BRAIN ANOMALIES IN EARLY PSYCHOSIS: FROM SECONDARY TO PRIMARY PSYCHOSIS

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ABSTRACT

Brain anomalies are frequently found in early psychoses. Although they may remain undetected for many years, their interpretation is critical for differential diagnosis. In secondary psychoses, their identification may allow specific management. They may also shed light on various pathophysiological aspects of primary psychoses. Here we reviewed cases of secondary psychoses associated with brain anomalies, reported over a 20-year period in adolescents and young adults aged 13 to 30 years old. We considered age at first psychotic symptoms, relevant medical history, the nature of psychiatric symptoms, clinical red flags, the nature of the brain anomaly reported, and the underlying disease. We discuss the relevance of each brain area in light of normal brain function, recent case-control studies, and postulated pathophysiology. We show that anomalies in all regions, whether diffuse, multifocal, or highly localized, may lead to psychosis, without necessarily being associated with non-psychiatric symptoms. This underlines the interest of neuroimaging in the initial workup, and supports the hypothesis of psychosis as a global network dysfunction that involves many different regions.

KEYWORDS

Primary and secondary early psychoses
Brain anomalies
Neuroimaging
Pathophysiology

CONTENTS

INTRODUCTION

Neuroimaging has become essential in psychosis' assessment, both in clinics and in research, but the relevance of morphological brain anomalies in psychosis constitutes a challenge for clinicians and neuroscientists alike (Schmidt and Borgwardt 2020).
From a clinician's perspective, as there is no psychotic symptom specific to any primary schizophrenia spectrum disorder (Bergsholm 2016), it is crucial during differential diagnosis to consider brain anomalies that could constitute non-psychiatric causes of psychosis. Such cases would then be defined as secondary psychosis (Keshavan and Kaneko 2013). Nevertheless, it is difficult to attribute the causality of psychosis to any particular lesion, as many can also be incidental, or aggravative on a brain already vulnerable to psychosis, following a multiple hit model (Davis et al. 2016). Brain lesions could also occur as a consequence of a pre-existing primary psychotic disorder. This is exemplified by the increased rates of head injury among patients with mental disorders (David et al. 2014), and toxic-related brain injury in a population where substance-use disorder is very frequent (Hunt et al. 2018). This difficulty in disentangling primary psychoses, secondary ones, and incidental findings, is heightened by their frequencies. First, psychotic spectrum disorders, and subthreshold psychotic symptoms with clinical distress, are very prevalent in the general population - 3 and 4 % respectively (van Os et al. 2009). Second, estimates of secondary psychosis' prevalence may range from 3 % in adolescents and adults with first-episode psychosis (Johnstone, MacMillan, and Crow 1987), to around 10 % in children and adolescents (Giannitelli et al. 2018). Many conditions show particularly elevated prevalences of psychosis : traumatic brain injury (9 %), systemic lupus erythematosus (11 %), stroke (4 %), multiple sclerosis (4 %), or epilepsy (6 %) (Keshavan and Kaneko 2013; Hilger et al. 2016). Third, incidental radiological findings are also very frequent, ranging in healthy or asymptomatic subjects from 2.7 to 12 % prevalence (Morris et al. 2009; Sommer 2013; R. E. Gur et al. 2013). Moreover, an important rate of clinically-relevant abnormal findings in individuals with psychosis may still not be considered a substrate for secondary psychosis and do not lead to therapeutic modifications (Endres et al. 2020; Falkenberg et al. 2017; Borgwardt 2006).

From a neurobiological perspective, the frequent structural brain anomalies found in psychosis could also improve our understanding of pathophysiology and provide useful biomarkers of disease risk or progression in primary psychotic disorders. Schizophrenia-spectrum disorders

are associated with abnormal neurodevelopmental trajectories in adolescence and early adulthood (Driver 2020; McCutcheon, Reis Marques, and Howes 2019). This time frame is critical because although the overall brain volume remains stable, it undergoes important gray and white matter structural changes corresponding to the last phases of brain maturation : i) synaptic pruning, ii) axonal myelination, and iii) interneuron maturation (Marín 2016). This leads to improved functional network segregation and efficiency (Gilmore, Knickmeyer, and Gao 2018). Dysregulation in brain connectivity patterns is well-known in psychosis (Uhlhaas and Singer 2010) and might be underpinned by many morphologic changes, both cortical and subcortical, which are reported in antipsychotic-naïve patients in early stages of disease, from at-risk-mental state to first episode psychosis, and early-stage schizophrenia. They can be distinguished into fixed “trait” anomalies, possibly neurodevelopmentally-related (such as cortical folding or midline anomalies), and dynamic “state” ones, occurring during disease progression (such as cortical gray matter decreases in fronto-temporo-limbic regions) (Takahashi and Suzuki 2018). However, despite robust group-level differences in case-control studies, the heterogeneity of anomalies in healthy controls and subjects with psychosis only allows such designs to identify small average effect-size changes at population level that are not necessarily relevant at individual level (Wolfers et al. 2021; 2018). Conversely, more uncommon causes of psychosis, such as temporal lobe epilepsy, 22q11 syndrome, or NMDAR encephalitis, can illustrate specific aspects of psychosis’ pathophysiology (Keshavan and Kaneko 2013). Since etiologically-based psychotic syndromes may offer an easier grasp on pathophysiology, they could enhance our understanding of psychotic syndromes without known etiology (Fraguas et al. 2017).

Therefore, we propose an approach similar to the genetic models of psychosis that consider genetic risk to include both very rare mutations with strong Mendelian effect-size expression, and frequent mutations with small effect-sizes (Sullivan, Daly, and O’Donovan 2012). We propose to distinguish in this review brain morphological anomalies in two categories : 1) well-identified neurological lesions with a possible strong pathophysiological determinism at individual level that may be linked to psychotic symptoms, as seen in secondary psychoses; and 2) frequent abnormalities, significant at population level in case-control studies, but with a small effect-size at individual level, as found in primary psychoses. While we do not suggest brain lesions in secondary psychoses can be used as phrenologic models to explain all aspects of complex multifactorial and heterogeneous syndromes such as schizophrenia, we believe primary psychosis may share common ground with psychotic syndromes due to other medical

conditions - so that rare etiologically-based manifestations of psychosis can shed light on the more common idiopathic ones.

Here, we present an extensive review of brain lesions clinically-relevant for early psychosis, reported over the course of 20 years. Our primary aim is to provide the clinician with support for the interpretation of brain anomalies during early psychosis' differential diagnosis, by providing a dictionary of causative or comorbid brain lesions co-occurring with psychotic symptomatology, and classified by general region and disease type (**Supplementary Tables 1 to 4**). In addition, we discuss how brain lesions in secondary psychosis may contribute to our understanding of the disrupted network interplay leading to primary psychosis.

METHODS

We searched PubMed using the combination of words ((brain) OR (mri) OR (imaging)) AND (psychosis), and filtered by case reports from January 2000 to June 2021, considering both English and French articles. Inclusion criteria required: 1) psychotic symptoms to be among the initial presenting features, 2) brain MRI to show abnormal findings, and 3) symptom emergence to happen between 13 and 30 years old. Psychotic symptoms included positive (hallucinations and delusions), negative ones (social withdrawal, lack of energy and motivation, blunted affect), and disorganized behavior. The early time frame of 13 to 30 corresponds to when emergence of primary psychosis is most probable (Solmi et al. 2021), making differential diagnosis between primary and secondary psychoses a critical issue. Among the initial 1187 results of the PubMed search, 223 were relevant secondary psychosis' case reports, and 129 concerned patients whose symptoms started between 13 and 30 years old. For each of the 129 cases, we considered age at first psychotic symptoms, relevant medical history, the nature of psychiatric symptoms, clinical red flags (atypicalities upon physical examination or evolution that should suggest a secondary psychosis), the nature of the brain abnormality reported, and the underlying disease. **Supplementary tables 1 to 4** respectively sum these results based on general localization (cortical, subcortical, midline and ventricles, cerebellum). For each brain region with lesions associated with psychotic manifestations, we discuss their relevance in light of normal brain function, recent case-control studies, and postulated pathophysiology. Illustrations were drawn using the Allen Human Reference Atlas - 3D parcellation (S. Ding et al. 2020),http://download.alleninstitute.org/informatics-archive/allen_human_reference_atlas_3d_2020/version_1/ and applied with ITK-SNAP 3.6.0 (Yushkevich et al. 2006) onto the ICBM 2009b

Nonlinear Symmetric template (Vladimir Fonov et al. 2011; Vs Fonov et al. 2009), available at: http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009.

ANOMALIES IN CORTICAL REGIONS

Diffuse or multifocal lesions

In secondary psychosis

In secondary psychosis with cortical damage, the vast majority of cases report diffuse or multifocal lesions, affecting several regions among frontal, temporal, parietal, insular, and cingulate cortices (**Table 1, Supplementary Table 1**).

Autoimmune and inflammatory disorders are among recurrently reported cases of psychosis associated with diffuse cortical lesions in subjects 13 to 30 years old. MRI anomalies are known to be nonspecific and present only in 40 % of patients with anti-NMDAR encephalitis (Pollak et al. 2020). But some reports of early secondary psychosis described inflammatory lesions in the left precentral and anterior cingulate gyri, the medial temporal lobes and bilateral insular cortices, or in fronto-parietal and bi-occipital gyri (Söylemez et al. 2015; Sabbula et al. 2020; Le Foll and Pelletier 2010). Diffuse white matter lesions have also been described in settings where isolated psychotic symptoms revealed the onset of neurolupus (Jghaimi, Kabbaj, and Essaadouni 2009) or of demyelinating disorders such as multiple sclerosis (Jongen 2006) and acute disseminated encephalomyelitis (Neeki et al. 2016).

Among *infectious disorders* initially presenting as psychosis, neurocysticercosis with multifocal scolex localizations was recurrently reported (Miranda 2020; Verma and Kumar 2013; Mahajan et al. 2004), although almost any pathogen can be associated with psychotic symptoms (J. Merritt et al. 2020). Beside direct neurological lesions, immune- and inflammatory- related injuries are probably involved in psychosis' pathophysiology, as suggested by the frequent association between primary psychoses and inflammatory infectious or auto-immune disorders (Cullen et al. 2019; Khandaker et al. 2015).

