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Historical postmortem studies on catatonia: Close reading and analysis of Kahlbaum's cases and scientific texts between 1800 and 1900

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ABSTRACT

In the 19th century, postmortem brain examination played a central role in the search for the neurobiological origin of psychiatric and neurological disorders. During that time, psychiatrists, neurologists, and neuropathologists examined autopsied brains from catatonic patients and postulated that catatonia is an organic brain disease. In line with this development, human postmortem studies of the 19th century became increasingly important in the conception of catatonia and might be seen as precursors of modern neuroscience. In this report, we closely examined autopsy reports of eleven catatonia patients of Karl Ludwig Kahlbaum. Further, we performed a close reading and analysis of previously (systematically) identified historical German and English texts between 1800 and 1900 for autopsy reports of catatonia patients. Two main findings emerged: (i) Kahlbaum's most important finding in catatonia patients was the opacity of the arachnoid; (ii) historical human postmortem studies of catatonia patients postulated a number of neuroanatomical abnormalities such as cerebral enlargement or atrophy, anemia, inflammation, suppuration, serous effusion, or dropsy as well as alterations of brain blood vessels such as rupture, distension or ossification in the pathogenesis of catatonia. However, the exact localization has often been missing or inaccurate, probably due to the lack of standardized subdivision/nomenclature of the respective brain areas. Nevertheless, Kahlbaum's 11 autopsy reports and the identified neuropathological studies between 1800 and 1900 made important discoveries, which still have the potential to inform and bolster modern neuroscientific research in catatonia.

1. Introduction

The idea that the origin of mental illnesses can be explained somatically and primarily by brain alterations was not generally accepted until the end of the 19th century (Schott and Tölle, 2006). During the 19th century, it was primarily Wilhelm Griesinger (1817–1868) who, within a broader etiological framework including psychoreactive factors, postulated a neurobiological and brain-associated origin of psychiatric disorders (Griesinger, 1845). Together with the Austrian physician Franz Joseph Gall (1758–1828; founder of "Organology") and his German collaborator Johann Gaspar Spurzheim (1776–1832) (Gall and Spurzheim, 1809; Spurzheim, 1833), Griesinger is considered one of the founders of the so-called "brain psychiatry" (Schott and Tölle, 2006). Other representatives of the "brain psychiatry" and neuropathological orientation of psychiatry were Carl Westphal (1833–1890) (Westphal, 1892), Theodor Meynert (1833–1892) (Meynert, 1868), and Carl Wernicke (1848–1905) (Wernicke, 1900). These historical authors suggested the future of brain research of psychiatric disorders in the application of neuropathological methods (for reviews see also Bogerts (1993) and Powchik et al. (1998)).

At the turn of the 20th century, other psychiatrists and neurologists have also used neuropathological methods to study mental illness,

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especially Karl Ludwig Kahlbaum (1828–1899), Emil Kraepelin (1856–1926), Alois Alzheimer (1864–1915), and Sigmund Freud (1856–1939). For instance, Kraepelin (Head of the Munich Psychiatric Department from 1903 to 1922) advised Alzheimer to carry out neuropathological examinations of his patients. Within the framework of his studies, in 1893, Alois Alzheimer described the thinning of the neocortex of patients with dementia praecox (Alzheimer, 1893). In 1907, Alzheimer published his most famous paper "Über eine eigenartige Erkrankung der Hirnrinde" (Alzheimer, 1907) (English: "On a peculiar disease of the cerebral cortex") (Alzheimer et al., 1995) in which he described his Frankfurt patient Aguste Deter, who suffered from senile dementia (today Alzheimer's disease). Later on, Emil Kraepelin stated that "*The fact is decisive that the morbid anatomy* [*of dementia precox*] *has disclosed not simple inadequacy of the nervous constitution but destructive morbid processes as the background of the clinical picture*." (Dastur, 1959; Kraepelin, 1913). It was also during this period that many neuropsychiatric disorders were described for the first time, including catatonia, paraphrenia, Parkinson's disease, Alzheimer's disease and dementia praecox, respectively. However, the idea that psychiatric disorders are brain disorders was rejected right at the beginning of the 20th century, partly because of a lack of sufficient methods to study the brain and the rise of psychoanalysis (Ron and Harvey, 1990).

