Pathological changes in the Salience Network in schizophrenia.

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Abstract

The Salience Network has not been a focus in schizophrenia research to the same extent other pathways have. It has been suggested to have a role in cognition, self-awareness, communication and social interaction, all processes disrupted in schizophrenia.

Here we briefly review the evidence for pathological change in the main structures of the Salience Network; the insular cortex, anterior cingulate cortex, substantia nigra, ventral striatum, amygdala and mediodorsal thalamus in schizophrenia to examine whether there is evidence for widespread disruption in this circuit to justify further consideration in ongoing research.

KEYWORDS: SALIENCE, INSULA, CINGULATE, PATHOLOGY, SCHIZOPHRENIA

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The Salience Network

The Salience Network (SaN) is a large-scale brain network most commonly examined in connection between the anterior insula and dorsal anterior cingulate cortex, although the SaN is more completely described by the inclusion three subcortical structures, the amygdala, the substantia nigra and the ventral striatum. The SaN has been suggested to be involved in multiple functional roles including social behaviour regulation, sensory, emotional, and cognitive information processing and even maintaining homeostasis (Seeley, 2019; Menon and Uddin, 2010; Gogolla, 2017) and suggested to be an intervening system between the default mode network and central executive network (Nekovarova et al., 2014; Sridharan, Levitin and Menon, 2008). Disruption of the SaN has been implicated in schizophrenia by means of dysregulation of cortical control (Uddin, 2015; Peters, Dunlop and Downar, 2016).

The insula cortex, usually shortened to 'insula', is a cortical structure little investigated in schizophrenia. It was first described by a German neurologist, JC Reil, in the 19th century. It is located deep within the lateral fissure of each hemisphere hidden below parts of the frontal, parietal and temporal

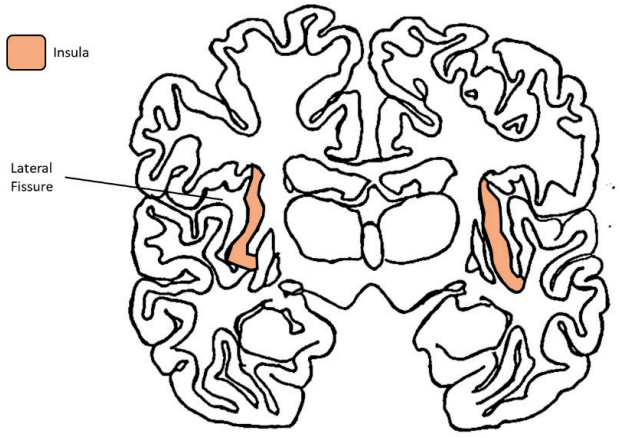

Fig. 1. Coronal cut at the level of the amygdala showing the location of the insula on the most medial surface of the later fissure.

lobes, folded over the insular in an arrangement known as the opercula (Gogolla, 2017). The structure has been shown to have a key role in interoception and emotional regulation, with anterior-originating projections reported to the anterior cingulate, amygdala and dmTh as part of the SaN (Wylie and Tregellas, 2010), with insula lesions repeatedly shown to impair disgust as well as facial recognition (Adolphs et al., 2000; Adolphs, Tranel and Damasio, 2003; Calder et al., 2000).

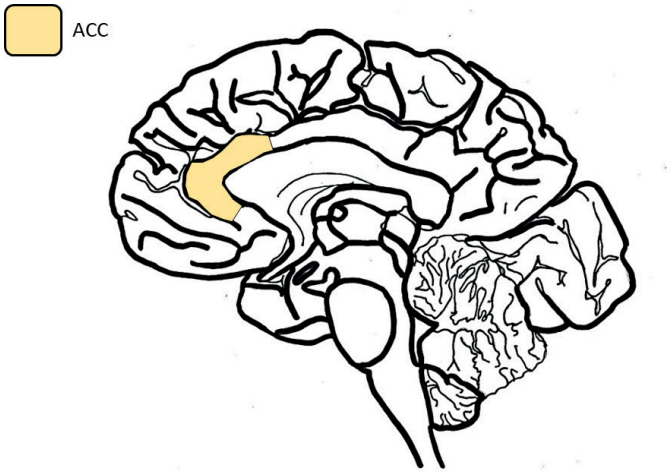

Fig. 2. Location of the Anterior Cingulate Cortex (ACC) as shown in sagittal section close to the midline of the brain. There are no clear neuroanatomical boundaries delineating the sub-regions of the cingulate cortex and therefore the anterior part of often described as following the callosal genu.