Traumatic brain injuries followed by the occurrence of psychotic symptoms have been associated with punctate lesions in frontal and parietal regions (Spiers, Kompardt, and Tait 2016), concussion foci in left temporopolar and medial orbitofrontal regions (Greene et al. 2010), and encephalomalacia in bilateral temporal and basifrontal regions - although in this last case, the underlying brain injury was not found (Das and Yadav 2018). Moreover, diffuse

encephalomalacic lesions after traumatic intracranial brain hemorrhage may also increase brain vulnerability to other disorders leading to psychosis, such as anti-NMDAR encephalitis (Lee, Liou, and Wu 2018).

Metabolic disorders can result in diffuse brain lesions which may explain the psychotic manifestations that sometimes occur before the rest of the multisystemic presentation. Thus, bilateral fronto-temporal atrophy was found in type-II adult-onset citrullinemia (Ikeda et al. 2001), global atrophy in Niemann-Pick type C (Walterfang 2006), and diffuse white matter lesions in propionic acidemia (Bâtie et al. 2014).

Neurodevelopmental or genetic disorders with initial psychotic symptoms are also frequently associated with multifocal anomalies: disseminated tubers in frontal and insular cortices, but also subcortically, in tuberous sclerosis (Pokharel et al. 2020; Hassan et al. 2014), diffuse gray matter heterotopia (Baroud, Hourani, and Talih 2019; Akanuma 2002), porencephaly (Douzenis et al. 2010), diffuse cerebral atrophy in Davidoff-Dyke-Masson syndrome associated with prolonged untreated seizures (Hegde et al. 2018), in 22q11 deletion syndrome (Starling and Harris 2008), or in juvenile Huntington's disease (Chuo et al. 2012). Notably in this last case, no caudate nucleus atrophy was reported, although it is a common finding not only in adult- but also in juvenile-onset Huntington's disease (Arraj et al. 2021). Given that diagnosis is often guided by motor symptoms, which may correlate with caudate atrophy (Tan et al. 2021), early caudate preservation in the context of diffuse cortical atrophy may be a hypothesis to explain why this patient initially presented with psychotic features, three years prior to motor dysfunction. Finally, genetical secondary psychoses with diffuse white matter atrophy have also been described in cases of adult-onset vanishing white matter leukoencephalopathy (Denier 2007) and X-linked adrenoleukodystrophy (Ramos-Ríos, Berdullas, and Santos-García 2009).

Table 1

SECONDARY PSYCHOSES WITH DIFFUSE OR MULTIFOCAL LESIONS IN CORTICAL GREY MATTER (GM) AND ADJACENT WHITE MATTER (WM)	
Auto-immune / inflammatory disorders	
NMDAR encephalitis	Diffuse cerebral atrophy or/and high T2 / FLAIR multifocal lesions
Multiple sclerosis	Multifocal sus- and sub-tentorial lesions, high T2 / FLAIR, low T1
Neurolupus	Localized lesion, in the left centrum semiovale, high T2 / FLAIR, low T1
Acute disseminated encephalomyelitis	Large T2 high signal lesion with mass effect and subcortical diffuse extension
Neuro-Behçet	Multifocal high FLAIR signal + contrast T1 filling defect in superior sagittal sinus

Genetic / neurodevelopmental disorders	
Davidoff-Dyke-Masson Syndrome	Diffuse right-sided cerebral atrophy, with enlarged ventricles
Juvenile Huntington's disease	Diffuse cortical atrophy and dilated ventricles
22q11 deletion	Diffuse cortical and cerebellar atrophy
X-linked adrenoleukodystrophy	T2 FLAIR high signal, symmetric, in parieto-occipital regions
Vanishing white matter leukoencephalopathy	Diffuse high T2 low T1 WM signal, also in cerebellum and brain stem
Tuberous sclerosis	Multifocal high T2 signals consistent with tubers (triangle shaped)
Diffuse grey matter heterotopia	Heterotopic gray matter nodules in frontal and subcortical white matter
Double-cortex syndrome	Bilateral hemispheric bands of heterotopic GM in WM + diffuse atrophy
Porencephalic cyst	Cyst on the left frontal and temporal lobes in the middle cerebral artery territory
Metabolic disorders	
Niemann-Pick type C disease	Marked global atrophy, particularly in frontal lobe and corpus callosum
Type-II adult-onset citrullinemia	Bilateral fronto-temporal atrophy
5,10-MTHFR deficiency	FLAIR high signal in white matter (around posterior horns of lateral ventricles)
Propionic acidemia	High FLAIR/T2 signal in centrum semiovale and temporal and insular WM
Traumatic brain injuries	
Head injury	Concussion low T1 signal in left temporopolar and medial orbitofrontal regions
Infectious disorders	
Neurocysticercosis	Circular lesions, low centre and high peripheral FLAIR signal, eccentric scolex
Toxic brain injury	
Toluene dependency	Widespread cerebral and cerebellar loss, extensive subcortical high T2 signal

In primary psychosis

This diffuse or multifocal aspect of the underlying brain lesion is in keeping with what is found in primary psychosis, where cortical thinning and the resulting ventricular enlargement involve the entire cortex rather than localize to particular regions (Vieira et al. 2021; Coyle, Ruzicka, and Balu 2020). It is also reflected by positron emission tomography (PET) studies, which find a more general metabolic disturbance between brain areas, rather than just an isolated frontal hypometabolism (Cumming, Abi-Dargham, and Gründer 2021). In patients with a first episode of psychosis, widespread decreases in frontotemporal, insular and occipital gray matter volume

have been confirmed by a multicentre mega-analysis, which adjusted for the effects of antipsychotic treatments, known to cause cortical atrophy (Vieira et al. 2021). The authors found the most significant volumetric decreases in the left gyrus rectus (orbito-frontal lobe) and the right lingual gyrus (occipital lobe), although the latter might also be strongly correlated with antipsychotic treatment. These areas were associated with positive and negative symptom severity and duration of illness. Significant decreases were also reported in the left inferior temporal gyrus and left fusiform gyrus, and correlated with positive symptoms. Likewise, a multimodal meta-analysis found similar patterns of general volumetric decreases in frontal, superior temporal, left hippocampal and insular cortices, both in antipsychotic-naive and antipsychotic-treated subjects (C. Shah et al. 2017).

Frontal lobe

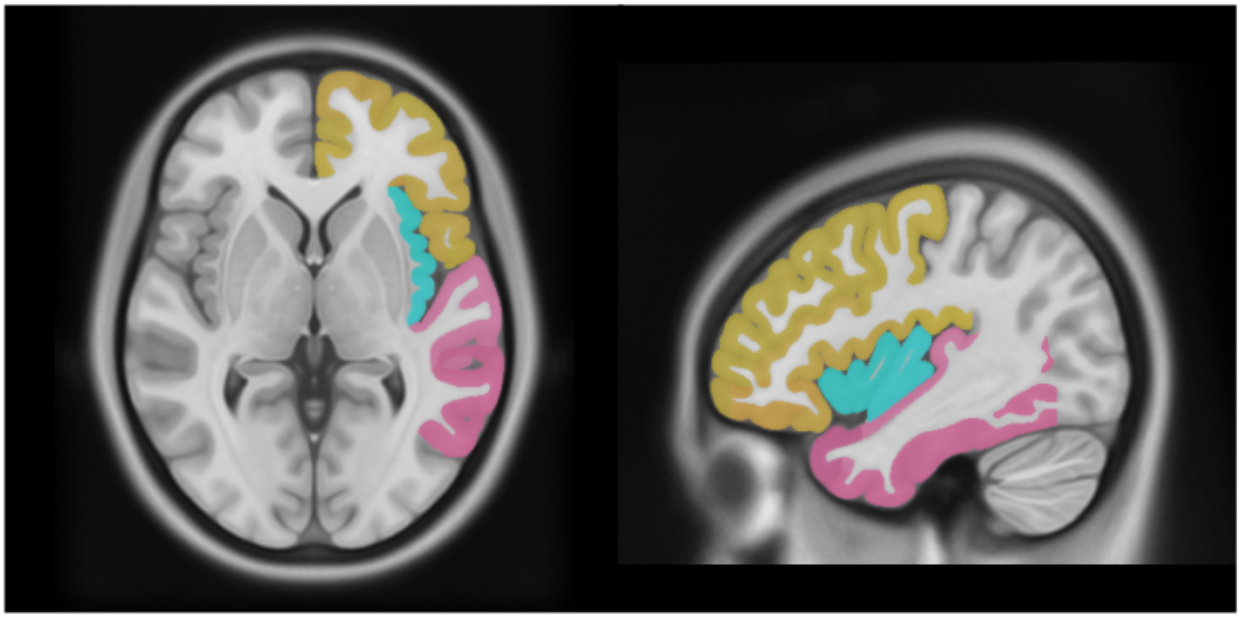
Anatomical and functional overview

The frontal lobe includes the prefrontal cortex, the motor and premotor cortex, the frontal visual field, and Broca's articulatory language center in the dominant hemisphere. The prefrontal cortex accounts for almost a third of the brain and is particularly involved in the development and regulation of voluntary action, cognitive and behavioral control, creativity, abstraction, and planning abilities (Gould and Brueckner-Collins 2016).

In secondary psychosis

Lesions more localized to this lobe have been associated with psychotic symptomatology in several case reports in adolescents and young adults (**Figure 1, Supplementary Table 1**). Isolated frontal nonspecific white matter lesions have been described in anti-NMDAR encephalitis (Endres et al. 2019; Gharedaghi et al. 2018). A left frontal lobe expansive lesion with well-defined limits was seen in a grade II meningioma of the cerebral falx in a patient who had been followed in psychiatry for 25 years (since he was 24) with various diagnoses along the schizophrenia spectrum. The post-surgery remission of his aggression and isolation suggested that the tumor played an important part in psychotic symptomatology (Gama Marques 2020). In two cases with 22q11 deletion syndrome, hyperdense foci were described in the frontal lobes, associated in one case with frontal gray matter heterotopia, cavum septum pellucidum and cavum vergae, and in the other with basal ganglia hyperdense foci as well. In this case, beside the reported positive symptoms such as auditory hallucinations or paranoid delusions, deteriorating self-care and aggression were symptoms that could be explained by the frontal

Figure 1: Secondary psychoses with lesions localized in specific cortical areas.



