortices and (relatively) increased activity/connectivity of the DMN[205, 207-229]. Thus, proneness to auditory hallucinations is associated mainly with increased connectivity of the auditory cortex and (relatively) increased activity/connectivity of the DMN[205, 207-218, 220-229]. In particular, auditory hallucination proneness is consistently associated with increased FC, global FC density, and FC distribution (possibly along with increased ALFF, CMR, and CBF) in the superior temporal gyrus; this includes increased FC (and/or decreased anti-correlation) of the superior temporal gyrus with SN areas (insula and anterior cingulate cortex) and DMN areas (medial prefrontal cortex, posterior DMN areas, and/or hippocampal complex); and such increased FC of the superior temporal gyrus specifically correlates with hallucinations[207-208, 210-212, 214-215, 218, 220-222, 224-229]. Moreover, auditory hallucination proneness is associated with increased CMR, CBF, and/or ALFF, along with increased FC, global FC density, and/or FC distribution, in DMN areas, i.e., middle temporal gyrus (especially), angular gyrus, medial prefrontal cortex, posterior cingulate cortex/precuneus, and hippocampus/parahippocampal gyrus; this includes increased/altered FC within DMN areas (such as increased FC of the medial prefrontal cortex and posterior cingulate cortex with the temporoparietal junction, as well as increased or decreased FC between medial prefrontal cortex and posterior cingulate cortex), increased FC (and decreased anti-correlation) of the DMN with SN areas (especially the insula), and increased FC (and decreased anti-correlation) of the DMN with CEN areas[205, 207-209, 212-218, 221-224, 228-229]. On the other hand, proneness to visual hallucinations (usually together with auditory hallucinations) is associated with increased connectivity/activity of the visual cortex and DMN areas, namely: increased FC between the occipital visual cortex and posterior cingulate cortex/precuneus, along with increased ALFF in the inferior temporal cortex (fusiform gyrus); increased ALFF in the middle temporal gyrus and hippocampus, along with increased FC between the medial prefrontal cortex and hippocampus[210, 217, 219]. Finally, proneness to hallucinations in SCZ is associated with deficits in the sensory systems (and related perception)[47-49, 230]. In particular, auditory hallucination proneness is consistently associated with reduced activation (and FC) in the superior temporal gyrus/auditory cortex during exteroceptive auditory stimulation[47-49, 231] (while visual hallucination proneness might be associated with visual processing deficits and retinopathy[230]). Analogously, proneness to auditory hallucinations in BD, especially during the depressive state, is associated mainly with increased FC and global FC density in the superior temporal gyrus and DMN areas (e.g., posterior cingulate cortex and parieto-temporal cortex)[225-226, 232]. Moreover, proneness to auditory hallucinations in MDD during the depressive state is associated mainly with increased global FC density in the superior temporal gyrus, along with hippocampus and cingulate cortex (but decreased FC density in post/precentral gyrus, occipital cortex, and insula)[233].

Delusions are fixed ideas that are not amenable to change through experience or reasoning (false beliefs). Delusions in SCZ (and other related psychotic disorders) are associated mainly with increased connectivity and activity in DMN areas, especially consistent in the medial (dorsal)