It took about 70 years until the development of computer tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and histochemical methods for postmortem studies made it possible to examine the brains of mentally ill people in vivo (Mehta et al., 2021; Prasad et al., 2022a, 2022b; Reddy-Thootkur et al., 2022). In particular, recent systematic reviews of postmortem studies in schizophrenia patients indicated an increase and decrease in neuroinflammatory markers (e.g. astrocytes, oligodendrocytes, microglia, cytokine and chemokine expression, arachidonic acid cascade, substance P, etc.), impaired synaptogenesis, and reduced hippocampal neuron density, among others, as crucial neuropathological processes in schizophrenia, while also acknowledging and discussing the heterogeneity of the identified findings (Falkai et al., 2015; Fillman et al., 2013; Roeske et al., 2021; Trepanier et al., 2016). This significant methodological development in the past two decades also decisively affected research into the pathophysiology of catatonia. Although modern postmortem studies on catatonia are still lacking, numerous structural and functional MRI studies have been published in the past years, suggesting alterations in orbitofrontal, medial prefrontal, and motor cortices, as well as in the cerebellum and brainstem as important sites underlying catatonia (Cattarinussi et al., 2022; Hirjak et al., 2020a; Hirjak et al., 2020b; Sambataro et al., 2021).

With regard to the pathophysiology of catatonia, especially in the last two decades, there has been a rapid increase in scientific work on catatonia (Hirjak et al., 2023a, b; Beach et al., 2023), but the majority of studies on patients were (for an ethical reasons) non-invasive neuroimaging studies (for more details see also (Haroche et al., 2020; Hirjak et al., 2020a)). In the last decades, there were no post-mortem studies with specific questions focusing on the pathogenesis of catatonia at all. Therefore, from today's perspective, the interesting question is what can be learned from the past and how informative earlier data are for today's pathophysiological understanding of catatonia? Therefore, the question arises of how psychiatrists, neurologists, and neuropathologists have viewed catatonia and its symptoms, or what brain changes have been postulated in connection with catatonia in the 19th century. To find answers to the above-mentioned questions, this study has three main goals: First, we review the 1874 monograph written by Karl Ludwig Kahlbaum. We will closely examine the autopsy reports of his catatonia patients. Second, we will perform a close reading and analysis of the relevant German and English historical texts on catatonia published between 1800 and 1900 and identified by our previous systematic review (Hirjak et al., 2022) to find autopsy reports and respective brain structures of catatonic patients. Finally, we briefly summarize the lessons learned from historical postmortem studies for scientists that seek to overcome methodological limitations when investigating the neuronal correlates of catatonia.

2. Methods

This study makes use of two research methods: (1) To examine historical postmortem studies on catatonia more concretely and illustratively, the first section provides an in-depth analysis of Kahlbaum's autopsy reports presented in his 1874 published monograph, drawing particular attention to different brain abnormalities of catatonia patients. (2) To answer the second question, we conducted a close reading (Heckers, 2020; Kendler, 2020) of 59 historical texts on catatonic symptoms published between 1800 and 1900 in German and English that were identified in our previous systematic review (for details see Hirjak et al. (2022)). The search strategy and study selection in the systematic review by Hirjak et al. (2022) followed PRISMA guidelines. In particular, we searched for historical literature using the following five electronic databases (a) https://archive.org, (b) www.hathitrust.org, (c) www.books.google.de, (d) https://link.springer.com, and (e) PubMed. Except for PubMed, the four other databases contain scanned historical psychiatric and neurological journal articles and textbooks. We were interested in journal articles and textbook sections authored by physicians published from 1800 to December 31, 1900. The main aim was to identify historical texts on catatonia published before and 25 years after the publication of Kahlbaum's monograph on catatonia. We used the following English (first term) and German (second term) search terms or their combinations: *"catalepsy", "Katalepsie", "stereotypies", "stereotype Bewegungen", "negativism", "Negativismus", "stupor", "stupor", "catatonia", "Katatonie"*. After reviewing the titles of journal articles and textbook sections and excluding duplicates and off-topic references in terms of the PRISMA flowchart, we closely reviewed 60 historical texts on catatonic symptoms. These texts were available as scannable PDFs so that we could also search for the presence of specific terms like "*autopsy*", "*brain*", "*dissection*", "*Obduktion*" (only in German texts), and "*pathology*", respectively. The majority of the identified text passages were in German. When working with English texts, we (DH and MA) used online translators and dictionaries. Similar to our recent historical study (Hirjak et al., 2022), we also used online translators and dictionaries to translate historical German texts into English. The respective text sections on the autopsy of catatonia patients were subsequently discussed by consensus among the first authors (DH and MA) of this manuscript.