DISEASE	BRAIN IMAGING
	FRONTAL LOBE
NMDAR encephalitis	FLAIR high signal in left precentral and anterior cingulate gyri
Grade II meningioma	Extra-axial, expansive, T1/T2 isointense in left lobe; gadolinium enhancement
22q11 deletion	Grey matter heterotopia (+ cavum septum pellucidum + cavum vergae)
Infarct after ependymal tumor resection	Right frontal lobe venous infarct with associated hypo-perfusion
	TEMPORAL LOBE (+ AMYGDALA + HIPPOCAMPUS)
NMDAR, LGI1, herpetic encephalitides	FLAIR / T2 high signals, bilaterally in temporal lobes + amygdala / hippocampus
Neuro-Behçet	FLAIR high signals amygdala, hippocampus, internal capsule, brainstem
Arachnoid cyst	Large cyst with CSF MRI features ; mass effect, intracranial pressure
Undefined transient lesion	FLAIR / T2 hyperintense signal in the left temporal lobe (vanished at remission)
Left temporal lobe tumor	T2 high / T1 low signals mass (low grade glioma ?)
Cannabis use disorder + acute psychosis	Bilateral increase of hippocampal fissure size and smaller left hippocampus
Synthetic drug use + acute psychosis	Bilateral prominence of hippocampal fissures
	INSULAR LOBE
right insular lobe tumor	T2 high signal mass (low-grade dysembryoplastic neuroepithelial tumour ?)

lesions (Starling and Harris 2008). Finally, as a complication of a right frontal lobe infarct that followed a resection of ependymal tumor, right frontal lobe and posterior fossa

encephalomalacia were found in a 28 years old patient after nine years of treatment-resistant psychotic symptoms. This was associated with hypo-perfusion in the right frontal lobe (Melanie M. Lewis-Lehr, James R. Sla 2000).

In primary psychosis

From a pathophysiological perspective, although the isolated hypofrontality hypothesis for schizophrenia has long been known to be insufficient (R. C. Gur and Gur 1995), frontal lobe defects still play a key role in psychosis' evolution. Volumetric decreases in prefrontal regions were shown to be significantly associated with the onset of psychosis (Dietsche, Kircher, and Falkenberg 2017). Electrophysiological studies reported dysfunctional gamma-band oscillations in the prefrontal lobe, which may underlie the cognitive impairments found in schizophrenia (Senkowski and Gallinat 2015). Supporting the implication of frontal areas in psychosis, a review of the effects of several treatments - antipsychotic medications, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, cognitive remediation or behavioral therapy - found that normalization of frontal cortical activity was the most consistent result. Notably, the authors highlighted that almost all frontal regions were involved, from the frontal pole to the anterior cingulate cortex, and that treatment-induced changes in frontal areas were always associated with changes in several other regions, depending on the study, suggesting frontal areas may be hubs in a broader dysregulated network (Kani et al. 2017). However, whether the frontal dysfunction observed as metabolism defects in FDG positron emission tomography is a marker of state or of trait in schizophrenia remains an open question (Cumming, Abi-Dargham, and Gründer 2021).

Temporal lobe and associated structures (amygdala and hippocampus)

Anatomical and functional overview

The temporal lobe includes the primary auditory cortex, Wernicke's language center in the posterior part of the superior temporal gyrus of the dominant hemisphere, the optic radiations projecting to the lower lip of the calcarine sulcus, and the primary olfactory cortex. The medial temporal lobe lies over and relates to the hippocampus, while the anterior temporal lobe contains the amygdala in its anteromedial part. Amygdalar and hippocampal regions are involved in the limbic system and support memory consolidation and emotional response to stimuli (Gould and Brueckner-Collins 2016). On the one hand, the amygdala plays an important

role in emotional response, learning and emotional memory encoding, and decision making. The uncinate, cingulate, and stria terminalis bundles connect the amygdala, respectively, to the orbitofrontal cortex and anterior temporal lobe, the medial temporal and cingulate cortex, and the hypothalamus and thalamus. On the other hand, the hippocampus supports the binding of information between stimuli and their context into a specific cognitive event, while the medial temporal and prefrontal lobes extract the information shared by several events to obtain a decontextualized generalization, which could then be extrapolated to other situations (Opitz 2010).

In secondary psychosis

Lesions in temporal, hippocampal and amygdalar areas are found to lead to secondary psychosis, especially in limbic encephalitis (Reddy et al. 2018; D. Wang et al. 2018; K. Shah et al. 2013). As previously stated, encephalitic lesions may often not be seen on MRI, but in front of a normal MRI, its repeat after some weeks could highlight their possible delayed appearance (K. Shah et al. 2013). Other delusional manifestations have revealed the inflammatory lesions of a relapse in multiple sclerosis (Gabelić et al. 2012; Yadav and Zigmond 2010), the onset of acute disseminated encephalomyelitis (Nasr, Andriola, and Coyle 2000), a herpetic encephalitis (Zabroug et al. 2015), or a neuro-Behçet disorder (Deniz et al. 2009). A left temporal lobe tumor, suspected to be a low-grade glioma, has also been described in a young adult with classical psychotic symptomatology (Shehane et al. 2018). Moreover, arachnoid cysts in temporal lobes, especially through mass effect or increased intracranial pressure, have been associated with hallmarks of psychosis such as auditory hallucinations and thought disorganization (Kuloglu et al. 2008; Vakis et al. 2006). In these last cases, there was a notable three years delay in diagnosis, and importantly, symptom recovery was obtained in one occurrence after a cysto-peritoneal shunt was introduced (Vakis et al. 2006). Interestingly, although no underlying cause was found, a case report described a young adult with psychotic symptoms and catatonia associated with the transient occurrence of a lesion in the left temporal lobe, which disappeared at recovery, after a course of electroconvulsive therapy (ECT). The “time-locked” appearance of this lesion supported the role of the temporal lobe in psychosis.

In primary psychosis

The implication of the temporal lobe, the hippocampus, and the amygdala, in the pathophysiology underlying psychosis is strengthened by the molecular anomalies found in these structures in schizophrenia - for instance, oligodendrocytes and myelin dysfunction,

glutamatergic pathway dysfunctions or synaptic alterations in the hippocampus; anomalies in interneuron cell populations and GABA-ergic dysregulation in the amygdala; or overall gene expression alterations in the superior temporal gyrus, the amygdala, and the hippocampus (Bobilev, Perez, and Tamminga 2020). Among these anomalies, the increased glutamatergic activity in hippocampal neurons of the CA1 region has been postulated to be an early index pathogenic mechanism for the emergence of psychosis (Lieberman et al. 2018). Glutamatergic and dopaminergic dysregulations in the hippocampal-striatal-midbrain network have also been postulated to explain the aberrant salience at the basis of delusions (Allen et al. 2019). Still in early phases of the disorder, decreases in gray matter in the superior, middle and inferior temporal gyrus have been frequently found in the first psychotic episode (C. Shah et al. 2017). The left superior temporal gyrus in particular appears to play a central role in the onset of acoustic-verbal hallucinations, through its role in language perception and processing. Disruptions in this region could lead to misattribution of the origin of internal language (Mathalon et al. 2019). The fusiform gyrus, at the inferior aspect of the temporal lobe, through its role in facial recognition, may also be involved in social cognition disorders characteristic of psychosis (Green, Horan, and Lee 2015).

The uncinate, cingulate, and stria terminalis bundles may also present with decreased functional connectivity in primary psychosis (Ho et al. 2019). Moreover, the bed nucleus of the stria terminalis is involved in the regulation of the hypothalamic-pituitary-adrenal axis, a stress axis whose disruption is frequently associated with psychosis (Lebow and Chen 2016). Impairment in the temporo-prefrontal-hippocampal networks may explain the lack of cognitive insight observed in psychotic disorders, where internally-built models of the environment do not properly integrate new external data (Pijnenborg et al. 2020).

Insular lobe

Anatomical and functional overview

The insular lobe is located inside the lateral sulcus that separates the temporal lobe at the bottom from the frontal and parietal lobes at the top. The anterior and posterior subregions differ anatomically and functionally. The anterior insula receives projections from the thalamus and amygdala and projects mainly to the amygdala and frontal lobe. It is thought to be involved in emotional processing (Craig 2009). The posterior insula includes regions of somatosensory and auditory processing, and is connected with the parietal and temporal lobes (Uddin et al. 2017).

In secondary psychosis

Isolated insular lesions may be associated with psychotic symptoms. For example, in a 16 years old patient with a year-long delusion of reference with thought disorder (diffusion of thought, thought insertions) and acoustic-verbal hallucinations, an insular tumor was found in the right lobe, and described as a probable low-grade neuroepithelial dysembryoblastic tumor (Kasinathan, Baker, and Perkes 2017).

In primary psychosis

The insula has been repeatedly implicated in interoceptive, self-referential, or emotional processing, the disruption of which leads to a disintegrating self-perception symptomatology (Scalabrini et al. 2020). Among subjects at ultra-high risk of psychosis, those who transited to a first psychotic episode had a significantly smaller bilateral insular volume than non-transitors (Takahashi et al. 2009; Takahashi and Suzuki 2018). Alterations in the right insula were also associated with a higher risk of psychosis (Smieskova et al. 2012). Importantly, the dorsal anterior insula's involvement in the salience network, through detection of novel stimuli in all sensory modalities, might be crucial to its role in psychosis pathophysiology (Uddin et al. 2017).

ANOMALIES IN SUBCORTICAL REGIONS

Diffuse or multifocal lesions

In comparison with cortical lesions, our review found subcortical ones to be more frequently localized, with only a few clinical cases reporting diffuse or multifocal lesions (**Table 2**). This might be because many smaller circumscribed subcortical areas are hubs of cortico-subcortical connections, where one localized lesion can be sufficient to dysregulate the whole network and lead to psychosis. Diffuse subcortical lesions were for instance described in neurolupus, where the association between psychosis, fever, and extrapyramidal symptoms was evocative of an underlying disorder (Hajjaj et al. 2012). However, among brain cancerous processes, primary brain T-cell lymphoma was reported to lead to florid psychotic symptoms with a normal CT and no focal neurological sign, while MRI revealed multifocal subcortical lesions (Lotan et al. 2012). A three month progressive deterioration in a 17 year old adolescent with self-neglect, negative symptoms, and auditory hallucinations also revealed an underlying intracranial germinoma with syncytiotrophoblast cells (Undurraga et al. 2010). Similarly, a suprasellar germinoma was discovered in the context of emergence of psychotic and obsessive-compulsive symptoms in a 13 years old patient (Mordecai et al. 2000). Finally, mild traumatic brain injury with multiple

subcortical white matter foci were found in a teenager initially diagnosed with schizoaffective disorder (Adelsky et al. 2017).