prefrontal cortex, namely: increased ReHo in the dorsomedial prefrontal cortex[234]; increased task-based activation in the medial (dorsal and/or ventral) prefrontal cortex and posterior cingulate cortex, along with increased or decreased activation in the middle temporal gyrus/temporoparietal junction, during the processing of self-referential, persecutory, and theory of mind-related stimuli (mainly relating to delusions of reference and persecution)[235-241]; increased task-based CBF in the temporoparietal junction (angular gyrus) during volitional processing (mainly relating to delusions of control)[242-243]; and increased task-based activation mainly in the medial prefrontal cortex and middle temporal gyrus/temporoparietal junction during cognitive processing (e.g., in relation to alterations in evidence integration and prediction error)[244-246]. Moreover, delusions in SCZ are also associated with altered activity in SN areas, namely: increased task-based activation in the insula, supragenual anterior cingulate cortex, and ventral striatum during the processing of self-referential and persecutory stimuli (relating to delusions of reference and persecution)[236, 238-239]; increased task-based activation in the insula and supragenual anterior cingulate cortex during the processing of non-salient (neutral or irrelevant) stimuli[238, 246]; and decreased task-based activation in the insula and supragenual anterior cingulate cortex during the processing of unspecifically salient (rewarding or aversive) stimuli[238-240]. Finally, delusions in SCZ are associated with decreased activity and connectivity in CEN areas, i.e., decreased task-based activation (and FC) in the dorsolateral prefrontal cortex (and posterior parietal cortex) during working memory and cognitive processing (in relation to reduced information updating, evidence integration, and prediction error)[240, 244, 246-248]. Interestingly, the experience of psychotic symptomatology can be induced by ketamine administration, which is related to a reduction of glutamate signaling via NMDA receptor antagonism onto GABA neurons (potentially associated with an increase in serotonin signaling, especially, and dopamine signaling) and increased FC in DMN/CEN areas (including the medial prefrontal cortex and dorsolateral prefrontal cortex), SN areas (including the insular cortex), and SMN areas (including the visual, auditory, and somatosensory/motor cortices)[249-250].

b) Thought inhibition

1. Attention deficit

Attention deficit can be defined as a reduction of focused ideas that are excessively deviated by external or internal environmental stimuli. Attention deficit represents a core symptom in attention-deficit/hyperactivity disorder, which is associated with reduced FC within the DMN[251] and decreased task-based activation in the CEN especially (and DMN)[4]. Manic states in BD typically show attention deficit like distractibility (attention deviated by external environmental stimuli) and are associated with decreased FC, along with reduced neuronal variability, ReHo, and DC, in the DMN (with the reduction of DMN DC specifically correlating with thought disturbances like distractibility)[5-6, 191, 252-254]. Coherently, manic states can also be induced by focal brain lesions causing FC deficits in associative cortices, such as the orbitofrontal cortex, temporal cortex, and/or other DMN/CEN areas[255]. Moreover, depressive states may show attention deficit (e.g., attention deviated by internal environmental stimuli or general decrease of attention) and can be associated with reduced ALFF and ReHo in the prefrontal areas of DMN and CEN (along with increased ReHo in the insula/interoceptive areas and decreased ReHo in the occipital cortex/exteroceptive areas), especially in the early stage of MDD[188-189].

2. Cognitive deficit

Cognitive deficit can be defined as a severe reduction/impoverishment of ideas and their associative patterns (manifesting in deficits of memory, anticipation, abstract thinking, language, and executive functions). Cognitive deficits represent a core domain of SCZ, which is consistently related to functional alterations of the DMN and CEN, especially detectable in the chronic stage of illness, including: decreased ALFF, ReHo, CMR, and/or CBF in DMN areas, such as the medial prefrontal cortex, posterior cingulate cortex/precuneus, inferior parietal lobule, and hippocampus[29, 43];

