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REVIEW ARTICLE

Clinical anatomy of the precuneus and pathogenesis of the schizophrenia

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Abstract

Recent evidence has shown that the precuneus plays a role in the pathogenesis of schizophrenia. The precuneus is a structure of the parietal lobe's medial and posterior cortex, representing a central hub involved in multimodal integration processes. Although neglected for several years, the precuneus is highly complex and crucial for multimodal integration. It has extensive connections with different cerebral areas and is an interface between external stimuli and internal representations. In human evolution, the precuneus has increased in size and complexity, allowing the development of higher cognitive functions, such as visual-spatial ability, mental imagery, episodic memory, and other tasks involved in emotional processing and mentalization. This paper reviews the functions of the precuneus and discusses them concerning the psychopathological aspects of schizophrenia. The different neuronal circuits, such as the default mode network (DMN), in which the precuneus is involved and its alterations in the structure (grey matter) and the disconnection of pathways (white matter) are described.

Keywords Default mode network · Multimodal integration · Parietal lobe · Precuneus · Schizophrenia

Introduction

Several data in the literature have highlighted that the precuneus, an area of the medial parietal cortex, plays a crucial role in the etiopathogenesis of schizophrenia (Whitfield-Gabrieli et al. 2009; Faget-Agius et al. 2012; Gong et al.2014; Rikandi et al. 2016; Zhu et al. 2017; Forlim et al. 2020; Aryutova et al. 2021; Li et al. 2021; Mäntylä et al. 2021). Literature for years has neglected precuneus functions. Since ischemic lesions of the precuneus are rarely observed and due to its hidden position on the medial surface of the parietal lobe, its exploration appears challenging. The involvement of the precuneus in multiple neural circuits and its widespread intracortical and subcortical-cortical connections make it an important hub in the networks of the brain involved in the perception, processing and integration of internal and external sensory stimuli, spatial navigation, memory, and self-awareness (Cavanna and Trimble 2006). A specific aspect of schizophrenia is the inability to harmonize the perception of external reality with the perception of self and the inner life experience. The lack of coordination between external and inwardly experienced reality represents a fundamental aspect of the psychotic experience. This paper will describe data from the literature regarding the role of the precuneus in different aspects of mental activity and the pathogenesis of schizophrenia.

In the first part, we will report the precuneal evolutionary and morphological aspects and interrelationships with other brain areas. We will describe the functions in which the precuneus is involved and the clinical aspects of schizophrenia related to alterations of the precuneus.

Clinical Anatomy of the precuneus

The precuneus, or square lobule, named by Achille Louis Foville (1844) because of its quadrangular shape, is located in the superior posteromedial cortex, corresponding to Brodmann area 7 and 31 (BA7-31) or 62–64 regions according to von Economo and Koskinas cytoarchitectural nomenclature (Al-Ramadhani et al. 2021). The marginal sulcus and the sub-parietal sulcus separate the precuneus from the

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paracentral lobule and the cingulate lobe respectively, while the parieto-occipital and calcarine sulcus delimit the precuneus from the occipital lobe (Cavanna and Trimble 2006).

The precuneus belongs to the so-called "rich club" together with the insula, the superior frontal and the parietal cortex, because of its network of multiple neural connections and of its executive role in multimodal integration (Van de Heuvel and Sporn 2011; Van de Heuvel et al. 2013). Three different subregions have been identified in the precuneus. The dorsal-anterior precuneus which is connected with the frontal-parietal cortex and is implicated in the mental representations of space, in object-body relations, and in visually guided movement (Knauff et al. 2003; Wenderoth et al. 2005; Sima et al. 2013; Dordevic et al. 2022). The dorsal-posterior precuneus is connected with the occipital-parietal lobes and hippocampus. It processes the visual-spatial information (Cavada and Goldman-Rakic 1989; Leichnetz et al. 2001), deductive reasoning (Knauff et al. 2003), spatial navigation (Ghaem et al. 1997), and motor imagery (Maloiun et al. 2003) and permits recreating spatial mental models used to cognitive and abstract reasoning processes (Johnson-Laid 1995; Knauff et al. 2002). The ventral precuneus is connected with the cingulate, temporal, and limbic lobe; it is involved in emotional and episodic memory processing (Margulies et al. 2009; Cauda et al. 2010; Zhang and Li 2012; Wang et al. 2019). Ventral precuneus is activated during episodic memory retrieval, which gathers autobiographical events and allows them to be placed in space and time (Tulving et al. 1994; Addis et al. 2004; Gilboa et al. 2004). In addition, visuospatial information passes through the precuneus before reaching the hippocampus, to be encoded and subsequently stored (Rolls and Wirth 2018).