Table 2

SECONDARY PSYCHOSES WITH DIFFUSE OR MULTIFOCAL LESIONS IN SUBCORTICAL GREY MATTER (GM) AND ADJACENT WHITE MATTER (WM)	
Auto-immune / inflammatory disorders	
Neurolupus	High FLAIR signal in bilateral lesions in striatum, thalamus, and perinuclear WM
Tumors	
Primary brain T-cell lymphoma	High FLAIR/T2, low T1 in midbrain, subthalamic nuclei, thalamus, amygdale, caudate, and corpus callosum
Germinoma with syncytiotrophoblast cells	Heterogeneous mass, necrotic and hemorrhagic regions in thalamus, mesencephalon, right mamillary tubercle, corpus callosum
Suprasellar germinoma	Thickened pituitary stalk + high T2 infiltrating lesions basal ganglia, internal capsules, frontal lobes, peduncles, pons
Traumatic brain injury	
Repeated concussions (soccer player)	High T2 foci in subcortical white matter, large focus in right centrum semiovale

Basal ganglia

Anatomical and functional overview

The basal ganglia include the caudate nucleus and the putamen (which together form the striatum), as well as the globus pallidus, the subthalamic nucleus, and the substantia nigra pars compacta. They are involved in two major cortico-baso-thalamo-cortical pathways that participate in selection of a specific movement plan. In the direct pathway, the striatum inhibits the internal part of the globus pallidus and the substantia nigra, thus releasing the thalamo-cortical loop from its tonic GABA-ergic inhibition, facilitating movement. In the indirect pathway, the striatum inhibits the external part of the globus pallidus, thus releasing the excitatory effect of the subthalamic nucleus on the internal part of the globus pallidus, resulting in inhibition of the thalamo-cortical loop and of the movement plan (Gould and Brueckner-Collins 2016). The basal ganglia have therefore been described as an “arena in which different movement plans compete to gain control of the effectors” by promoting their plan through the

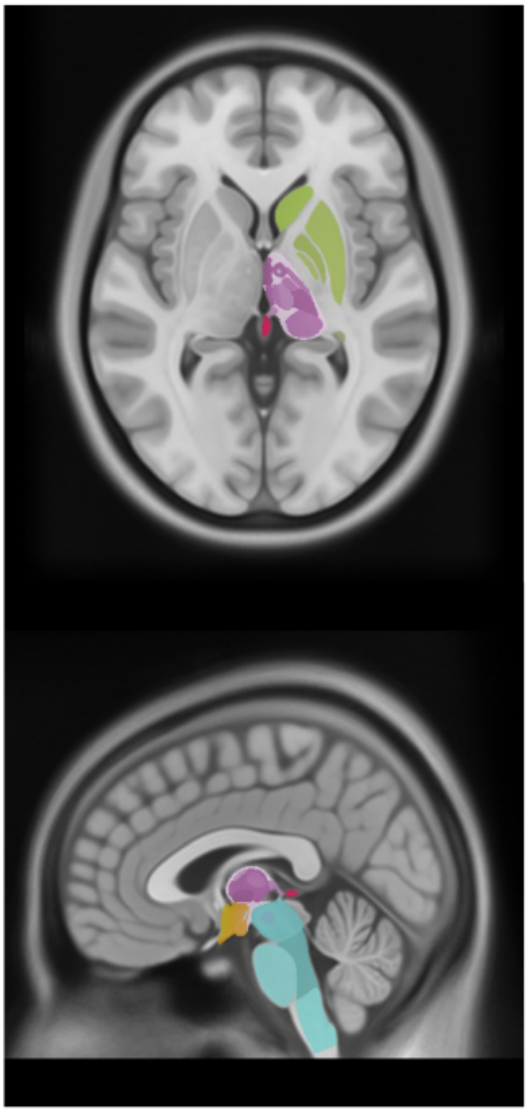
direct pathway and inhibiting others' through the indirect one (Fazl and Fleisher 2018). Moreover, a third hyperdirect pathway allows the cortex to directly activate the subthalamic nucleus, thus quickly stopping movement initiation. Its postulated role is to delay movement selection in the basal ganglia arena, in high uncertainty situations where the right action is not obvious and more time is needed to avoid impulsive actions (Fazl and Fleisher 2018). In this context, dopamine neurotransmission plays the role of a facilitator in the selection of a specific movement plan. Dopaminergic neurons originate mainly from the substantia nigra and the ventral tegmental area of the midbrain. These projections are divided into several pathways, including a mesocortical pathway (which connects the ventral tegmental area to the prefrontal cortex, and is involved in cognitive control, motivation, and emotional response), a mesolimbic pathway (which connects the ventral tegmental area to the ventral striatum - and in particular the nucleus accumbens, and is involved in motivational reinforcement and reward circuitry), and a nigrostriatal pathway (which connects the substantia nigra, pars compacta, with the dorsal striatum - caudate nucleus and putamen, and is involved in the production and regulation of movement). Initially described as parallel and relatively independent functional circuits, limbic, cognitive, and motor circuits have been known to share reciprocal connections for more than twenty years (Haber 2003).

In secondary psychosis

It is therefore not surprising that a variety of diffuse damage to the basal ganglia as a whole can be associated with psychotic presentations in 13-30 years old individuals (**Table 2, Supplementary Table 2**), particularly in relation to metal overload disorders that have basal ganglia tropism: in rare diseases with iron deposition - neuroferritinopathies, Hallervorden-Spatz disease, or neurodegeneration associated with a PLA2G6 mutation (Huang, Chiu, and Tsai 2018; Pilar del Valle-López 2011; Öner et al. 2003; Maciel et al. 2005), with copper deposition - Wilson's disease (A. Basu et al. 2015; Krstic, Antonijevic, and Spiric 2014), and in diseases involving calcium accumulation - Fahr's disease, 22q11.2 deletion, idiopathic or pseudohypoparathyroidism diseases (Uno et al. 2020; Plemeniti Tololeski et al. 2019; Shirahama et al. 2010; Rizvi et al. 2018; Otheman et al. 2011; Lu 2014). In other metabolic disorders such as adult-onset cobalamin C deficiency, which presented with severe paranoid delusions, brain imaging showed extensive basal ganglia involvement as well as diffuse periventricular and dorso-spinal white matter changes (Higashimoto et al. 2020). Most clinical presentations also present with extrapyramidal symptoms in the absence or at low doses of treatment, which should constitute a red flag to look for possible underlying brain pathology.

Figure 2: Secondary psychoses with lesions localized in specific subcortical areas.

DISEASE	BRAIN IMAGING
	BASAL GANGLIA
Neurodegeneration with brain *iron accumulation* (PKAN, PLA2G6, neuroferritinopathies)	Bilateral T2 signal anomalies in basal ganglia : high central T2 with low peripheral T2 signal in both globi pallidi, symmetrically - "eye-of-the-tiger" sign in PKAN ; low T2 signal in PLA2G6
Wilson's disease: *copper accumulation*	Bilateral T2 high signal in the basal ganglia
Calcium deposition: Fahr's disease, idiopathic or pseudo-hypoparathyroidism, 22q11 deletion	CT: bilateral basal ganglia calcification (+/- cerebellum) Multiple FLAIR anomalies in basal ganglia (low signal) and WM (high signal)
Adult-onset cobalamin C deficiency	High FLAIR/T2 basal ganglia signal + diffuse periventricular / spinal extension
Propionic acidemia	High FLAIR/T2 signal in globus pallidus bilaterally
Ischaemic or gliotic lesion	Unilateral FLAIR high signal in the left globus pallidus
McLeod syndrome	Caudate atrophy with enlargement of the anterior horn of lateral ventricles
	THALAMUS
Ischaemic disease	Unilateral high T2 due to infarcts (in ventral anterior or posterior left regions)
Mycoplasma infection sequelae	Bilateral nonspecific FLAIR anomalies consistent with encephalopathy
Dysembryogenic neuroepithelial tumor (?)	Mixed FLAIR and iso-T1, ill-perfused ovoid lesion in postero-lateral thalamus
Glioblastoma multiforme	CT: enhancing mass with central acute hemorrhage and hydrocephalus
Wernicke's encephalopathy and schizophrenia	Bilateral high T2/FLAIR - "pulvinar sign"
Aceruloplasminemia (iron deposition)	Low T2 signal in the thalamus and the dentate nucleus + cortical atrophy
	HYPOTHALAMUS AND PITUITARY GLAND
AQP4-IgG-seropositive neuromyelitis optica	High T2/FLAIR signal in hypothalamus and right optic nerve
Hypothalamic hamartoma	Hypothalamic mass with isointense T2 signal
Pituitary adenoma	Iso-intense pituitary mass
	PINEAL GLAND
Epidermoid cyst	High FLAIR/T2, low T1 homogeneous pineal mass
Mixed germ cell tumor	Pineal mass with isointense grey matter signal + small basal ganglia stroke
Pineal germinoma irradiation	Pineal mass with pituitary extension (psychosis occurred after irradiation)
	BRAIN STEM
Pilocytic astrocytoma	Cystic mass in left midbrain and cerebral peduncle + thalamus, hypothalamus
Central pontine myelinolysis	Low T1 and high T2 pontine signal + lenticular lesion
NMDAR encephalitis	High T2/FLAIR signal in brainstem, amygdala, hippocampus, internal capsule



However, psychosis can sometimes occur as an isolated symptom in this setting. Of note is the case of a 20 year old subject who had been presenting isolated psychiatric symptoms for two years, with social withdrawal, reduced verbal communication, hostility towards his family and suicidal ideas. At the age of 21, a diagnosis of paranoid schizophrenia was made, and it was only during a test one year later that a disturbance in the copper balance was found. At this point, brain imaging was made and identified metal deposits in the globus pallidus, the putamen,

and the pars compacta of the substantia nigra. The Kayser-Fleischer ring, a pathognomonic sign of Wilson's disease, did not appear until 3 months later, and there was no hepatosplenomegaly (Krstic, Antonijevic, and Spiric 2014). A focus on basal ganglia in brain imaging could therefore improve access to treatment and remission in this type of secondary psychoses, where delay to diagnosis is frequent and important, ranging from one to fifteen years (**Supplementary table 2**).

Psychotic symptoms can also result from lesions in specific nuclei of the basal ganglia (**Figure 2**), as it has been reported in propionic acidemia for instance (Bâtie et al. 2014). In a patient diagnosed with paranoid schizophrenia at 23, only the emergence at 54 of a triad of choreatic movement disorder, muscle atrophy, and areflexia led to further investigations which found caudate atrophy with enlargement of the anterior horn of the lateral ventricles, while genetic tests diagnosed McLeod syndrome (Miranda et al. 2007). Moreover, an old ischaemic or gliotic lesion in the left globus pallidus was found in a teenager who progressively developed paranoid persecutory delusions (Baroud, Hourani, and Talih 2019).