decreased FC within the DMN, especially in the precuneus/posterior cingulate cortex and medial prefrontal cortex (specifically correlating with disordered thought and attention deficit), and decreased FC of the thalamus (and basal ganglia) with CEN and DMN areas, such as the middle frontal gyrus, anterior cingulate cortex, posterior cingulate cortex, and inferior parietal lobule/angular gyrus, mainly in the chronic stage (while increased FC in DMN/CEN areas, such as the middle frontal gyrus, medial prefrontal cortex, precuneus/posterior cingulate cortex, angular gyrus, and middle temporal gyrus, during the early stage)[29, 44-45, 183, 256-257]; decreased task-based activation in DMN areas, such as the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobule/temporoparietal junction (possibly along with the insula), during cognitive processing especially concerning theory of mind-related stimuli (along with increased activation in CEN areas, such as the posterior parietal cortex (mainly) and dorsolateral prefrontal cortex, potentially representing a compensatory response)[141, 258-260]; and decreased task-based activation in CEN areas, such as the dorsolateral prefrontal cortex (mainly) and posterior parietal cortex (possibly along with the insula/claustrum), during cognitive processing especially concerning executive, memory, and attention-related functions (along with increased activation in DMN areas, such as the medial prefrontal cortex and posterior cingulate cortex, during working memory processing, potentially representing a compensatory response)[260-265]. Cognitive deficits can also characterize the acute phase of substance use, and substance administration (e.g., opioids, alcohol, LSD, and cannabis) is associated with reduced FC, ALFF, ReHo, and/or activation in DMN areas, such as the posterior cingulate cortex, medial prefrontal cortex, and/or superior frontal gyrus[52, 98, 198, 266-267]. Moreover, cognitive deficits like reduced mind-wandering are related to focal brain lesions causing FC deficits in the DMN (and CEN)[268]. Analogously, cognitive deficits in Parkinson's disease are associated with functional deficits in the posterior DMN, i.e., reduced CMR in areas mainly connected with the middle temporal gyrus/temporoparietal junction (in mild cognitive impairment) and hippocampus (in dementia)[269]. Importantly, cognitive deficits define dementias such as Alzheimer's disease, which is consistently associated with functional deficits in the posterior DMN, including: reduced CMR and CBF in areas mainly connected with the posterior cingulate cortex/precuneus, temporoparietal junction, and parahippocampal areas; reduced FC mainly in the posterior cingulate cortex/precuneus and parahippocampal areas (along with the raphe nuclei); and reduced task-based activation mainly in the posterior cingulate cortex during cognitive processing[146, 270-271].

3. Loss of consciousness

Loss of consciousness may represent the extreme pole of thought inhibition since it can be defined as a complete (or almost complete) abolishment of thought (with the behavior, and potentially the phenomenal experience, if any, reduced to elemental sensorimotor reflexes). Loss of consciousness in slow-wave sleep and general anesthesia has been preliminarily related to reduced CMR in the associative frontal, parieto-temporal, and posterior cingulate areas, mainly belonging to the DMN[272]. Analogously, loss of consciousness as manifests in epilepsy is related to decreased FC within DMN areas (medial prefrontal cortex and posterior DMN areas) during generalized seizures[273] or decreased CBF in similar associative cortices (medial prefrontal cortex, posterior cingulate cortex, temporoparietal junction, and dorsolateral prefrontal cortex) during complex partial temporal lobe seizures[274]. Finally, loss of consciousness characterizes the disorders of consciousness, such as minimally conscious states and vegetative states, which are consistently associated with decreased activity (ALFF, FC, DC, ReHo, CMR, and/or CBF) in DMN areas, i.e., posterior cingulate cortex/precuneus, middle temporal gyrus, middle frontal gyrus, and dorsomedial nucleus of thalamus[275]. Importantly, loss of consciousness during general anesthesia and disorders of consciousness has been recently associated with a degradation of the sensorimotor-to-transmodal gradient (principal connectivity gradient) of cortical organization, along with shortened network distance of the DMN with SN and dorsal attention network and a related decreased occurrence of CAPs involving DMN (and dorsal attention network) areas (suggesting a degradation of the

functional differentiation of the associative areas from the sensorimotor areas and corresponding breakdown of the hierarchical processing from sensory inputs to abstract contents)[50].

B) Three-dimensional model of neural activity and phenomenal-behavioral patterns: application to neuropsychiatric disorders

The proposed working model may represent a coherent framework to investigate the relationship of neural activity with phenomenal experience and behavioral patterns in psychopathology across different neuropsychiatric disorders.