3. Results

First, in the fourth chapter of his monograph, Kahlbaum presented detailed autopsy reports of 11 catatonic patients. Kahlbaum described various tissue alterations which can - for a better understanding - be localized in the following brain areas: (a) frontal lobe, (b) parietal lobe, (c) temporal lobe, (d) occipital lobe, (e) basal ganglia and limbic system, (f) meninges, (g) brainstem, (h) grey and white matter, and (i) ventricular system (Table 1 and Fig. 1). Second, we searched 60 historical texts identified in our previous review (Hirjak et al., 2022) for autopsy findings of catatonic patients. By a close reading of the 60 texts, we were able to identify four additional texts by historical authors (Charles F. Folsom (1842–1907), W. Julius Mickle (unknown–1917), T. Claye Shaw (1841–1927), and Daniel Hack Tuke (1827–1895)) discussing potential brain mechanism underlying catatonia. Although approximately 30 of 64 identified texts discussed pathophysiological processes underlying catatonia, besides Kahlbaum's reports, we were able to identify only four other autopsy findings stemming from historical authors and their own catatonic patients (Table 2).

4. Discussion

This study is the first of its kind to address historical

Table 1
Selected quotes from Karl Kahlbaum's autopsy reports (lines 1–10) and from his remarks on the pathogenesis of catatonia (lines 11–13).