In primary psychosis

The intricacy between movement, emotion, and decision is particularly relevant for psychosis' pathophysiology. The selection of adequate emotional response patterns, reward feedback, reward anticipation and prediction error, is encoded by dopaminergic neurons in basal ganglia (Pierce and Péron 2020), and may be disrupted in schizophrenia (Conn, Burne, and Kesby 2020). While the mesolimbic pathway and the nucleus accumbens have long been considered the substrate of such abnormalities, recent in vivo neuroimaging studies have shown the nigrostriatal pathway and the dorsal striatum to be the most affected by dopaminergic dysfunction in schizophrenia (Conn, Burne, and Kesby 2020; McCutcheon, Abi-Dargham, and Howes 2019). Several hypotheses have therefore been proposed to explain the mechanisms by which striatal dysfunction could lead to psychosis : (i) aberrant salience of irrelevant environmental stimuli due to excessive dopaminergic activity in the nigrostriatal pathway; (ii) because the dorsal striatum is an integrative hub that participates to synchronization of cortical oscillations, its perturbation may lead to disrupted integration between associative motor, emotional, and cognitive areas; (iii) disruption in the top-down transmission of efference copies of a motor signals - as efference copies signal an act as self-authored, this may contribute to false attribution to an external agent, not only of motor phenomena, but also of inner speech; (iv) finally, dysregulation in frontal cortico-striatal loops and impaired reward-based learning in

the striatum may lead, respectively, to cognitive and negative symptoms (McCutcheon, Abi-Dargham, and Howes 2019).

Thus, volumetric studies of subcortical regions found gray matter losses associated with psychosis, particularly in the basal ganglia, where the extension of volumetric deficits seemed to be associated with disease progression (Liloia et al. 2021). Moreover, motor dysfunctions such as dyskinesia, dystonia, and tremor on the one hand (Hirjak et al. 2018), and minor neurological signs on the other (Quispe Escudero et al. 2020), can occur in psychosis independently of antipsychotic treatment side-effects, as an intrinsic characteristic of the disease. Highlighting basal ganglia dysfunction, they may constitute endophenotypes of psychosis. The crucial role of basal ganglia in psychosis is therefore increasingly recognized and both hypo- and hyper-kinetic movement disorders, and their neuroanatomic and functional substrates, appear to be an intrinsic part of psychotic disorders where anomalies of affect, thought, and psychomotricity are deeply interconnected (Walther et al. 2020).

Thalamus

Anatomical and functional overview

The thalamus is the largest structure in the diencephalon and its role is essential in sensorimotor integration and associative functions, through the feedback loops that it establishes with adjacent subcortical regions, as well as higher cortical regions. Although the complexity of its structure leads to continuous revisions of its functional neuroanatomy (Mai and Majtanik 2019; Cassel and Pereira de Vasconcelos 2021), some circuits need mentioning for their relevance in psychosis. The anterior nucleus of the thalamus receives the mammillothalamic tract and projects to the cingulate gyrus, as part of the limbic system. The mediodorsal nucleus is connected to the prefrontal cortex and also has a limbic function, in emotional and behavioral expression. The centromedial nucleus receives afferences from the globus pallidus and projects to both the striatum and the whole cortex (Gould and Brueckner-Collins 2016). The nucleus pulvinar is reciprocally connected with the associative cortex of the posterior temporal, parietal, and occipital lobes, involved in visual, auditory, and somesthetic integration, and its dysfunction has been described in schizophrenia (Benarroch 2015). Finally, in addition to ventral nuclei strongly involved in perception and interconnected with the striatum, the reticular nucleus of the thalamus might play a particularly important role in the pathophysiology of psychosis. Surrounding the thalamus as a layer of GABAergic inhibitory neurons, it receives collateral excitatory afferents from the cortico-thalamic and thalamo-cortical

fibers, and inhibits the activity of the rest of thalamic nuclei. It plays an important part in the regulation of sleep rhythms (Li et al. 2020).

In secondary psychosis

The centrality of the thalamus in the cortico-subcortical networks may explain why psychosis can occur even in the context of very isolated, localized lesions of the thalamus. For example, infarctions of the left anterior ventral nucleus (on ischaemia of the tuberothalamic artery) (M. Mittal and Khan 2010), or of the posterior region of the thalamus, including pulvinar, dorsolateral and dorsoposterior nuclei (Arıkan et al. 2009), led to psychotic symptomatology, such as delusions of persecution and hallucinations, more or less in isolation (transient hemihypoesthesia with language and concentration difficulties had also been reported in the second case). Likewise, the vasculitic sequelae of a mycoplasma pneumoniae infection seem to have been associated with bilateral thalamic lesions consistent with nonspecific encephalopathic changes, which manifested clinically by delusions (Banerjee and Petersen 2009). Tumoral processes involving the thalamus have also led to psychotic presentations without any neurological anomaly associated. A suspected dysembryogenic neuroepithelial tumor appeared on MRI as an ill-perfused ovoid lesion in the postero-lateral thalamus, internal capsule, and posterior putamen, in a patient who presented with periodically re-occurring psychiatric symptoms since adolescence (Dutschke et al. 2017). A glioblastoma multiforme with an enhancing mass in the right (and probably left) thalamus with central acute hemorrhage was described in a young adult with depression and auditory hallucinations (Moise and Madhusoodanan 2006). Finally, thalamic lesions can also occur as a comorbidity complicating schizophrenia, for instance in the case of Wernicke's encephalopathy, in a delusional patient who did not eat food for three months. Interestingly, the bilateral thalamic hyperintensities ("pulvinar sign") found on initial MRI were normalized after adequate treatment (Gopalakrishnan et al. 2014).

In primary psychosis

In case-control studies of primary psychosis, resting-state functional imaging found thalamic dysconnectivity in subjects at-risk or with early schizophrenia, compared to healthy subjects. This dysconnectivity was more marked in schizophrenia than in the at-risk group (Fryer et al. 2021). Moreover, a recent study using segmentation techniques based on partial volume analysis (where proportions of gray and white matter are estimated in each voxel, which is more accurate than assuming a particular voxel consists only of gray or white matter) further explored

the structural thalamic anomalies in psychosis. Gray matter deficits were found in the pulvinar at all stages of psychosis, early and late, whereas mediodorsal nucleus gray matter atrophy was only found in early psychosis. The authors therefore concluded that gray matter anomalies in the thalamus did not evolve linearly with age, nor between each region (Alemán-Gómez et al. 2020). Dysfunction of the reticular nucleus of the thalamus has been associated with impaired attention and sleep in schizophrenia (Baran et al. 2019; Young and Wimmer 2017). More generally, it seems that positive symptoms of psychosis may be partly explained by thalamic dysconnectivity patterns between sensory, cerebellar, and cortical regions (Ferri et al. 2018).

Hypothalamus and pituitary gland

Anatomical and functional overview

At the inferior part of the diencephalon, the hypothalamus is composed of many nuclei participating in the homeostasis of autonomic, endocrine, and limbic functions (Gould and Brueckner-Collins 2016). Notably, the anterior hypothalamus plays an excitatory role in parasympathetic pathways and downregulates temperature, while the posterior hypothalamus is excitatory for sympathetic pathways and upregulates temperature. The suprachiasmatic nucleus receives retinian afferences and is involved in circadian rhythms' regulation. The paraventricular nucleus projects to the posterior pituitary to secrete the antidiuretic hormone, for water homeostasis, and oxytocin, involved in reproduction, social bonding, and stress modulation (of note, oxytocin secretion is stimulated by estradiol which itself is considered a modulator of the hypothalamo-pituitary-adrenal (HPA) axis and a protective factor against psychosis (Riecher-Rössler 2017)). The paraventricular nucleus also releases the corticotropin-releasing hormone and the thyrotropin-releasing hormone into the anterior pituitary gland.

In secondary psychosis

The strong relations between biological stress, its anatomical substrates in the HPA axis, and psychosis, may contribute to the occurrences of secondary psychoses implicating these structures. In one case, incoherent and delusional thinking with self-neglect was observed in a patient who presented with hypothalamic lesions in the context of aquaporin 4 antibody seropositive neuromyelitis optica spectrum disorder (Ruiter et al. 2017). In another, a hypothalamic hamartoma caused ictal psychosis, which manifested by episodes of sudden outbursts of aggressive and agitated behavior, with paranoid delusions. Its pathogenic role was confirmed by the hamartoma's resection, which led to full recovery of psychotic symptoms

(Al-Hail et al. 2010). Finally, three cases of pituitary adenomas reported to be associated with primary psychosis have been found. In all cases, symptomatic micro-adenomas and prolactinomas were comorbidities aggravated by initial first generation antipsychotic treatment (Ali, Klahr Miller, and Freudenreich 2010; Wix-Ramos et al. 2011; Pal and Sarino 2000).

In primary psychosis

The HPA axis may therefore be crucial to many aspects of psychosis pathophysiology. In particular, its long-lasting response to early-life stress activates cortisol secretion (Creutzberg et al. 2021), which in turn leads to : (i) glucocorticoid secretion affecting core stress reactive regions such as the hippocampus, the amygdala, and the medial prefrontal cortex, implicated in emotional processes; and (ii) dopamine secretion in the mesolimbic dopamine pathway (nucleus accumbens and orbitofrontal cortex), implicated in reward processes (DeRosse and Barber 2021). The increased levels of basal cortisol observed in psychosis lead to increased circulating glucocorticoids which reduce the sensitivity of the HPA negative feedback loop, disrupt the rhythmic release of glucocorticoids essential for stress termination, thus maintaining the stress response, while inducing blunted responses to acute stress. This results, among others, in increased immune and psychiatric dysfunctions (Sheng et al. 2021; Pruessner et al. 2017). Moreover, HPA axis hyperactivity has been shown to impact the structural and functional integrity of the temporal lobe, which may explain the frequent comorbidities between epilepsy and psychiatric disorders (T. Basu, Maguire, and Salpekar 2021).

Pineal gland

Anatomical and functional overview

The pineal gland is an oval-shaped structure situated in the epithalamus, posterior to the thalamus. Following light-dark cycles through their connection with retinal ganglion cells, suprachiasmatic nuclei situated in the hypothalamus control the pineal gland’s melatonin secretion, thus modulating circadian rhythms. The pineal gland is also involved in many other endocrine or immune functions, through close relationships with the thymus gland for instance (Rezzani et al. 2020).

In secondary psychosis

We found several cases of tumors involving the pineal gland in young subjects who initially presented with typical prodromal or clear-cut psychotic symptoms: a cyst in the pineal gland

(Jiang et al. 2018) and a pineal mixed germ cell tumor (V. A. Mittal et al. 2010). In both cases, tumor treatment either through resection or chemotherapy and autologous stem cell rescue led to symptom remission. It is however important to note that psychosis can also occur as a complication of pineal germinoma irradiation (Craven 2001).