1) Pathological changes of neural activity/structure in local areas within the external, internal, or associative neural units

Anxiety disorders and addictive disorders could be mainly characterized by pathological changes in specific clusters of neuronal associations within the associative neural unit, manifesting in corresponding pathological ideas. In particular, once formed, such pathological clusters of neuronal associations could be characterized by minimal changeability by environmental stimuli, manifesting in fixed ideas and corresponding maladaptive phenomenal-behavioral patterns. Anxiety disorders, along with other disorders such as obsessive-compulsive disorder and anorexia nervosa, are consistently associated with increased stimulus-induced activation in associative (e.g., DMN) areas, along with insular and sensory areas, during provocation of specific pain-related symptomatology[65-69]. Accordingly, these disorders could be primarily associated with pathological clusters of neuronal associations in the associative neural unit (driving related activations in the internal/external neural units), manifesting in fixed ideas with pain-like components driving compulsive behaviors (e.g., phobias). Analogously, addictive disorders are consistently associated with increased stimulus-induced activation in associative (e.g., DMN) areas, along with insular and sensory areas, during provocation of specific pleasure-related symptomatology[86-87]. Accordingly, these disorders could be primarily associated with pathological clusters of neuronal associations in the associative neural unit (driving related activations in the internal/external neural units), manifesting in fixed ideas with pleasure-like components driving impulsive behaviors (e.g., craving).
On the other hand, various disorders (e.g., focal brain lesions) can be associated with a local damage in areas of the external, internal, or associative neural units, manifesting in a corresponding loss of (clusters of) exteroceptions-somatomotor responses, interoceptions-autonomic responses, or ideas.

2) Pathological reconfigurations of intrinsic neural activity across the external, internal, and associative neural units

Major psychiatric disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ), could be mainly characterized by pathological reconfigurations of the functional architecture of intrinsic neural activity across the external, internal, and associative neural units, manifesting in corresponding pathological changes in the expression of the phenomenal-behavioral patterns across psychomotricity, affectivity, and thought. In particular, heterogeneous disease-related alterations could induce pathological changes in transmitter signaling, subcortical-cortical coupling, and cortical network activity, which may lead to a re-setting of the pre-existing baseline in intrinsic neural activity and phenomenal-behavioral pattern of the individual. Thus, the predominant neural state and related activity of the neural units can change and/or become abnormally represented in duration and/or intensity (with respect to the pre-existing baseline), manifesting in abnormal expression (in duration and/or intensity) of the corresponding phenomenal-behavioral state and related dimensions (i.e., symptoms). Accordingly, this results in a

diminished adaptability of neural activity and related phenomenal-behavioral patterns to the changing environment.

Major depressive disorder

MDD has been consistently associated with: chronic low-grade inflammation (e.g., increase in pro-inflammatory mediators)[276-278]; atrophy of gray matter in SN areas, i.e., insula and anterior cingulate cortex[279]; and increased intrinsic activity in the SN, along with decreased activity in the SMN and altered activity in the DMN/CEN (decreased activity in the early stage, while increased activity in the chronic stage)[280].

The inflammatory signaling, which represents a key component of the interoceptive signaling[281], may induce changes in: brain activity, e.g., directly increasing the activity in the insula and anterior cingulate cortex[282-284]; brain structure, e.g., altering the structure of the insula[285]; and neurotransmitter signaling, e.g., decreasing the dopamine and serotonin availability[282, 286-287]. Accordingly, MDD could be associated with an immune dysregulation characterized by chronic low-grade inflammation that induces alterations in the insula and a related reconfiguration of the functional architecture of intrinsic neural activity, primarily resulting in a tilting of the network balance toward the SN (at the expense of the SMN).