1	*Case #2:* "*Head: Ears free of hematoma. Skull very white, sutures smoothed, only lambdoids and part of coronaria present. Diploi' normal width and normal blood content Dura easily separated from skull Sinus bloodless. In the crescent process above the crista ethmoidalis a row of bones 1 cm. in diameter. Arachnoid very weakly opacified; on left side above centre a denser opacity the size of a grain of millet; at base very strongly opacified on the free leaf extending from pons to chiasma. No super- or subarachnoideal hydrops. Pacchionic granulations very weakly developed, Meyer 'see epithelial granulations completely absent'. Pia of fairly normal blood content, easily peelable from the surface of the brain, tearing, blackish over the medulla oblongata. Large blood vessels above atheroma. Gyri somewhat narrow, sulci forming large bays at confluence points. Grey matter pale and narrow. White matter contains normal amount of blood, consistency not abnormal, no edematous condition. Chicken cavities not dilated. Surface of all cavities, including the fourth, with a strongly developed mucilaginous coating. Optic thalamus very pale on average. Grey matter of medulla oblongata and spinalis very pale.*" (*p. 62*)
2	*Case #16:* "*Head.* (…) *Inner surface of dura completely smooth and white. Arachnoid membrane thin and clear, not opaque between pons and chiasm, but very opaque between cerebellum and oblongata. Pia rather strongly hemorrhagic, especially in the finest vessels, easily and smoothly peelable from the surface of the brain. Subarachnoid tissue not seriously infiltrated. Brain rather strongly blood-containing; cortical substance of medium width, showing in places increased vessels, the three layers very blurredly indicated, merging into each other. White substance: Blur spots abundantly protruding, besides the whole surface pale rose-red mottled, gelatinous. Lateral brain cavities not dilated, both hind horns reaching very far back. Surface of thalami and corpora striata mucilaginous, no ependymal granulations. In the left anterior horn a small adhesion of the lower surfaces. IV. Ventricle also with strong mucilaginous coating and here also the beginning of granulations formation. Medial oblongata and spinalis without perceptible abnormality.*" (*p. 64*)
3	*Case #17:* "*Arachnoid membrane strongly diffusely opacified and at several confluence points of the cerebral sulci with whitish, millet-sized condensations. The free part of the arachnoid between the pons and the chiasm is strongly developed and below it, at some distance between this leaf and the nerve parts, there is a special meshed leaf with several holes. Between cerebellum and oblongata weak opacity. Epithelial granulations barely indicated by traces. Pacchion. Granules, not very numerous. Sub-arachnoidal tissue not seriously swollen. Blood content of piaceal vessels very reduced.* (…) *Brain: At the convolutions, a sinking of the surface below the level of the surrounding areas to a rather significant degree can be observed in several places. The grey matter, seen from the outside, is conspicuously pale as on the average, the width somewhat reduced in some places. The blood content of the grey matter is completely absent, that of the white matter normal. On the average, the white matter shows a sheen of watery moisture. The same is seen on the average of the large ganglion bodies. Cerebral sinuses not dilated with massive serum content. Stria cornea very clearly developed and in its vicinity the ependymal granulations are small but quite distinctly developed, in the other parts they are present only in traces.*" (*p. 68*)
4	*Case #18:* "*Head.* (…) *Dura normal except for the frontal region; here in a few pea-sized areas quite firmly adhered to the arachnoid. Cerebrospinal fluid in the cavum durae not increased. Arachnoidea strongly opaque, epithelial granules finely punctate. Pacchionic granular cones not increased. The opacity of the arachnoidea is nominally strong in a stripe next to the midline of the convexity and in the areas glued to the dura, in the frontal region several thin bone platelets are found in the arachnoidea.* (…) *The brain is also only weakly injected with the coarser vascular network. Adherence to the surface of the brain nowhere abnormal. Brain as a whole soft. Bark substance somewhat pale in all layers, but showing fine vascular stripes. White substance with quite numerous blood spots. Soft consistency, watery appearance. Cerebral ventricles posteriorly wide and long with very developed relief; fluid somewhat increased. Surface of ventricles with mucilaginous softened and thickened ependyma, underlying cerebral layers and fornix very soft; almost runny. The large vessels of the ventricular surface more injected than normal on both sides. Average of the corpus cavernosum very pale. Cerebellum, med. oblong, and spinalis without visible changes.*" (*pp. 70–71*)
5	*Case #19:* "*Head: Skull dense but massively thick, light, sutures well traced. Deep impressions pacchion. Granules; but easy to peel off from dura. Dura pale, blood vessels quite empty. Little serum over arachnoid. Arachn. rather strong, but quite diffusely clouded. Epithelial granules very dense and clearly developed, but individual granules not particularly large. Subarachnoid spaces strongly serous infiltrated. Free arachnoid leaflet (between pons and chiasm) somewhat opacified and thickened. Pia mater rather strongly hemorrhagic; fine light red colored vascular network easily peelable from brain and smooth.*" (*pp. 71–72*)
6	*Case #20:* "*Brain: Quite numerous convolutions. Grey matter peculiarly grey-yellowish in color. The part of the coloration due to the blood content seems to be reduced; different layers not visible, width somewhat narrowed, but not strongly; blood vessel stripes not visible. White substance quite numerous, but only fine blood spots on the average. Gloss somewhat peculiar, in a sense a middle ground between fat and water sheen. Consistency normal and even. Cave surface without granulations, but the ependyma in the region of the posterior end of the striae corneae peculiarly whitish turbid and thus distinct from the underlying grey substance. Water content of the cavities not increased. Posterior horns equal on both sides, of medium length. Plexus normal. Grey substance of large ganglia, like bark substance somewhat yellow-grey and at the same time pale. Small brain and bridge and medulla normal. Black substance very ducely colored, of small circumference.*" (*p. 73*)