In primary psychosis

A recent review highlighted the various potential anomalies in the pineal gland that may be related with schizophrenia: suprachiasmatic nuclei dysfunction, decreased melatonin secretion, reduced pineal gland volume, and enlarged pineal gland calcifications, which all appear to be independent of disease duration or treatment (Bastos Jr. et al. 2019). The authors note that since the pineal gland has only a modulatory role in a circadian process otherwise regulated by suprachiasmatic nuclei, the latter may constitute the primary circadian rhythm defect in schizophrenia. Moreover, recent studies found reduced pineal gland volume to be stable across the stages of schizophrenia, and also present in schizotypal disorder, thus suggesting its volumetric decrease could be a neurodevelopmental trait marker of vulnerability (Takahashi, Nakamura, Sasabayashi, Nishikawa, Takayanagi, Nishiyama, et al. 2019; Takahashi, Nakamura, Sasabayashi, Nishikawa, Takayanagi, Furuichi, et al. 2019). Further adding to the relevance of the pineal gland to psychosis, a study compared the specificity of action of clozapine, an atypical antipsychotic used in treatment-resistant schizophrenia or schizo-affective disorder, to a typical antipsychotic one, and found it may rely, among other mechanisms, on its dopamine D4 receptor targets in the pineal gland (Cardozo et al. 2017).

Brain stem

Anatomical and functional overview

Comprised of the midbrain, the pons, and the medulla, the brain stem's involvement in psychosis might mainly be explained by dysregulation of the midbrain dopamine system, connecting the ventral tegmental area to the striatum (Sonnenschein, Gomes, and Grace 2020).

In secondary psychosis

Several case reports have been found to involve midbrain or pontine regions in secondary psychosis. Isolated pontine lesions were observed in a young woman with anti-NMDAR encephalitis on an ovarian teratoma, and who presented with agitated and bizarre behavior suggestive of catatonic symptoms (Ramlackhansingh et al. 2019). In another case, psychosis

with catatonic features was found in an adolescent with a history of treatment for a midbrain pilocytic astrocytoma. However, as the tumoral mass had been stable since before the apparition of psychotic symptoms, no clear diagnosis could be made (Andrews et al. 2016). Lastly, central pontine myelinolysis has been found in a 30 years old patient with no previous history and presenting with hallucinations and delusions in the context of hyponatremia, and aggravated by hyponatremia overcorrection. Persistence of psychosis after sodium equilibrium stabilization led to the diagnosis of psychotic disorder secondary to central pontine myelinolysis (Schneider, Nejtek, and Hurd 2012).

In primary psychosis

Dopaminergic hyperactivity in the midbrain system may result in aberrant salience attribution, which could explain hallucinations and delusions (Miyata 2019). Moreover, the midbrain is among the regions involved in the anticipation of social reward and punishment avoidance, as well as the receipt of social rewards, whose disruption is relevant for psychosis (Martins et al. 2021). By its extensive cortical norepinephrine secretion through the dorsal adrenergic bundle, the locus coeruleus, situated in the pons, may also play an important role in the cognitive aspects of psychosis (Mäki-Marttunen, Andreassen, and Espeseth 2020). A recent review also summarized its implications in mechanisms of fear generalization (Webler et al. 2021), a dimension of adaptive behavior that may be perturbed in psychosis.

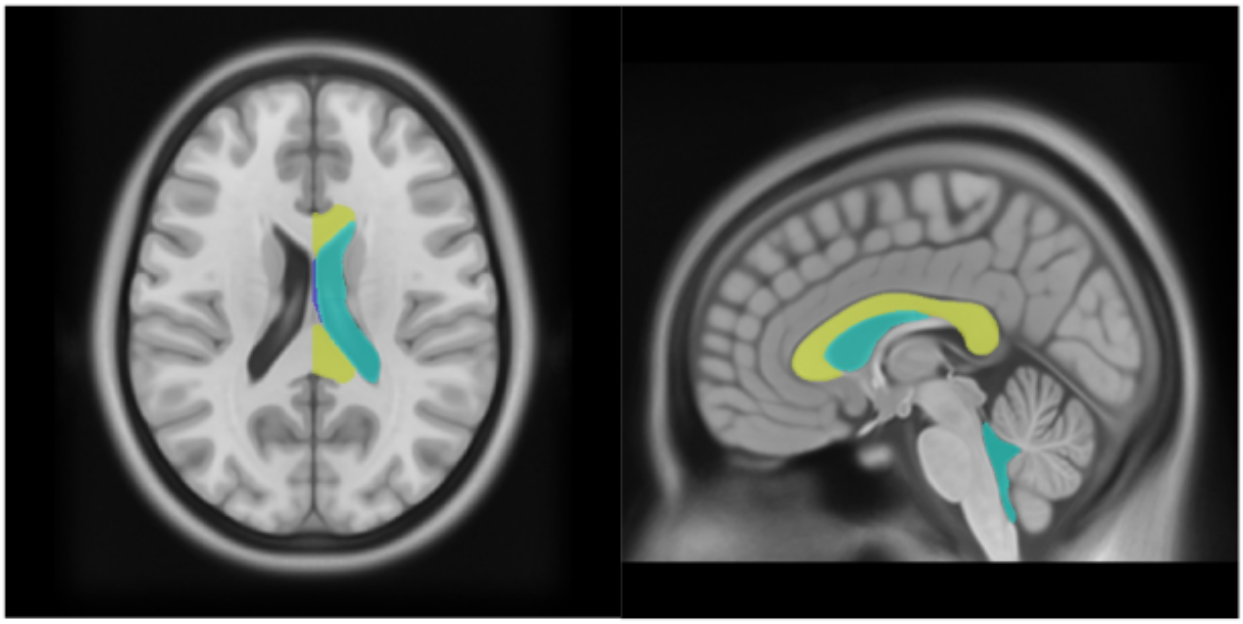
ANOMALIES IN OTHER MIDLINE REGIONS AND IN THE VENTRICLES

Corpus callosum

Anatomical and functional overview

The corpus callosum is the largest transverse commissural tract of white matter that connects the two cerebral hemispheres. It is composed of subregions that correspond topographically to the cortical regions it unites: (i) the rostrum and knee fibers connect the frontal associative areas; (ii) the middle third connects the dorsofrontal, temporal and parietal hemispheres, linking motor, somatosensory, and auditory areas; (iii) posteriorly, the anterior fibers of the splenium connect the temporoparietal associative areas, in continuity with the hippocampal commissure which parahippocampal fibers go through; finally, (iv) the posterior splenium connects the visual cortices.

Figure 3: Secondary psychoses with lesions localized in midline regions and the ventricles.



DISEASE	BRAIN IMAGING
	CORPUS CALLOSUM
Unknown genetic origin	Complete or partial corpus callosum agenesis +/- cavum septum pellucidum
High-dose corticotherapy for nephrotic syndrome	Well-defined high FLAIR/T2 lesion in the splenium, with restricted diffusion
Postpartum psychosis	High FLAIR/T2 with restricted diffusion in the corpus callosum
Hereditary spastic paraplegia + baclofen trial	Diffuse white matter loss and marked thinning of the corpus callosum
Susac's syndrome	High FLAIR/T2 signal with restriction evoking ischaemic processes
Multiple sclerosis	High FLAIR/T2 in the corpus callosum
	MIDLINE MORPHOLOGICAL ANOMALIES
Unknown genetic origin	Cavum velum interpositum
22q11 deletion	Cavum septum pellucidum and cavum vergae + grey matter heterotopia
Central neurocytoma	Homogeneously enhancing mass in the lateral ventricle, mass effect, midline shift
	VENTRICLES
Obstructive hydrocephalus due to colloid cyst	Ventriculomegaly of the lateral ventricles, small hyperdense colloid cyst near the foramen of Monro
Normal pressure hydrocephalus	Ventriculomegaly

In secondary psychosis

We found several clinical cases reporting associations between lesions of the corpus callosum and psychotic manifestations that illustrate the pathophysiologic involvement of this structure in secondary psychosis (**Figure 3, Supplementary Table 3**). In complete or partial agenesis of the corpus callosum (Bhatia 2016; Simon et al. 2008), or in X-linked adrenoleukodystrophy (Smith, Williams, and Misra 2018), delusions and hallucinations may be in the foreground, sometimes without association with neurological symptomatology. Corpus callosum's pathogenicity in psychosis is also highlighted by the description of a reversible splenial lesion in a teenager treated for a nephrotic syndrome. The lesion's transitory occurrence coincided with psychotic symptomatology and high-dose corticosteroid treatment. In this case, MRI found evidence of a diffusion restriction, suggestive of exocytotoxic edema (Aksu et al. 2015). Another isolated splenial lesion coinciding with psychosis has also been described in the context of postpartum psychosis (Udaya, Chauhan, and Philip 2014). Nevertheless, corpus callosum abnormalities can also be present long before the emergence of psychosis, perhaps contributing to an increased vulnerability to the disease. Thus, a 26 years old patient, with a hereditary spastic paraplegia diagnosed in his mid-teens, developed psychotic symptoms during a baclofen trial. The drug trial was therefore considered as a potential trigger stressor on an already vulnerable brain. In this case, MRI revealed diffuse white matter loss and marked thinning of the corpus callosum (Osmolak, Wallenberg, and Caplan 2012). Inflammatory lesions in this area have also led to psychotic symptomatology, such as Susac's syndrome, a microvessel vasculitis of possible auto-immune origin (Barrio et al. 2017). Notably, a typical first episode of psychosis without associated neurological signs was inaugural of multiple sclerosis, up to three years prior to motor anomalies in one case (Enderami, Fouladi, and Hosseini 2018; Blanc et al. 2010).

In primary psychosis

White matter lesions in the corpus callosum are already found in early stages of the disease. For instance, white matter volume and fractional anisotropy were reported to be reduced in the corpus callosum in genetic or clinical high-risk subjects who converted to psychosis, suggesting a decline in white matter maturation (K. Merritt et al. 2021). While decreased fractional anisotropy is commonly described in the corpus callosum of psychotic patients, an increase in fractional anisotropy has also been reported in psychosis with catatonia, above values of healthy controls and non-catatonic patients. This was suggested to be connected to catatonia's motor activity, which can alternate between hyper- and hypo-activity, and translate more complex maladaptive functional connections (Viher et al. 2020). On a larger scale, a study

comparing the corpus callosum volumes of 1381 subjects with schizophrenia, bipolar disorder with psychotic features, schizoaffective disorder, their first-degree relatives, and healthy subjects, found significant decreases in anterior and posterior splenium in patients, and intermediate decreases in their healthy relatives. Thus, damage to the splenium of the corpus callosum appears to occur across the spectrum of psychosis (Francis et al. 2016). Conversely, antipsychotic treatment seems to lead to an increase in the volume of the corpus callosum (de Moura et al. 2018).