Thus, in our model, depressive symptomatology in MDD is primarily associated with hyperactivity of the internal neural unit (e.g., increased intrinsic activity in the SN), manifesting in affective excitation (increased expression of interoceptions and visceromotor/autonomic responses, e.g., anxiety and dysphoria). This corresponds to an overtuning of neural activity and phenomenal-behavioral pattern to the current internal/body environment. Additional alterations in the external and associative neural units may manifest in additional alterations in the psychomotor and thought dimensions. In particular, hypoactivity of the external neural unit (e.g., decreased intrinsic activity in the SMN) may manifest in psychomotor inhibition (decreased expression of exteroceptions and somatomotor responses, e.g., psychomotor retardation). On the other hand, hypoactivity of the associative neural unit (e.g., decreased intrinsic activity in the DMN and CEN, mainly occurring in the early stage) may manifest in thought inhibition (decreased expression of ideas, e.g., attention deficit). Conversely, hyperactivity of the associative neural unit (e.g., increased intrinsic activity in the DMN and CEN, mainly occurring in the chronic stage) may manifest in thought excitation (increased expression of ideas, which may have strong interoceptive-like components, e.g., repetitive thinking with anxiety/dysphoria-like experiences, like depressive ruminations). Such dimensional alterations can combine, characterizing different psychopathological states. In particular, the hyperactivity of the internal neural unit may be associated with external neural unit hypoactivity and associative neural unit hypoactivity, manifesting in affective excitation along with psychomotor inhibition and thought inhibition (e.g., anxiety/dysphoria along with psychomotor retardation and attention deficit), in the typical depressive state during the early stage of MDD. Moreover, the hyperactivity of the internal neural unit can also be associated with external neural unit hypoactivity and associative neural unit hyperactivity, manifesting in affective excitation along with psychomotor inhibition and thought excitation (e.g., anxiety/dysphoria along with psychomotor retardation and depressive ruminations), in the depressive state during the chronic stage of MDD.

Bipolar disorder

BD has been consistently associated with: chronic low-grade inflammation (e.g., increase in pro-inflammatory mediators)[288-289]; alterations of white matter (since the early stage), especially in the tracts of the limbic system, such as the fornix and the cingulum[290-291]; atrophy of gray matter in SN areas, i.e., insula and anterior cingulate cortex[279, 291-292]; and increased intrinsic activity in the SMN along with decreased intrinsic activity in the DMN during mania, while decreased intrinsic activity in the SMN along with increased intrinsic activity in the DMN during depression[293-294].

According to our recently proposed model, BD is associated with chronic low-grade inflammation and immune dysregulation that induce (together with functional/structural alterations in the insula and related areas) additional white matter damage in the limbic network (including the fornix and cingulum), thus destabilizing the neurotransmitter signaling, such as dopamine and serotonin signaling[294]. Changes in such neurotransmitter signaling (potentially triggered by heterogeneous stressors onto a structurally-damaged limbic network) lead to phasic (and often recurrent) reconfigurations of the functional architecture of intrinsic neural activity[294]. This may typically result in a tilting of the network balance toward the SMN (at the expense of the DMN) during the manic states and toward the DMN (at the expense of the SMN) during the depressive states[293-294]. However, different combinations of changes in neurotransmitter signaling could induce different coupling and balancing between networks (such as the SMN, SN, and DMN), characterizing the different manic, depressive, and mixed states of BD[293-294]. Finally, each pathological state could be prone to switch into the opposite mirror-like state (e.g., via compensatory up/down-regulation of neurotransmitter receptors/transporters), resulting in the typical bipolar cycle of BD[294].