7	*Case #21:* "*Dura strongly folded anteriorly (atrophy of the brain), arachnoid on the convexity weakly opacified, only in one place around the pacchionic granulations somewhat more opacified. At the tip of the lower lobes of the brain, the arachnoid was attached to the dura by a mucilaginous felt-like mass. The free leaf of the arachnoid thickened between pons and chiasm. Pia normal with blood, no hydrops exteruus. Brain small, of increased resistance, poor in blood. Inner surface covered with small, shiny granulations about the size of a grain of millet. Little serum.*" (*p. 74*)
8	*Case #22:* "*Section: Cranium very firmly fused to the dura by pacchionic granulations. Dura externally rich in blood, in the region of the posterior lobe of the right half towards the base a thin layer of extravasation is spread between dura and skull. Dura itself dirty discolored.* (…) *Arachnoid strongly opacified, especially over the right hemisphere in the upper and anterior parts, further at the base in all places provided with subavachnoid spaces; on the free leaf only massively strongly opacified. Meyer's epithelial granulations spread over the entire circumference of the brain. Pacchionic granulations rather strongly developed, but only on the bands of the median fissure. Pia massively blood-rich, smoothly peelable.*" (*pp. 77–78*)
9	*Case #23:* "*Skull normally developed, anemic. Dura externally normal. Blood vessels contain some clots. When the dura sac is opened, much fluid flows out and afterwards the membrane lies folded many times on the brain. When the membrane is removed from the couvexity, it is noticeable how a mucilaginous membrane is attached to the dura in individual points, detaches from it and remains on the arachnoidea.* (…) *Arachnoidea strongly opacified over the whole convexity, uniformly diffuse, in 3 places a cheesy-white thickening the size of a lens. Epithelial granulations weakly developed, but present all over the convexity. At the base, the arachnoid is strongly opacified over the Sylvian fossa, more weakly opacified over the angle between pons and chiasm, uniformly without thickening. Over the 4th ventricle also weak opacity. Subarachnoid tissue strongly serous infiltrated. Pia seems to be more firmly soldered to the brain than normal, in that the brain mass is pulled along; however, it is finally possible to pull off the membrane smoothly everywhere. Most of the blood vessels of the pia are injected in a dense net, but in one part of the right parietal region they are completely empty. Larger vessels weakly filled, in the basilaris a partly fatty, friable clot, no visible atheromata, but the vessel walls appear very tough.*" (*pp. 78–79*)
10	*Case #24:* "*Dura strong pachymeningitic residues on right side over entire convexity, on left side same and in cranial pits. Arachnoid membrane on the convexity strongly opacified everywhere, so that the whole skin appears white like tendons, at the base only in single small spots and in larger patches along the vessels. The thickness and firmness of the arachnoid at the convexity very conspicuously increased. Free leaflet in front of pons and that behind 4th ventricle only slightly 'thickened'. Pacchionic granulations strongly developed along fissure, epithelial granulations weakly developed. Ependymal granulations only in the fourth ventricle.*" (*pp. 79–80*)
11	*Case #25:* "*Pacchymeningitis with only weakly developed membranes in the pit and frontal lobe regions. Arachnoid membrane transformed into a uniform pier-like membrane over the whole convexity, at the base only at the points bridging the larger fissures of the brain, also the angle between pons and chiasm. Epithelial granulations weak, but developed everywhere. Pacchionic granulations small but very dense along the entire middle fissure. Subarachnoid tissues strongly swollen. - Brain cavities dilated, hydropic. Ependyma thickened only at stria. Ependymal granulations abundant but small.*" (*p. 80*)
11	"*This predilection of arachnoidal opacities for the base corresponds also to the slight development of Pacchionic granulations in catatonia, while these, as well as opacities on the convexity, are otherwise so significantly developed in mental brain diseases.*" (*p.82*)
12	"*For the catatonia, which on the whole can also be traced back to the general degeneration process leading through an initial hyperplasia to a final atrophy, the great transitoriness and low intensity of the congestion symptoms and the insignificance of the hyperplasia in the first phase of the process must be emphasized as characteristic, while the second phase is characterized by the late onset of retraction (atrophy) of the cerebral tissue, which is probably also related to the absence of more significant cavity dilatation. In general progressive paralysis,* (…) *the first stage of the general degenerative process is characterized by very severe hyperemia and massive exudations, while atrophy is not long in coming, very early not only the cortical substance shows gaps, but also the white substance retracts and often leads to cavity dilatation.*" (*pp. 83–84*)
13	"*A further characteristic difference of catatonia is the limitation of the location or direction of the exudate deposits in the cerebral membranes, especially in the arachnoid, in that, as shown above, the base shows relatively denser and more frequent opacities, and the free leaf of the arachnoid, overlapping from the pons to the chiasm and to the frontal lobe, together with the strip of the arachnoid extending along the fossa Sylvii, is preferably the seat of this exudation. This predilection of exudate deposition near the sylvian fossa and the second and third frontal lobe, i.e.*