Midline morphological anomalies

Anatomical and functional overview

Anterior midline cysts occur between the two hemispheres, are ovoid, and can be distinguished into cavum septum pellucidum, cavum vergae, and cavum velum interpositum. Because all occur during early fetal stages (Tubbs et al. 2011), they are relatively stable after birth and have been considered as potential markers of abnormal neurodevelopment in schizophrenia (Takahashi and Suzuki 2018).

In secondary psychosis

Since morphological midline anomalies are relatively prevalent in the general population, the question of their relevance for psychosis still remains an ongoing debate. Thus, in a cohort of youth volunteering for MRI research, the small subsample of subjects with cavum septum pellucidum seemed to show a significantly greater incidence of reported psychotic symptoms (R. E. Gur et al. 2013). Our review found one report of a typical brief psychotic episode associated with cavum velum interpositum in a 25 years old patient, while his asymptomatic twin did not present with this morphological anomaly (Supprian et al. 2000). Another subject with 22q11 deletion, who also had gray matter heterotopia near the frontal horns and an incidental pineal cyst, presented with cavum septum pellucidum and cavum vergae (Starling and Harris 2008). Midline regions can also be the sites of tumors such as central neurocytomas, whose extensive lesions may only manifest with psychotic symptoms and without neurological signs (Karakula-Juchnowicz et al. 2018). Moreover, immediate resolution of all psychotic symptoms has been obtained after resection in another case of central neurocytoma with psychotic-only symptoms (Ouma 2004).

In primary psychosis

It was suggested that only large cava septa pellucida correlate with schizophrenia spectrum disorders, while small ones may be considered normal neuroanatomical variations (Trzesniak et al. 2011). A more recent meta-analysis found that psychosis greatly increased the risk of cavum septum pellucidum with a 1.39 odds ratio, albeit with high variance (L.-X. Wang et al. 2020).

Ventricles

In secondary psychosis

We found several cases of ventricular enlargement due to acquired hydrocephalus and associated with psychosis. While psychotic symptoms were accompanied by other neurologic signs such as gait and coordination deficits in a case of obstructive hydrocephalus caused by a colloid cyst (Højlund et al. 2018), red flags suggesting a secondary psychosis might sometimes be less obvious. Thus, subtle bradykinesia and mild non-localizing cognitive impairment may have been overshadowed by the initial psychotic presentation with aggressive behavior and delusions of persecution, in a case of normal pressure hydrocephalus due to idiopathic aqueductal stenosis (Chatziioannidis et al. 2013). Likewise, a 27 years-old patient, who had been presenting with treatment-resistant psychotic symptoms for the last ten years, and which began to present neurological gait and coordination deficits, was found to have a normal pressure hydrocephalus (B. R. Mishra et al. 2011).

In primary psychosis

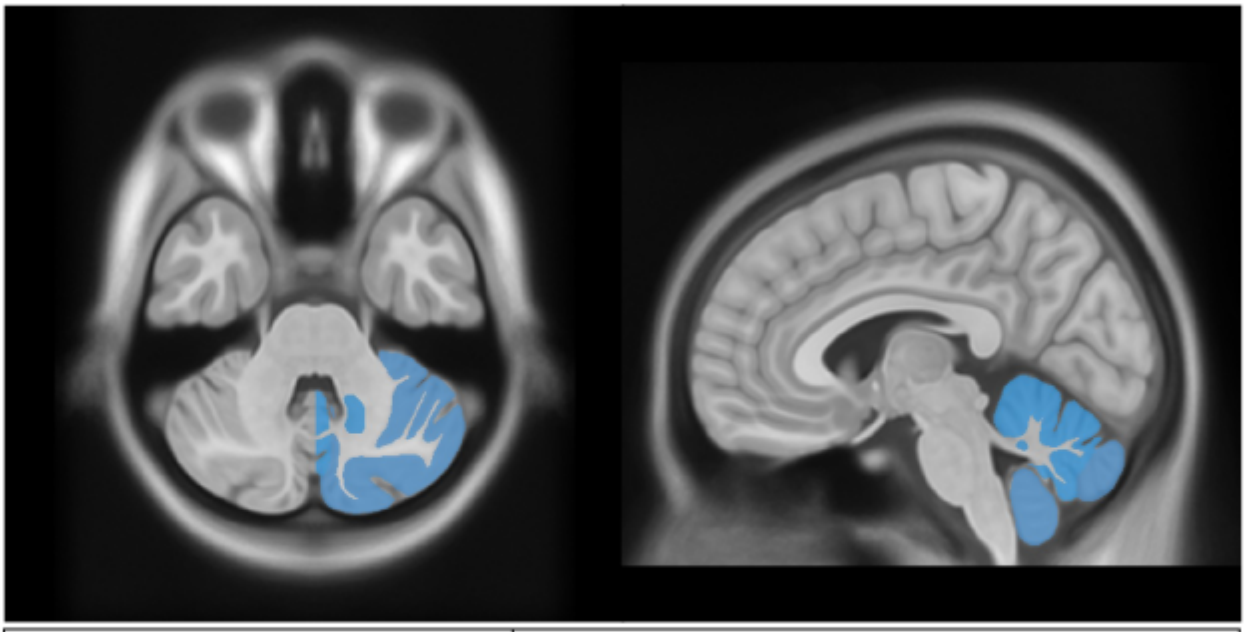
Ventricular enlargement is one of the most common and stable features observed in primary psychosis, but it is not specific to a particular psychiatric disorder. It is mainly linked to overall gray matter atrophy and seems to increase with disease progression (Svancer and Spaniel 2021). Because it has not been confirmed in early stages of the disease or before psychosis' onset, it is generally considered a marker of state rather than trait (Berger et al. 2017), although a recent study, reporting increased bilateral lateral ventricles in at-risk-mental states subjects, suggested otherwise (Sasabayashi et al. 2020). Moreover, ventricle enlargement seems to be correlated with negative symptomatology (Hepdurgun et al. 2021).

ANOMALIES IN THE CEREBELLUM

Anatomical and functional overview

The cerebellum consists of two hemispheres, englobing the vermis. It takes part in a large cortico-thalamic-cerebellar loop, involving all cortical areas, not only motor ones. Its consacrated role in sensorimotor and vestibular feedback has been extended over the last few decades to the regulation of cognition, emotion and autonomic functions. It is posited that the cerebellum automatically maintains behavioral homeostasis, based on implicit learning and according to the context. The cortex is considered to be involved in unsupervised learning, based on associations between stimuli and responses, and the basal ganglia to support reinforcement learning by increasing the likelihood of a behavior based on previous positive rewards. Conversely, the cerebellum is believed to support supervised learning that improves performance by minimizing prediction errors (Pierce and Péron 2020; Moberget and Ivry 2019). Among its ten functionally different lobules, sensorimotor activity seems to rely on the anterior lobe with a second location in the VIII lobule, and cognitive and limbic functions on the posterior lobe. A disturbance of cerebellar function could lead to an equivalent of "thought dysmetria", as described in the cognitive-affective cerebellar syndrome (Schmahmann 2019). But the precise mechanisms involved are not well understood (Moberget and Ivry 2019). Replicated findings have nevertheless associated decreased volumes in the vermis with thought disorders, mainly in the setting of positive symptoms (Sumner, Bell, and Rossell 2018). Overall, this postulated state of emotional dysregulation associated with executive disorders could shed light on the symptomatology found in psychosis, autism, but also in cerebellar neurological pathologies, often associated with psychotic manifestations. Moreover, genetic anomalies, or early developmental or toxic injuries, can converge on specific aspects of the cerebellum’s structure, such as a tropism for the parasagittal stripes’ pattern of Purkinje cells in very different disorders like Niemann-Pick type C or viral infections (Beckinghausen and Sillitoe 2019). This may explain similarities in cerebellar defects between developmentally-related schizophrenia spectrum disorders and other non-psychiatric disorders.

Figure 4: Secondary psychoses with lesions localized in the cerebellum



DISEASE	BRAIN IMAGING
	CEREBELLUM
Genetic / neurodevelopmental disorders	
Spinocerebellar ataxia type-10	Peripheral vermian and cerebellar hemisphere atrophy
Charlevoix-Saguenay spastic ataxia	Atrophy of the superior cerebellar vermis / "tigroid" aspect of the pons
Dandy-Walker syndrome	Hypoplasia of cerebellar hemispheres and vermis +/- 4th ventricle hydrocephalus / posterior fossa arachnoid cyst
Sporadic olivopontocerebellar atrophy	Atrophic cerebellar hemispheres, vermis, pons, inferior olivary nuclei
Undefined neurodevelopmental syndrome with cerebellar dysfunction	Low T1 signal areas in both cerebellar hemispheres, increased depth of the folio of the cerebellum, subcortical hyperintensities in the right insula and frontal lobes bilaterally
Arnold-Chiari malformations types I and II	Herniated cerebellar tonsils, medullary kinking, and tectal beaking in ACM type II; herniated cerebellar tonsils, ascent of odontoid peg, flattened skull base, partially empty pituitary fossa
Acute right intra-cerebellar hematoma following a rupture of arterio-veinous malformations	CT: acute right intracerebellar hematoma High FLAIR/T2 and low FLAIR/T1 signals in right cerebellar hemisphere
Metabolic disorders	
Niemann-Pick type C disease	Atrophy of the superior cerebellar vermis
Succinic semialdehyde dehydrogenase deficiency	Cerebellar atrophy predominantly in the vermis, subtle high T2 signal in globus pallidus
Auto-immune / inflammatory disorders	
Anti-NMDAR encephalitis on right ovarian teratoma	Non-specific, non-gadolinium enhancing high T2/FLAIR signals in cerebellar hemispheres and in occipital horn of left lateral ventricle

In secondary psychosis

Paranoid delusions, hallucinations, and thought content disorders have been described in adolescents and young adults with spinocerebellar ataxia (S. Mishra, Trikamji, and Singh 2014), Charlevoix-Saguenay spastic ataxia (Mignarri et al. 2014), Dandy-Walker syndrome with hypoplasia of the vermis and cerebellar hemispheres (Tréhout et al. 2019; Dawra 2017; Buonaguro, Cimmarosa, and Bartolomeis 2014; Gan et al. 2012; Turner, Poole, and Ghadiali 2001), sporadic olivopontocerebellar atrophy (Duggal 2005), in Arnold-Chiari malformations types I and II (Hoederath et al. 2014; Del Casale et al. 2012), and in metabolic disorders such as Niemann-Pick type C disease with superior vermian cerebellar atrophy (Walterfang et al. 2010; Tyvaert et al. 2005) or succinic semialdehyde dehydrogenase deficiency (Gibson et al. 2003). Anti-NMDAR encephalitis with localized cerebellar lesions (Yu and Moore 2011) and acute right intra-cerebellar hematoma following a rupture of arterio-veinous malformations (Almeida et al. 2011) have also been reported to manifest as acute psychosis (**Figure 4**).