MRI examination has shown that overall insula shape is distorted in schizophrenia (Jang et al., 2006), although it is not clear how much this is a true effect of the insula itself rather than a consequence of overall brain torque change (Luchins, Weinberger and Wyatt, 1979; Zhao, Hietala and Tohka, 2009). Reduced fractional anisotropy between the amygdala and insular cortex in schizophrenia compared is negatively correlated with avolition and apathy but not with expressive behaviours, suggesting a key role in the interaction between these structures in cognitive functions that is disrupted in schizophrenia (Amodio et al., 2018). A positive correlation with negative symptoms in schizophrenia has also been reported in the right insula as measured by DTI (Skelly et al., 2008).

Anterior Cingulate Cortex

The Anterior Cingulate Cortex (ACC) lies on the medial surface of the cerebral hemisphere, covering the anterior part of the corpus callosum, extending from the subgenual ventral terminus and continues rostral to the genu of the corpus callosum following the dorsal surface and has been a focus in neuropsychiatric research. The cingulate sulcus defines its inner boundary and the superior rostral sulcus its ventral boundary, and cytoarchitecturally it is bounded internally by the ACC, externally by medial margins of the agranular frontal area 6, intermediate frontal area 8, granular frontal area 9, frontopolar area 10, and prefrontal area 11 (Brodmann, 1909). The ACC has anatomical connections with several frontal gyri, insula and amygdala.

Whilst there are reported changes in neuron density, particularly pyramidal cell density, in Layer V of the ACC, there are reports of decreased neurons in schizophrenia (Benes, Davidson et al. 1986), and broader study of the ACC cortical thickness reported decreased neuron density across layer II-VI (Benes, Davidson and Bird, 1986; Chana et al., 2003). Layer II of the ACC has shown specific changes in schizophrenia, with decreased neurons reported from direct stereological examination and confirmed by meta-analysis, and a possible 25% drop in GABA-neurons in the ACC layer II in schizophrenia (Benes and Bird, 1987; Cotter et al., 2002a).

This complexity of findings may not be a result of typical heterogeneity of results in the field but instead reflective of an uneven change across neuronal populations as there is some evidence of neuronal clumping or clustering changes in schizophrenia that alters depending cell type (Benes and Bird, 1987; Benes, Sorensen and Bird, 1991; Ongür, Drevets and Price, 1998). Similarly, examination in neuron size has revealed contradictory findings with both no neuron size change (Benes, Davidson and Bird, 1986; Cotter et al., 2001) and the aforementioned decreased neuron size in pyramidal Layers III & V in schizophrenia (Chana et al., 2003). Examination of parvalbumin-immunoreactive neuronal soma has revealed an increase in density in layer V of the ACC, consistent with the reported shrinkage of this region in schizophrenia (Kalus, Senitz and Beckmann, 1999; Williams et al., 2013a).

The ACC in schizophrenia has been reported to have increased density of small and large calibre vertical fibres, repeatedly shown in layers II and III, axospinous & dendritic synapse density, and TH-immunoreactive fibres in layers V and VI, with no corresponding change in horizontal axons (Benes et al., 1992; Baldessarini et al., 1997; Aganova and Uranova, 1992). Ultrastructural examination of the ACC has revealed an overall decrease in synaptic density, and specifically a 30%, decrease of axospinous synapses in layers III, V and VI in schizophrenia cases (Aganova and Uranova, 1992). Additionally, mean capillary diameter was significantly decreased in the dorsal and subgenual ACC in bipolar and unipolar depression cases, both in layers III and V, whereas schizophrenia patients were comparable with controls (Sinka et al., 2012).

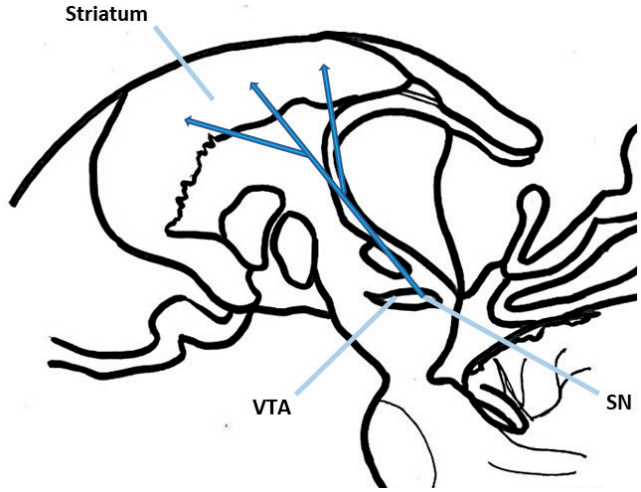

Fig. 3. Sagittal cut showing the nigrostriatal DA-pathway (blue arrows) from the Substantia Nigra (SN) to the ventral striatum. VTA – Ventral Tegmentum Area.