Thus, in our model, the core manic symptomatology in BD is primarily associated with hyperactivity of the external neural unit (e.g., increased intrinsic activity in the SMN), manifesting in psychomotor excitation (increased expression of exteroceptions and somatomotor responses, e.g., psychomotor hyperactivity). This corresponds to an overtuning of neural activity and phenomenal-behavioral pattern to the current external environment. Conversely, the core depressive symptomatology in BD is primarily associated with hypoactivity of the external neural unit (e.g., decreased intrinsic activity in the SMN), manifesting in psychomotor inhibition (decreased expression of exteroceptions and somatomotor responses, e.g., psychomotor retardation). This corresponds to a detuning of neural activity and phenomenal-behavioral pattern from the current external environment. Additional alterations in the internal and associative neural units may manifest in additional alterations in the affective and thought dimensions. In particular, hyperactivity of the internal neural unit (e.g., increased SN activity) may manifest in affective excitation (increased expression of interoceptions and visceromotor/autonomic responses, e.g., anxiety and euphoria and/or dysphoria). In contrast, hypoactivity of the internal neural unit (e.g., decreased SN activity) may manifest in affective inhibition (decreased expression of interoceptions and visceromotor/autonomic responses, e.g., anhedonia and apathy). On the other hand, hypoactivity of the associative neural unit (e.g., decreased DMN activity) may manifest in thought inhibition (decreased expression of ideas, e.g., attention deficit). In contrast, hyperactivity of the associative neural unit (e.g., increased DMN activity) may manifest in thought excitation (increased expression of ideas, which may have strong interoceptive-like components, e.g., mind-wandering or repetitive thinking, possibly with anxiety/dysphoria/euphoria-like experiences, like flight of ideas or ruminations). Such dimensional alterations can combine, characterizing the different manic, depressive, and mixed states. In particular, the hyperactivity of the external neural unit may be associated with internal neural unit hyperactivity and associative neural unit hypoactivity, manifesting in psychomotor excitation along with affective excitation and thought inhibition (e.g., psychomotor hyperactivity along with anxiety/euphoria/dysphoria and attention deficit), in the typical manic state of BD. Conversely, the hypoactivity of the external neural unit may be associated with internal neural unit hypoactivity and associative neural unit hyperactivity, manifesting in psychomotor inhibition along with affective inhibition and thought excitation (e.g., psychomotor retardation along with anhedonia/apathy and repetitive thinking with anxiety/dysphoria-like experiences), in the typical depressive state of BD. However, the hyperactivity of the external neural unit could also be associated with hyperactivity of the internal and associative neural units, manifesting in global excitation of psychomotricity, affectivity, and thought, in another potential manic state, while the hypoactivity of the external neural unit could also be associated with hypoactivity of the internal and associative neural units, manifesting in global inhibition of psychomotricity, affectivity, and thought, in another potential depressive state. Moreover, hyper/hypoactivity of the external and internal neural units can dissociate (and combine

with hyper/hypoactivity of the associative neural unit) manifesting in counter-polar alterations in psychomotricity and affectivity (associated with alterations of thought) in the various mixed states of BD. Finally, extreme alterations in the activity of the external, internal, and associative neural units can manifest in extreme alterations in psychomotricity, affectivity, and thought (e.g., catatonia, panic or depersonalization, and psychosis or cognitive deficit).

Schizophrenia

SCZ has been consistently associated with inflammatory changes, structural white/gray matter damage, and brain activity alterations. In particular, SCZ is associated with chronic low-grade inflammation (e.g., increase in pro-inflammatory mediators)[295-297]. Moreover, SCZ is associated with alterations of white matter, especially in the tracts of the limbic system (such as the fornix and the cingulum)[290]. Importantly, SCZ is associated with: atrophy of gray matter in SN areas (insula and anterior cingulate cortex), along with SMN areas (postcentral/precentral gyri and superior temporal gyrus) and limbic network areas (orbitofrontal cortex and hippocampus/amygdala complex), during the early stage; and additional atrophy of gray matter in the basal ganglia and thalamus (especially the pulvinar and dorsomedial nucleus), possibly along with their connected cortices in the DMN/CEN, during the chronic stage (as well as neurodevelopmental alterations in brain structure)[279, 298-303]. Finally, SCZ is associated with: decreased intrinsic activity in SMN areas (e.g., superior temporal gyrus and postcentral gyrus) and altered activity in SN areas, along with relatively increased activity (and connectivity) of DMN/CEN areas, mainly during the early stage and psychotic states; while decreased intrinsic connectivity of the thalamus with DMN/CEN areas (along with dysconnectivity of the thalamus with SMN areas) and decreased intrinsic activity in DMN/CEN areas, mainly during the chronic stage[29, 42-45, 183, 228-229, 257, 304].