The subdivision of the precuneus and the specialization of the sub-regions are indicative of its complexity. The involvement of the precuneus in several functions and its multiple interfaces with areas of the limbic system, sensory and motor cortex, which integrate sensory-motor with limbic information, direct goal-oriented reasoning and behavior (Passarelli et al. 2021), generating the distinctive mental processes of Homo Sapiens (Cavanna and Trimble 2006; Margulies et al. 2009).

The precuneus in human evolution

In Homo Sapiens, the precuneus represents a significant area, and the parietal lobe is more extensive than the remaining lobes (Fig. 1) (Bruner et al. 2014a). As some authors have noted, the evolutionary leap between primates and Homo Sapiens appears to be related to the morphogenesis of the parietal lobe primarily (Bruner et al. 2014a). Therefore, a hallmark of human brain evolution was the modification and the bulging of the parietal lobes, compared with other

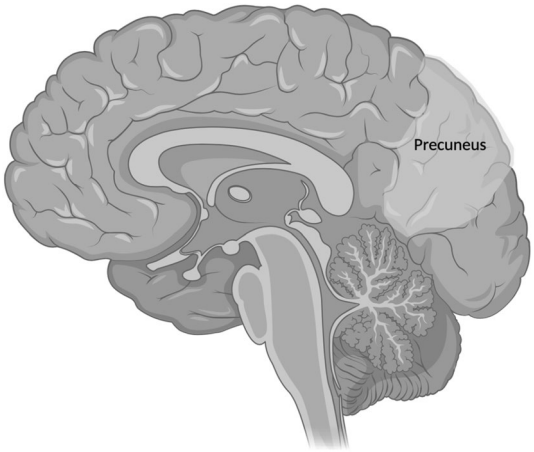

Fig. 1 Topography of the precuneus Created with BioRender.com

species (Bruner 2004; Bruner et al. 2017a; Kaas and Stepniewska 2018).

In particular, the enlargement of the medial parietal cortex appears to be closely related to the volumetric increase of the precuneus (Bruner et al. 2017b), which gradually evolves in the phylogenesis of mammals (Morgane et al. 1980). Such rapid and remarkable growth has no parallel in primates, nor has it ever been evidenced in the fossil remains of Neanderthals.

In this regard, fossils found of parietal skull bones of individuals belonging to the Neanderthal homo species or earlier hominid did not have dimensions consistent with an expansion of the parietal lobes such as that shown by Homo Sapiens (Bruner et al. 2010; Gomez-Robler et al. 2013).

During human evolution, the growth of the precuneus allowed Homo Sapiens to develop high cognitive functions and self-awareness (Bruner et al. 2017a, b). Primary, the expansion of the parietal cortex was an acquisition of Homo Habilis; compared to Australopithecus, Homo Habilis, who lived between 2.4 and 1.4 million years ago, showed greater brain capacity with more significant enlargement of the parietal lobes (Fig. 2) (Tobias 1987).

Interestingly the increase of the precuneus, of which the fossil remains of skulls attest to the progressive volumetric increase, coincides with the appearance of the earliest forms of cave paintings made by the first hominids (Bruner 2018). The emergence of language, mathematics, constructive skills, and ultimately culture as a distinguishing feature of the human species is a consequence of the development of the precuneus (Bruner et al. 2022). The expansion of the precuneus represented a pivot of crucial importance in the transition from "hominid animals" to "hominid humans" (Tobias 1987).