In primary psychosis

A meta-analysis of cerebellar structure and function, between first-episode or drug-naive patients with schizophrenia, and matched healthy controls, found significant cerebellar gray matter volume decreases associated with functional connectivity anomalies. Some of them correlated with illness duration and severity (Y. Ding et al. 2019). At earlier stages of disease, in high-risk individuals, a resting-state functional connectivity study of dentate nuclei (deep nucleic structures in the cerebellum that constitute its main output) found anomalies in subjects who then developed psychosis compared to those who did not. These anomalies affected the specific default-mode, motor-salience, and visual processing networks (Anteraper et al. 2021). Furthermore, neurological soft signs, which describe non-focal impairments that may be a relevant endophenotype for schizophrenia, seem also to be explained by altered cerebellar - prefrontal resting-state connectivity (Cai et al. 2021). Finally, a detailed parcellation study of the cerebellum identified in diseased subjects a decreased global cerebellar volume, with most of the changes localized in the cognitive part of the cerebellum (Crus II and lobule VIIb). Interestingly, these abnormalities have not been detected in bipolar disorder, and may therefore constitute a distinct type of abnormality specific to schizophrenia (Laidi et al. 2019).

DISCUSSION

Relevance of brain lesions in psychosis

This paper reviewed cases of psychosis associated with brain lesions, which have been reported over a twenty years span in adolescents and young adults aged 13 to 30 years old (**Supplementary tables 1 to 4**). The first observation is that lesions in all brain regions, both cortical and subcortical, can be associated with psychosis. This supports the hypothesis of a disruption of general connectivity (Bassett, Xia, and Satterthwaite 2018), where any damage may destabilize the network and lead, for example, to the abnormalities in synchronization and neural oscillations often described in primary psychosis (Grent-‘t-Jong et al. 2020; Senkowski and Gallinat 2015; Uhlhaas and Singer 2010). The second observation is that uncommon cases of secondary psychosis illustrate the pathogenic role of key regions of the network, which are also highlighted by case-control studies in common primary psychoses. In particular, beside large cortical involvement, localized lesions in specific cerebellar or subcortical areas (thalamic nuclei, globus pallidus, pineal gland, hypothalamus) highlight the importance of cortico-subcortical networks such as cortico-thalamic-cerebellar loops (**Figures 1 to 4**). Our results therefore support transdiagnostic and multimodal strategies, which aim at improving our understanding of psychosis by focusing on complex psycho-motor-affective phenotypes. This endeavor is already represented by the cooperation between working groups specialized in movement disorder and sensori- or psychomotor functioning in psychoses, which recently published a roadmap of challenges to be addressed in the field (e.g. improving the assessment of sensorimotor dysfunction in schizophrenia, including antipsychotic-naïve subjects in order to get rid of the bias related to treatment effects, or extending the use of MRI in these populations) (Walther et al. 2020). Conversely, a more systematic psychiatric characterization of individuals with neurological disorders, with the use for instance of phenomenological scales such as the examination of anomalous self-experiences (Parnas et al. 2005), may provide insight into subtle prodromal disturbances of the self that may bridge the gap between neurology and psychiatry.

This review further illustrates that identifying an underlying brain abnormality, causal or not, can be highly relevant for clinical management. First, brain anomalies can sometimes explain all or part of psychotic symptomatology, and full recovery is then achieved with appropriate treatment. This was found to be the case: (i) in autoimmune or inflammatory diseases, as reported in the many cases of anti-NMDAR encephalitis, requiring immunosuppressive therapy and surgery of

ovarian teratomas (Sabbula et al. 2020; Lwanga et al. 2018), or in multiple sclerosis and neurolupus, where psychosis also remitted after immunosuppressive therapy (Jghaimi, Kabbaj, and Essaadouni 2009; Jongen 2006); (ii) in tumoral processes where surgical resection led to full remission in the case of an epidermoid cyst in the pineal gland or a hypothalamic hamartoma (Jiang et al. 2018; Al-Hail et al. 2010), or clear improvement in a grade II meningioma (Gama Marques 2020), and in morphologic anomalies like arachnoid cysts, where the treatment of the subsequent intracranial pressure could also bring full recovery; finally, (iii) in metabolic disorders such as 5,10-methylenetetrahydrofolate reductase deficiency or Niemann-Pick type C, where adequate supplementation achieved full recovery (Iida et al. 2017; Walterfang 2006).

Nevertheless, many and probably most clinically-relevant brain anomalies play a less obvious pathophysiological role. Thus, a brain lesion may constitute a precipitating factor for psychosis, which then follows its own course despite treatment of the underlying lesion, or it may merely add to the burden of a brain already vulnerable to psychosis. For instance, a case of neurocysticercosis on the background of long-term cannabinoid use during adolescence, a known schizophrenia risk, required both antiparasitary and antipsychotic drugs on the long term (Miranda 2020). Another example is a case of onset of psychosis after a traumatic brain injury in a subject with genetic vulnerability to psychosis and a premature birth (Greene et al. 2010). However, whether underlying brain injuries allow immediate treatment or are mere comorbidities, their identification has relevant implications for symptomatic management of psychosis. Because they underpin higher brain sensitivity to psychotropic medication, a “start low, go slow” paradigm is preferred, with antipsychotic treatments known to have low extrapyramidal side-effects, and used in mono-therapy. Olanzapine, risperidone, aripiprazole, quetiapine, or clozapine are therefore recommended over first-generation antipsychotics. Careful side-effects monitoring is required, notably because of the lowering of the epileptogenic threshold (Plantier and Luauté 2016; Bhatnagar, Iaccarino, and Zafonte 2016). Interestingly, one case of psychosis secondary to traumatic brain injury, which dramatically improved after the patient experienced a tonic-clonic seizure, also highlighted the potential utility of electroconvulsive therapy (ECT) in such conditions (Spiers, Kompardt, and Tait 2016). ECT is well-tolerated and there is no formal contraindication to it, although the presence of an intracranial mass requires an assessment of the risk incurred by the ECT-induced transient increase in intracranial pressure (Benson and Seiner 2019). Primarily recommended in treatment-resistant depression and frequently used in catatonia - which itself is often entailed by underlying medical conditions, ECT has also shown efficacy in the treatment of refractory

psychiatric symptoms in Huntington's disease (Adrissi et al. 2019) or Parkinson's (Rosenquist et al. 2018).

Clinical red flags for secondary psychosis

Symptoms or signs suggestive of an underlying non-psychiatric etiology are found in a majority of cases with secondary psychosis. Precise history taking and physical examination are therefore crucial in identifying such red flags (Pollak et al. 2020; Giannitelli et al. 2018; Bonnot et al. 2015). They include :

- *Atypicalities related to the family background* : the absence of a family history of psychiatric disorder or conversely the aggregation of numerous cases in the same family, or the presence of a family history of non-psychiatric pathologies.
- *Atypicalities linked to personal history and disease course* : these may include early or late onset of symptoms, acute onset, a particular context (fever, medication, etc) or the presence of associated developmental abnormalities.
- *Symptoms suggestive of multivisceral pathology*.
- *Atypical psychiatric symptoms*: visual, cenesthetic or olfactory hallucinations without an auditory component, the existence of an unambiguous critique of these hallucinations or the well-systematized nature of delusional elements.
- *Atypical evolution of the disease* : spontaneous fluctuation of symptoms, paradoxical response to treatment, marked adverse effects to low doses of antipsychotics, catatonia or neuroleptic malignant syndrome.
- *Atypicalities on clinical examination,* including neurological, metabolic, or inflammatory findings.

Should brain MRI be a routine assessment in early psychosis ?

We emphasize that we specifically considered psychosis onset between 13 to 30 years of age. First episodes of psychosis prior to or following this time frame are for the clinician more systematically evocative of a possible secondary underlying cause, because childhood-onset schizophrenia is a rare disease, with an estimated prevalence around 0.04 % (Driver 2020), and adult- or late-onset episodes of psychosis in the absence of prior history are also grounds for further extensive investigations, including brain imaging. Conversely, because the emergence of primary psychosis is expected to occur in adolescents and young adults, differential diagnosis between primary and secondary psychosis does not systematically include brain imaging if

there is no focal neurological sign, and international recommendations on the topic are not consensual (Khan and Lachman 2020; Orygen 2016). However, this review showed that typical psychotic symptoms, including auditory hallucinations, delusions, and thought disorder, can be the first and only initial expression of many different severe brain disorders. Among the 129 cases reviewed, more than 10 % presented without any neurological focal sign or major clinical atypicality. Adding to this proportion are cases where the only red flags consisted of poor treatment response or severe side-effects to low-dose antipsychotics, after a first diagnostic hypothesis was made and treatment initiated. These observations are corroborated by a recent retrospective review on 125 inpatient adolescents with brain imaging (115 CT and 10 MRI) performed during admission, where 11 CT (9.2 %) scans were clinically-relevant, with changes in diagnosis and management in five cases. In the smaller MRI subset, three out of ten were abnormal, with changes in diagnosis or management in two cases. The authors also noted the absence of correlation between clinical presentation and relevant anomalies, further supporting the relevance of routine brain imaging in first episodes of psychosis (Khan and Lachman 2020). Finally, the prevalence of clinically-relevant brain lesions during psychosis' onset has been repetitively reported above the often cited 1 % that would justify the use of MRI from a cost-effectiveness perspective (Albon et al. 2008; Schmidt and Borgwardt 2020). Overall, the generalization of MRI accessibility, the frequency of underlying treatable disorders, and the severe consequences of ignoring these disorders in young populations support the use of systematic brain MRI in routine screening of psychotic presentations (Schmidt and Borgwardt 2020; Falkenberg et al. 2017; Jardri 2013).

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None of the authors report any competing interest.

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