Accordingly, SCZ could be associated with chronic low-grade inflammation and immune dysregulation (possibly associated with neurodevelopmental alterations) that induce (together with functional/structural alterations in the insula and related areas and white matter damage in the limbic network tracts like fornix and cingulum) additional gray matter damage in sensory cortices, such as the superior temporal gyrus and postcentral gyrus (nearby the insula), in the early stage, as well as in subcortical structures, such as the thalamus, in the chronic stage. Thus, in the early stage and psychotic states, changes in the neurotransmitter (dopamine/serotonin) signaling (potentially triggered by heterogeneous stressors onto a structurally-damaged limbic network) could induce reconfigurations of the functional architecture of intrinsic neural activity that occur onto structurally-damaged sensory (and insular) cortices, leading to a relative increase in intrinsic activity/connectivity of DMN areas associated with deficits of the sensory systems[42, 44, 47, 49, 228-229, 298, 301, 304]. In particular, DMN hyperactivity (in relation to sensory deficits) may be associated with delusions, while DMN hyperactivity driving transient activations of (modality-specific) sensory cortices (in relation to sensory deficits) may be associated with hallucinations (e.g., activation in the superior temporal gyrus/auditory areas during auditory hallucinations, or activation in the occipital cortex/visual areas during visual hallucinations)[47, 49, 201, 204, 206, 228-229, 301, 304]. On the other hand, in the chronic stage, the additional structural damage of the thalamus may lead to its functional disconnection and related decrease of intrinsic activity in DMN areas, which could be associated with the progressive (and mostly irreversible) emergence of cognitive deficits[43-44, 256, 258, 298].

Thus, in our model, psychotic symptomatology in SCZ is primarily associated with extreme hyperactivity of the associative neural unit relative to hypoactivity of the external/internal neural units (e.g., increased intrinsic activity in the DMN relative to deficits of the sensory systems, typically occurring in the early stage and psychotic states). This manifests in extreme excitation of thought, corresponding to hallucinations and delusions, i.e., increased expression of ideas composed of exteroceptive-like and interoceptive-like components showing: abnormally increased phenomenal intensity, in relation to decreased phenomenal intensity of perceptions (so that such ideas show an intensity indistinguishable from perceptions' and thus are considered related to the current environment, i.e., subjectively real); and minimal changeability by environmental stimuli

(so that such ideas are fixed). This corresponds to an extreme dissociation of neural activity and phenomenal-behavioral pattern from the current environment. Conversely, cognitive deficits in SCZ are primarily associated with severe hypoactivity of the associative neural unit (e.g., decreased intrinsic activity in the DMN, typically occurring in the chronic stage), manifesting in severe inhibition of thought (decreased expression of ideas and their complexity). This corresponds to a severe inability to purposefully detach neural activity and phenomenal-behavioral pattern from the current environment. Moreover, the alterations in the external and internal neural units may manifest in additional alterations in the psychomotor and affective dimensions. In particular, hypoactivity of the external neural unit (e.g., decreased SMN activity) may manifest in psychomotor inhibition (decreased expression of exteroceptions and somatomotor responses, e.g., psychomotor retardation and hypokinesia, up to catatonia). On the other hand, hypoactivity of the internal neural unit (e.g., decreased SN activity) may manifest in affective inhibition (decreased expression of interoceptions and visceromotor/autonomic responses, e.g., anhedonia and apathy, up to depersonalization). Such dimensional alterations can combine, characterizing different psychopathological states. In particular, the extreme hyperactivity of the associative neural unit may be associated with external neural unit hypoactivity and internal neural unit hypoactivity, manifesting in extreme thought excitation along with psychomotor inhibition and affective inhibition (e.g., psychosis along with psychomotor retardation/hypokinesia/catatonia and anhedonia/apathy/depersonalization), in the typical psychotic state during the early stage of SCZ. Additionally, the extreme hyperactivity of the associative neural unit could also be transiently associated with external and/or internal neural unit hyperactivity, manifesting in extreme thought excitation along with psychomotor and/or affective excitation, in other (transient) psychotic states in the early stage. Finally, a severe hypoactivity of the associative neural unit may occur and associate with external/internal neural unit hypoactivity, manifesting in severe thought inhibition along with psychomotor/affective inhibition (e.g., cognitive deficit along with psychomotor retardation/hypokinesia/catatonia and anhedonia/apathy/depersonalization), in the chronic stage of SCZ.