(Northoff and Bermpohl 2004). In this complex model, the precuneus represents a node of integration between

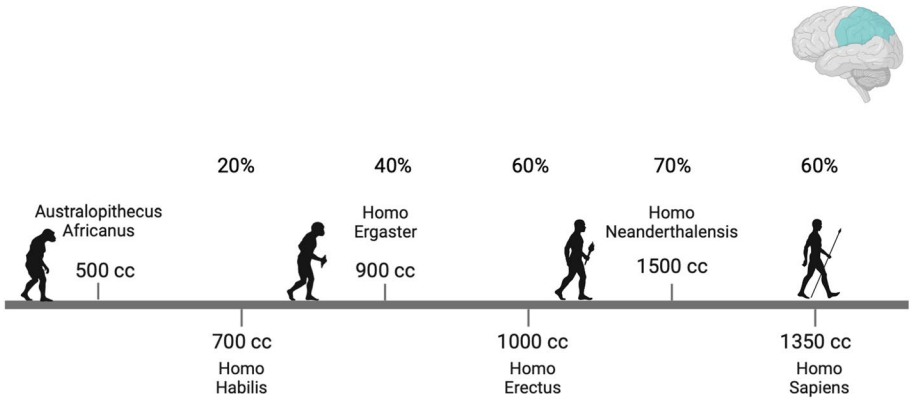

Fig. 2 Relative frequency (%) of Parietal lobe's emissaryforamina veins against mean cranial capacity (cc) during Homo species evolution (Falk 2009) Created with BioRender.com

environmental, internal stimuli and the emerging self (Northoff and Bermpohl 2004).

Precuneus and default mode network

The precuneus is also a fundamental hub in the Default Mode Network (DMN) (Fransson and Marrelec 2008; Hagmann et al. 2008; Utevsky et al. 2014; Yang et al. 2014; Raichle 2015; Schilibach et al. 2015; Aryutova et al. 2021; Fuentealba-Villarroel 2021), that represents an extensive neuronal network connecting different cerebral regions and activating when the brain is in a state of rest, focused on the internal mental state and not engaged in goal-oriented tasks (Raichle et al. 2001). In the first instance, the DMN is activated in spontaneous cognition, i.e., when the brain is relaxed, free to wander from one thought to another, without external stimuli (Andrews-Hanna et al. 2010; Raichle 2015). Other prominent functions of the DMN that involve the precuneus are sensory processing, emotional processing, referential self-activity, storage of past experiences, spatial navigation, future imagination (Raichle 2015) and skills needed for the successful development of sociality such as social cognition and the ability to attribute mental states to others (theory of mind) (Mars et al. 2012). Concerning the importance of the precuneus as a nodal structure in the circuits involved in the DMN, Deng et al. (2019) speculated the precuneus as a constituent of a network separate from the DMN. What differentiates the DMN from the precuneus network is the context-processing information (Deng et al. 2019). Context processing calls for the combination of various tasks, such as the multisensory decoding of information, the integration with cognition and internal state, and to maintain an abstract representation needed to execute goal behavioral (Cohen and Servan-Schreiber 1992).

Schizophrenia

Schizophrenia is a severe psychotic disorder with a prevalence of 1%, widespread almost evenly throughout the world (Salomon et al. 2013) and burdened by health and social costs. The pathophysiology distinguishing schizophrenia lies in the severe dysfunction of typically human higher cortical functions, such as thought, perception, cognition, behavior, and social functioning. Schizophrenia is a cognitive and neurodegenerative disorder (Lieberman 1999; Ashe et al. 2001; Stone et al.2022), characterized by: (i) positive or productive symptoms, such as paranoid delusions and primarily auditory hallucinations, although any sensory modality can be affected; (ii) negative or deficit symptoms, such as flat affect, poor thought, reduced motor initiative and disorganized behavior (Mueser and McGurk 2004). Moreover, a maladaptive characteristic linked with the poor mentalizing ability of schizophrenia is impaired social cognition, a consequence of the disability to perceive own and other mental states required to decode social information and process social constructs. Altered social cognition frequently co-occurs with the lack of disease awareness (Adolphs 2001; Smith and Semin 2007; Lysaker et al. 2011).