(*continued on next page*) |

Table 1 (*continued*)

that place which is considered to be the seat of psychic language formation due to the facts of aphasia, is very remarkable in the case of cerebral symptoms in the field of language (mutism and verbigeration!) which are clinically very prominent for catatonia. Therefore, from the constancy of the speech symptoms and the preferred location of certain exudate deposits, a closer connection between disturbances in those parts of the brain and the latter could be assumed." (*p. 84*)

neuropathological (autopsy) correlates of catatonia. It is an extension of our systematic analysis of historical texts which dealt with catatonic symptoms before and after Kahlbaum. A close reading of historical texts converged in two main findings: First, Kahlbaum reported on 11 patient autopsies and postulated a number of brain alterations underlying catatonia, particularly abnormalities in the meninges, the ventricular system, and the grey and white substance (s. Fig. 1 for an overview). Second, other historical authors have also examined the brains of catatonia patients in the 19th century and have been discussing its pathogenesis. Similar to Kahlbaum, these authors found softer and moister brain tissue, redundancy (overfilling) of blood in the vessels of the brain, thickened and injected meninges, cerebral anemia, brain atrophy, and/or cerebral edema, respectively (s. Fig. 2 for an overview).

Our first aim was to search Kahlbaum's monograph for the neural correlates of catatonia and to shed light on his understanding of the neurobiological underpinnings leading to catatonia. What is particularly interesting and valuable is that Kahlbaum examined and treated his catatonic patients for months and sometimes even years before they died. He knew their disease courses and symptom severity and could relate these to his neuropathological findings. Kahlbaum examined catatonia patients with an age range between 26 and 44 years and different duration of illness. In 15 of 25 Kahlbaum's patients, the diagnosis could be formulated (Barnes et al., 1986): Nine patients had an affective disorder, five patients had most likely an organic disorder and one patient had schizophrenia. In ten patients, the diagnosis could not be determined precisely on the basis of Kahlbaum's reports. In patients with a shorter duration of illness (6 months–2 years), Kahlbaum identified (i) greater congestion of the blood in the free vessels surrounding both the inner and outer surface of the brain, (ii) serious soaking and softening of the brain tissue without reduction of the brain circumference, and (iii) exudate formation on the inner surface and in the arachnoid. In catatonia patients with a longer duration of illness (2–7 years), Kahlbaum postulated (i) brain atrophy and (ii) the reorganisation of the ependymatic soft exudate into dry granulations as a possible pathomechanism of catatonia. Kahlbaum had a clear hypothesis of the brain changes that could lead to catatonia and its typical symptoms. He postulated a number of brain alterations underlying catatonia. Although Kahlbaum's most important finding in catatonia patients was the opacity of the arachnoid, he hypothesized other regions also to be also affected (see Table 2). The arachnoid mater, or short "arachnoid", is the middle meninges between dura and pia mater. Kahlbaum wrote that the arachnoid is the main locus of neurobiological changes in catatonia patients. Only in the youngest patients, the opacity of the arachnoid was confined to a site between the cerebellum and the medulla oblongata (behind the fourth ventricle). In all other cases, the free leaf between pons and chiasm was also more or less clouded. Kahlbaum postulated that the opacity would spread towards the base of the brain. In a letter by De Crespin de Billy et al. (de Crespin de Billy et al., 2021), the authors pointed out that the brain abnormalities underlying catatonia reported by Kahlbaum were mainly located in the medial frontal and premotor cortices, which Kahlbaum probably may not have exactly known, (the work of Fritsch and Hitzig (Fritsch and Hitzig, 1870), which address the location of the human motor cortex was published only four years earlier in 1870; see also (Gross, 2007; Carlson and Devinsky, 2009). The supplementary motor area (SMA) was described even later, i.e. in 1949 (Penfield and Welch, 1949). Furthermore, Kahlbaum attributed the above- mentioned brain changes to increased nutritive processes (e.g. hyperemia, swelling, exudation). In line with this, the insistence of Kahlbaum and his colleagues on detailing the state of the meninges in catatonia was not by chance. We might speculate that the main reason for this assumption was that the meninges were the tissue that was inflamed or overdeveloped in cases of general paralysis of the insane (GPI), the only accepted neuropsychiatric pathology at that time. The fact that Kahlbaum reported alterations of the meninges underlying catatonia is one possible explanation why Jules Seglas (1856–1939) and Philippe Chaslin (1857–1923) thought that