Whilst there are reporting no overall changes in glial cells in the ACC in schizophrenia (Ongür, Drevets and Price, 1998; Höistad et al., 2013), other studies have shown ACC glial changes in schizophrenia, with decreases in glial density in Layers V with an increase in glial size in Layers I, III and V (Cotter, Pariante and Everall, 2001; Cotter et al., 2002b). No change in cingulate grey or white matter oligodendrocyte number, density or clustering as identified using histological stains (Williams et al., 2013b; Williams et al., 2014a; Segal, Schmitz and Hof, 2009; Mosebach et al., 2013) and no changes are reported in microglial density (Radewicz et al., 2000; Steiner et al., 2006). GFAP-labelled astrocytes are decreased in the ACC cortical grey and white matter, with an overall decrease in GFAP area fraction and increase clustering in schizophrenia (Hercher, Chopra and Beasley, 2014; Williams et al., 2014a), with the astrocyte decrease composed primarily due to a loss of fibrillary astrocytes (Williams et al., 2013a; Williams et al., 2014a). These findings reinforce the suggestion that the ACC is a vulnerable structure in schizophrenia, supporting the model of the SaN being specifically disrupted in this disorder.

Ventral Striatum and Substantia Nigra

The primary focus of investigation of the basal ganglia in schizophrenia has to do with the DA system and the various sites of antipsychotic drug action in the striatum. The DA-projection from the Substantia Nigra (SN) to the striatum is known as the nigrostriatal pathway and is the most well characterised long DA-pathway in the brain. The nigrostriatal pathway is formed from axons projecting from the large DA-producing neurons in the SN, identified above as A8 and A9 cells, and rises dorsally to terminate in the superior part of the striatum across areas of the caudate and putamen (Dahlström and Fuxe, 1964; Fallon and Moore, 1978). This large DA-projection is the site of action for antipsychotic medication and has been the central focus of the DA-theory of schizophrenia, proposing subcortical DA-dysfunction underlies many symptoms (Davis et al., 1991; Howes and Kapur, 2009).

DA influence on striatal medium spiny neurons is receptor-specific, with D1 (excitatory) and D2 (inhibitory) receptors leading to excitatory and inhibitory striatal responses, which permit discrimination of motor programs to suit the required task, the primary function of the nigrostriatal pathway. D1 receptors are found in high concentrations in the caudate, the medial putamen and accumbens, with the highest are found in the lateral putamen (De Keyser et al., 1988; Hall et al., 1994). The D2 receptor has a similar distribution with high concentrations observed in the caudate, the lateral and medial putamen and accumbens (Camps et al., 1989; Khan et al., 1998; Murray et al., 1994). Ultrastructural examination of the spiny neurons of the striatum show changes in spine shape and axon density in the adjacent caudate, not the putamen, arguing against drug treatments as a cause (Kung et al., 1998; Kung and Roberts, 1999), whereas stereological examination of the putamen in schizophrenia confirmed the imaging finding of decreased volume and showed a decrease in total neurons (Kreczmanski et al., 2007).

In schizophrenia the primary interest in the SN is due to it being the origin of the nigrostriatal pathway. Post-mortem studies have found altered tyrosine hydroxylase mRNA levels, increased amount and variability of Tyrosine Hydroxylase (TH) levels in the substantia nigra of schizophrenia patients (Howes et al., 2013a; Perez-Costas et al., 2012). TH staining was significantly increased in nigral DA-neurons in schizophrenia, unrelated to medication effects. These cells did not have elevated DA-mRNA suggesting that this increase in regulated post-transcriptionally (Howes et al., 2013b; Rice et al., 2012), with DA-producing oval cells also having increased somal size, nuclear cross-sectional area and increased nucleolar volume compared with controls in addition to decreased astrocyte density in schizophrenia. Examination of the DA-neurons themselves suggest their soma and nuclei are physically swollen in schizophrenia presenting with psychosis (Williams et al., 2014b).

Mediodorsal Thalamus

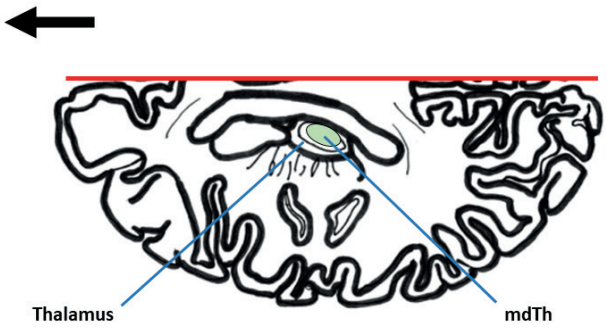

Fig. 4. Axial cut showing the location of the thalamus close to the midline of the brain (indicated in red) with the mediodorsal Thalamus (mdTh) location shown in green.