Several pathogenetic hypotheses have been advanced over the past two centuries since Emil Kraepelin first described schizophrenia as "dementia praecox" (Kraepelin 1893). To date, there is no certain theory on the causes and pathophysiology of schizophrenia. Nevertheless, because of the complexity and clinical heterogeneity of the disease, various cortical and subcortical areas interconnected by dopamine, serotonin, and glutamate cortico-subcortical circuits are reputed as responsible for the etiopathogenesis of schizophrenia.

Over the past decade, several evidences have accumulated on the disconnection hypothesis as a key element in the pathogenesis of schizophrenia. Underlying the varied symptomatic expression is a disconnection of different brain areas involved in perception processing, cognitive function, and multimodal integration (Friston and Frith 1995; Friston et al.2016). This disconnection bias also includes the concept of "cognitive dysmetria", which represents a conceptual framework of schizophrenic cognitive processing. (Andreasen et al. 1996, 1998; Wiser et al. 1998; Crespo

Facorro et al. 1999; Kim et al. 2000; Cao et al. 2018). The definition of "cognitive dysmetria" overlaps with the functions of the DMN, and the disconnection of cortical and subcortical areas engaged in the DMN of schizophrenic patients is implicated in both psychopathological symptoms and impaired social skills (Garrity et al. 2007; Rotarska-Jagiela et al. 2010; Kong et al. 2022; Saris et al. 2022).

Brain disconnection is a consequence of the white matter disruption that connects grey matter areas. For neurotransmission between the cortical and subcortical regions to be effective and efficient, it is necessary that myelin, which lines the axons, is intact (Höistad et al. 2009). Diffusor tensor imaging, which measures fractional anisotropy, permits the integrity of nerve bundles to be assessed and their conduction capacity to be evaluated, allowing to quantify the myelination of the axon, and correlating it with schizophrenia (Karoutzu et al. 2008; Birur et al. 2017). Several extensive studies, such as ENIGMA Schizophrenia Working Group and metanalytic analysis, concluded that white matter is diffusely reduced in several brain areas of schizophrenic patients (Ellison-Wright and Bullmore 2009; Dennis et al. 2019; Chee et al. 2020). In schizophrenia most of the white matter alterations were found in : (i) the cingulate bundle, which connects certain regions of the limbic system, such as the parahippocampal cortex and the anterior cingulate cortex (Whitford et al. 2014); (ii) the inferior longitudinal fasciculus, which connects temporal and occipital areas (Ashtari et al. 2007; Herbet et al. 2018); (iii) the uncinate fasciculus, which connects frontal and temporal lobe (Kubicki et al. 2002); (iv) the splenium of the corpus callosum, connecting both hemispheres (Koshiyama et al. 2018); (v) the superior longitudinal fasciculus, which represents the most extensive fiber bundle connecting the frontal, temporal and parietal lobes (Karlsgodt et al. 2008; Podwalski et al. 2022).

Several studies have shown that grey matter and white matter are affected in the first episode and chronic schizophrenia (Gur et al. 1999; Vita et al. 2012), with degeneration of the cortical neuropil (dendritic tree, terminal axons, synapses, and glial cells) (Glausier and Lewis 2013), damaged by chronic activation of microglia (Zhang et al. 2016).

Precuneus and schizophrenia

In schizophrenia, dysfunction of the precuneus, due to its centrality in multiple integrative functions and in subcortical-cortical and cortico-cortical connections, plays a key role in neural disconnection, described in different neural networks such as the parietal, frontal, and temporal lobes (Friston and Frith 1995; Fransson and Marrelec 2008; Bruner et al. 2014b; Utevsky et al. 2014; Hu et al. 2017; Dong et al. 2018; Lammeyer et al. 2019; Rolls et al. 2020; Lyu et al. 2021).

Specifically, the disruption of the cortico-cerebellar-thalamic-cortical loop, in which precuneus has a central function, underlies the cause of cognitive impairment, motor incoordination, behavioral disinhibition (i.e., disorganization and catatonia) and loss of sensory integration (Cai et al. 2021; Xie et al. 2021).