Analogously to SCZ, BD with psychotic features could be associated with additional gray matter damage in regions including the superior temporal gyrus, while BD with cognitive deficits could be associated with additional gray matter damage in associative cortices[305-307]. Thus, in BD (analogously to SCZ), psychotic symptomatology may be associated with extreme hyperactivity of the associative neural unit (relative to hypoactivity of the external/internal neural units), manifesting in extreme excitation of thought, while cognitive deficit may be associated with severe hypoactivity of the associative neural unit, manifesting in severe inhibition of thought.

Other disorders

Parkinson's disease is related to a deficit in dopamine (substantia nigra-related and retinal) signaling that may lead to a functional reconfiguration of intrinsic neural activity resulting in decreased SMN activity, along with increased DMN activity[53-55]. In particular, SMN hypoactivity may be associated with hypokinesia, while DMN hyperactivity driving transient activations of the occipital cortex/visual areas (in relation to deficits in the visual system) may be associated with visual hallucinations[53, 55, 308-310]. Accordingly, Parkinson's disease may be primarily associated with severe hypoactivity of the external neural unit, manifesting in severe inhibition of psychomotricity (hypokinesia), which possibly leads to extreme hyperactivity of the associative neural unit (relative to external neural unit hypoactivity), manifesting in extreme excitation of thought (visual hallucinations). Conversely, Tourette syndrome may be associated with a functional reconfiguration of intrinsic neural activity resulting in increased SMN activity[15-16]. Accordingly, Tourette syndrome may be primarily associated with severe hyperactivity of the external neural unit, manifesting in severe excitation of psychomotricity (hyperkinesia).

3) Pathological changes of neural structure in the external, internal, and/or associative neural units

Dementia could be mainly characterized by pathological changes of neural structure in the external, internal, and associative neural units, manifesting in corresponding pathological deficits in the phenomenal-behavioral patterns of psychomotricity, affectivity, and thought. In particular, different dementia groups are associated with gray matter atrophy that specifically maps onto (or mirrors the topography of) the different neural units, manifesting in a progressive (and irreversible) reduction of expression (e.g., complexity) of the corresponding phenomenal-behavioral dimension. Corticobasal syndrome is consistently associated with gray matter loss in SMN areas (especially primary and secondary sensorimotor cortices)[271, 311]. Accordingly, this syndrome may be primarily associated with a progressive hypoactivity of the external neural unit, manifesting in a progressive deficit in the psychomotor dimension (decreased expression of exteroceptions and somatomotor responses, e.g., hypokinesia). The behavioral variant of frontotemporal dementia is consistently associated with gray matter loss in SN areas (especially the fronto-insular cortex, orbitofrontal cortex, and anterior cingulate cortex)[271, 311]. Accordingly, this syndrome may be primarily associated with a progressive hypoactivity of the internal neural unit, manifesting in a progressive deficit in the affective dimension (decreased expression of interoceptions and visceromotor/autonomic responses, e.g., apathy). Finally, Alzheimer's disease is consistently associated with gray matter loss (and beta-amyloid deposition) in DMN areas (especially the posterior cingulate cortex/precuneus, temporoparietal junction, and medial temporal areas)[271, 311-312]. Accordingly, this syndrome may be primarily associated with a progressive hypoactivity of the associative neural unit, manifesting in a progressive deficit in the thought dimension (decreased expression of ideas, e.g., cognitive deficit).

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