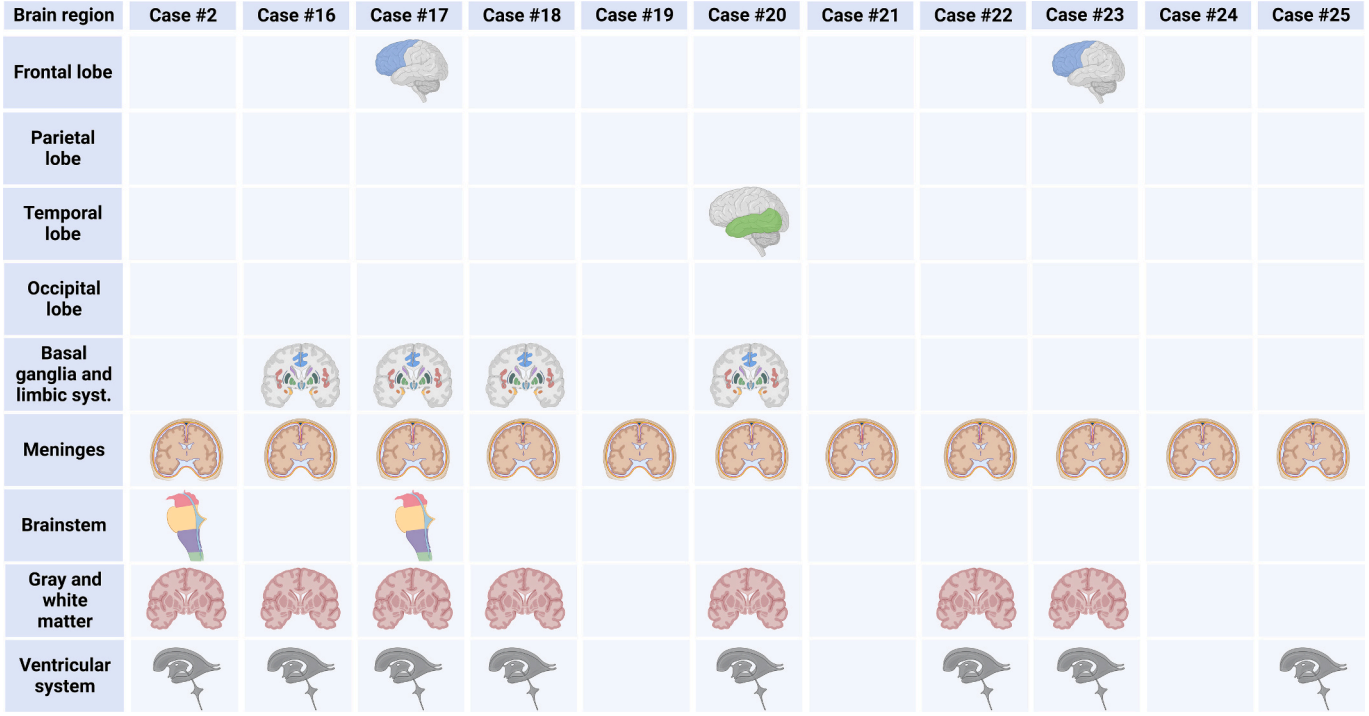

Fig. 1. Brain structures mentioned in Karl Kahlbaum's autopsy reports of his 11 catatonia patients.

Table 2
Selected quotes on postmortem findings in catatonia from historical authors mentioned in the Discussion section.

Quote no.	Author	Text
1	Johann Gaspar Spurzheim (1776–1832)	"*I really think that all morbid effects which are observed in other parts may also be distinguished in the brain, such as a too defective or too large development of its substance, distension of blood vessels, inflammation, suppuration, serous effusion, dropsy, rupture, or ossification of blood vessels. I even maintain that morbid changes of the physical appearances of color and texture might be pointed out in the brains of many who have died insane, if those who examine them were better acquainted with the appearances of the brains of individuals who had no particular determination of blood to the head, and preserved their manifestations of the mind to the last moment of life. In fever with delirium, in phrenitis, in insanity with too powerful manifestations of the faculties, in children who from birth were able to manifest their powers of the mind, but lost them by accidental disease, and in those who after violent mania became fatuous, or who died apoplectic, I was always able to detect some morbid appearances or organic alterations, either in the substance of the brain, or in the blood-vessels, or membranes, or even in the skull, which sometimes is uncommonly thick, or dense like ivory.*" (pp. 116–117)
2	Gabriel Andral (1797–1876)	"*Meanwhile, some authors have succeeded in finding organic changes caused by catalepsy. A young cataleptic maniac, who had suffered from frequent recurrences of the coincidences, died some years ago in the hospital at Charenton. The soft meninges were found thickened and injected; the superficial grey matter was of low consistency and rose-colored; the white matter showed numerous vascular and blood-filled layers; the middle septum was softened. In another, also cataleptic alien, the cortical substance was found to be violet and the white substance very injected.* (…) *Pelletier considers catalepsy as an irritation of the brain, with habitual overfilling of the vessels of this organ, by which it is disposed to convulsive or cataleptic movements, which, according to P., have their reason in the compression of the origin of the nerves.*" (*pp. 482–483*)
3	Clemens Neisser (1861–1940)	"*XII. Case.* (…) *The pia mater at the convexity was nowhere clouded or thickened, at the base the sheet extending from the medulla obl. to the cerebellum showed a more sinewy texture. The venous vessels were found as thick blue cords in the most extreme state of filling, in the meshes of the arachnoidal space much serous fluid was found.* (…) *The lateral ventricles contained a little increased and slightly flocking turbid fluid, the ependyma was smooth.*" (pp. 72–80)
4	Theodor Meynert (1833–1892)	"*I know a case of stuporous obsessive-compulsive disorder, which by its nature must have been maintained by the subcortical center of the visual mound. Therese K., a 14-year-old day laborer's daughter, came to the psychiatric clinic on November 7, 1871.* (…) *Since March 7, she had been lying in bed with the stereotyped position, every bite had to be brought to her mouth.* (…) *The brain, weighing only 1164 g, shows anemia and severe dampness with in parts very different consistency of the hemispheres and the trunk on sections, in addition to a small degree of shrinkage, because the hemispheres do not quite make up 78 % of the whole brain and the frontal lobes not quite 40 % of the hemispheres. The brainstem shows sclerotic hardness on sections, especially on the average of the right-sided cap of the cerebral peduncle. Microscopic examination indicated this sclerosis as a result of exudative processes into the perivascular tissue gaps of His and into the brain parenchyma. These masses compressing the vessels were not a mere edema, but convex bodies clustered together, pale in ordinary light and of little sharp contours,* (…)." (*p. 58–60*)