In support of these assumptions, a recent metanalysis, which considered twenty-five structural Magnetic resonance imaging (MRI) and thirty-two functional MRIs of schizophrenic patients, has described the impairment of thalamus-precuneus circuity and of networks between the precuneus and the temporal, frontal, and parietal lobe, which also anatomically support the neural connection of the DMN (Zhu et al. 2022). The failure of the activation during rest brain states, and the non-deactivation when the brain is engaged in specific tasks are hallmarks of the disrupted DMN observed in schizophrenia (Rotarska-Jagiela et al. 2010; Orliac et al. 2013; Aryutova et al. 2021; Stoyanov et al. 2021). Moreover, the hyperactivation and the hypoactivation of the DMN resulting from fluctuations in temporal frequency and spatial location in medial areas of the cortex generate an aberrant connection between these areas and other brain regions (Garrity et al. 2007).

Thus, the disturbed activity of DMN, overlapped with precuneus-related impairments of emotional processing, mental imagery, visuospatial ability, and mentalization, was observed in patients with greater dominance of unfavorable symptoms such as apathy (Forlim et al. 2020) and impaired abstract reasoning (Mashal et al. 2014). Instead, the positive symptoms are derived from alterations involving precuneus/DMN processing that provides for self-awareness and perceptions elaboration/integration. Positive symptoms were associated with the disintegration of the precuneal networks with the posterior cingulate cortex, the temporal parietal junction, and the prefrontal cortex (Hirjak et al. 2017; Larivière et al. 2017; Fuentes-Claramonte et al. 2022). Very often, in the prodromal phase of schizophrenia, before positive symptoms and paranoid delusions manifest, suspiciousness is frequently observed. Suspiciousness, derived from a reduced ability to assign an appropriate value to external stimuli, is associated with an aberrated salience and with the inability to differentiate self from others (Fuentes-Claramonte et al. 2020); disrupted connection between the precuneus, the insula of Reil (Soldevila-Matìas et al. 2022) and the parahippocampal gyrus (Zhu et al. 2017) were observed in patients with suspiciousness. Morphologic alterations of the insula and parahippocampal gyrus increase the risk of psychotic disorders (Curtis et al. 2021; Sheffield et al. 2021). Interestingly, the treatment with antipsychotic drugs, effective in controlling symptoms and preventing relapse, has also been shown to improve integration between the precuneus and posterior cingulate cortex and even promote DMN

neural circuits integration and connectivity (Guo et al. 2014; Zong et al. 2019; Deng et al. 2022; Li et al. 2022a).

In the most severe forms of schizophrenia, lack of illness awareness is a characteristic associated with poor outcomes. The presence of adequate disease awareness is closely dependent on adequate metacognitive skills and preserved self-awareness and (Lysaker et al. 2009).

In patients with schizophrenia, the lack of awareness of the disease is associated with the DMN-disrupted connections between the precuneus, the posterior cingulate cortex, and the prefrontal cortex (Clark et al. 2018). In addition, the precuneus shows decreased perfusion in patients with a lack of awareness disease (Faget-Agius et al. 2012). At the same time, altered connections between the precuneus and prefrontal cortex were observed in schizophrenic patients with poor social functioning (Fox et al. 2017).

The connections between the precuneus and cortical areas depend on the integrity of white matter and are most supported by the superior longitudinal fasciculus (SLF), the largest intracortical association bundle. Reduced integrity of the SLF has been correlated with dysfunction of the DMN and the frontoparietal circuitry, both of which are thought to be responsible for both positive and negative symptoms of schizophrenia (Karlsgodt et al. 2008; Podwalski et al. 2022).

Reduced cerebral blood flow and cortical thinning of the precuneus were observed in schizophrenic patients concerning healthy controls (Zhu et al. 2017; Massey et al. 2017), and in fact, cortical precuneus thinning was found in patients with poor awareness of the disease compared with healthy controls. In the precuneus of schizophrenic patients grey matter loss and cortical thinness were associated with a longer duration of untreated illness, a more significant presence of positive symptoms, lower cognitive performance (Li et al. 2022), poor awareness of the disease (Buchy et al. 2018; Mäntylä et al. 2021), and the inability to recognize and to differentiate own another's emotions, known as alexithymia (Jàni et al. 2021).