The medial nuclear group is composed of a single large nucleus, mediodorsal thalamus (mdTh), a nucleus involved in cognition and memory that has been implicated in schizophrenia pathology by several studies. The mdTh has multiple separate connections to the frontal cortices and receives inputs from multiple subcortical structures (Mitchell and Chakraborty, 2013), hence suggesting that the mdTh which has a key role in higher cognitive functions such as foresight. Projections into the mdTh are also present from the amygdala, another subcortical structure of the SaN.

The mdTh has been reported to have reduced mean volume and decreased total neuron number in schizophrenia in both the magnocellular and parvocellular regions. The most typical segmentation method of the structure based on neuron sizes (Pakkenberg, 1990; Thune and Pakkenberg, 2000; Popken et al., 2000; Byne et al., 2002; Young et al., 2000), but in contrast also shows no changes reported in volume, neuron density, number or size in the mdTh when examined using stereological investigation (Cullen et al., 2003; Dorph-Petersen et al., 2004; Danos et al., 2005; Lesch and Bogerts, 1984; Pakkenberg, 1992), (Kreczmanski et al., 2007) or by MRI (Kemether et al., 2003), although the possible distortion of the whole thalamus has been suggested as possibly accounting for these discrepancies (Csernansky et al., 2004).

Corticomedial Amygdala

The amygdala is not one single nucleus but is made up of up to twelve subnuclei depending on definitions (LeDoux, 2007; Munn et al., 2007) often merge with adjacent non-amygdala structures or have further subdivisions (McDonald, 1998). The main regions, comprised of compartmentalised smaller sub-nuclei, are the basolateral region consisting of the basal, lateral and accessory basal nuclei proximal to the lateral ventricle and the entorhinal cortex and the corticomedial region comprising of the cortical, medial and central

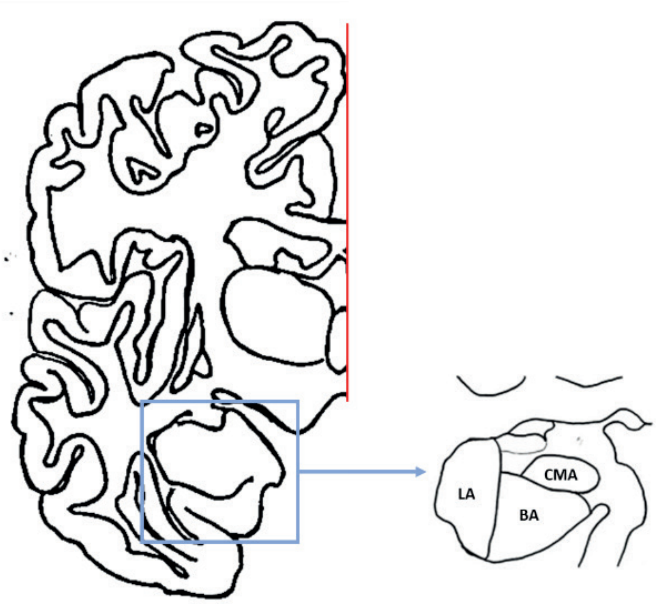

Fig. 5. Location and subdivisions of the amygdala in coronal section. LA – Lateral Amygdala, BA – Basal Amygdala, CMA – Corticomedial Amygdala.

nuclei, the more superficial amygdala group. Corticomedial amygdala projections are involved in arousal and attention, primarily connecting to frontal cortices and the thalamus, providing regulation of the reward system (Izquierdo and Murray, 2010).

Multiple neuropathological studies have reported changes in neuron shape and size as well as glial cells numbers in the basolateral amygdala but not the corticomedial region in schizophrenia (Williams et al., 2013c; Williams et al., 2016; Pantazopoulos et al., 2010; Byne et al., 2002; Joyal et al., 2003; Moncrieff and Leo, 2010).

Summary

Overall disruption of the main two parts of the SaN is shown in schizophrenia. The ACC is one of the most studied structures in the disorder, and although the insula has had nowhere near the focus of research the ACC has, what evidence there is does suggest the structure is affected. Likewise, the mdTh is a significantly implicated nucleus, with both pathological and imaging evidence of disruption, and the striatum and substantia nigra are well known in any study or schizophrenia or psychosis with them being at either end of the nigrostriatal pathway, and both reported to have neuronal changes in schizophrenia. However, as the corticomedial amygdala is often seen as an output nucleus the changes in the adjacent basolateral part of the nucleus may be more important here than the strict SaN circuit organisation may imply.

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