Many higher cognitive and social competencies, such as social cognition are due to the presence of VENs, predominantly diffuse in the V layer of the cortex of the precuneus (Funtealba-Villarroel et al. 2021). Reduced density of VENs, observed in the precuneus of schizophrenic patients (Brüne et al.2010; Krause et al.2017; Lòpez-Ojeda and Hurley 2022), reinforces the suggestion of a causal link between precuneus cortical degeneration and schizophrenia. In addition, the alteration of grey matter in the precuneus of schizophrenic patients is also associated with the polymorphism of disrupted-in-schizophrenic-1 (DISC1 gene), a scaffold protein associated with dopaminergic receptors and involved in pre- and post-synaptic signaling, in the neuron migration, and the dendrite pruning (Gong et al. 2014). Schizophrenic patients with genetic polymorphism of DISC-1 show alterations of volume and aberrant functional connectivity of precuneus (Gong et al. 2014). The association between the precuneal grey matter and DISC-1, which is the gene most likely to be involved in the onset of schizophrenia (Dahoun et al. 2017), provides further data to support the hypothesis that the precuneus plays a significant role in the onset of schizophrenia.

Conclusion

- The precuneus and DMN represent the anatomical substrate of overlapping sensorial, motor, cognitive and social elaborating, and processing functions so that the precuneus and DMN can represent a valid pathogenetic model of schizophrenia.
- In schizophrenia, alterations of the precuneus can affect the integrity of connections between the precuneus and other brain areas, the cytoarchitectonic of the precuneus (degeneration of VENs), such as the degree of cortical thinness.
- The precuneal intracortical relations are mediated by SLF, which represents the main cortical white matter association fasciculus.
- In schizophrenia, grey matter reduction of precuneus is characterized by a loss of neuropile rather than a mere neuronal loss.
- Genetic data relating to the association between the morpho-functional features of the precuneus and the DISC-1 gene reinforce the hypothesis of the causal role of the precuneus in schizophrenia.

Referred data regarding the precuneus and schizophrenia are still limited, despite the importance of the precuneus in schizophrenia that emerged from recent pioneering studies. Future research needs to be further investigated considering the fundamental role that the precuneus plays in the pathogenesis of the different domains of schizophrenia.

Large samples of patients divided by psychopathological clusters should be investigated by fMRI to assess the activity of the precuneus, comparing it with healthy subjects. Post-mortem studies could investigate the histological structure of the precuneus cortex, grey matter thinness and microglia activity because of its role in schizophrenia-related neuroinflammation. Finally, connectomes studies can elucidate and describe the maps of connections between the precuneus, and other brain areas involved in DMN concerning schizophrenia.

Heuristically, the appearance of schizophrenia can be due to the increased complexity of the brain in homo sapiens. The precuneus is the neuroanatomical substrate of the ability to imagine, transform and reproduce images in mind (Mahayana et al. 2014). The enlargement and development of the precuneus, involved in the introspection, in

the autobiographical memory, and in the ability to imagine the future represents a peculiar achievement to homo sapiens. Visuospatial imagery permits the mental manipulation of spatial, geometric, and numerical concepts, an essential typical skill of homo sapiens, and is a prerequisite for emerging abstract and logical-mathematical thinking (Benson and Park 2013). In fact, developing new ideas requires the activity of the DMN (Beaty et al. 2014; Silberstein and Camfield 2021) and the integration of the DMN with the frontoparietal network produces creative thinking (Shi et al. 2018).

The precuneus and the DMN were allowed to reach a higher evolutionary degree than in other species, yet schizophrenia took its toll on human evolution and the developing language and the social brain (Crow 1997, 2000). However, it was primarily the price to be paid for developing the precuneus and all related functions.

Indeed, many genes involved in the most characteristic functions of human beings, such as language, creativity, and visuospatial abilities (Nettle and Clegg 2006; Power et al. 2015; Liu et al. 2019), are shared with schizophrenia. In conclusion, schizophrenia, absent in other species, is a disease of homo sapiens and is related to the evolution of the brain and specific system as the precuneus.

Data availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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