some of Kahlbaum's patients had GPI. Overall, Kahlbaum considered catatonia to be a well-defined disease, supported by 26 patient cases and 11 fine-grained autopsy reports.

Interestingly, in the modern literature, there are few case reports of arachnoid alterations (mostly arachnoid cysts) and localized or diffuse thickening of the dura mater which may have led to catatonic symptoms (Ito et al., 2010; Kastenholz et al., 2014; Kumar et al., 2011; Margetic et al., 2013). In particular, Kumar et al. (2011) and Pandurangi et al. (2014) showed that mega cisterna magna might lead to recurrent catatonic episodes. As early as 1987, Orland and Daghestani (1987) described a 51-year-old man with several episodes of sudden-onset catatonia due to bacterial meningoencephalitis. Ito et al. (2010) presented a case of a 63-year-old woman with catatonia induced by idiopathic hypertrophic pachymeningitis. Similarly, Saini et al. (2013) described a case of a 23-year-old Malay man with a lifelong history of bipolar type I disorder who developed malignant catatonia (characterized by excitement followed by a stuporous state with waxy flexibility) secondary to meningoencephalitis (positive for HSV IgG and cytomegalovirus IgG). More recently, Posada et al. (2021) presented a female patient with catatonia and delirium secondary to neurosarcoidosis. Her MRI revealed severe thickened and nodular leptomeningeal enhancement diffusely throughout the brain (Posada et al., 2021). Although larger MRI studies have not found manifest changes in the meninges in catatonic patients, there seems to be a link. The meninges (dura mater, arachnoid mater, and pia mater) surround the brain and protect it from external influences, injuries, and movements within the skull. Together they are responsible for venous blood collection from the cerebral veins, cerebrospinal fluid reabsorption, and the lymphatic system. In particular, the Pacchioni granulations (Granulationes arachnoideae) serve to drain the cerebrospinal fluid from the subarachnoid space into the venous blood system. In line with these physiological considerations, current evidence suggests that catatonia may also be associated with neurological disorders and especially encephalitis (Oldham and Lee, 2015; Ramirez-Bermudez et al., 2010; Smith et al., 2012). Interestingly, Jia et al. (2019) presented a rare case of a 68-year-old man with anti-NMDAR encephalitis presenting with concomitant hypertrophic pachymeningitis, which is mostly caused by inflammation of the dura mater. Further, Nikolaus et al. (2018) described a pediatric case of $GABA_A$ receptor encephalitis presenting with catatonia and encephalopathy. This said, encephalitis can also affect the meninges and lead to disruption of blood-liquor exchange and eventually to catatonia with severe neurological symptoms (e.g. delirium). Although cautiousness is mandatory when comparing previous and current studies because the results were obtained with completely different methods, there are obvious regional and conceptual overlaps regarding the pathophysiology of catatonia.

In the second section of this paper, we addressed further neuropathological findings reported by other historical authors and their pathophysiological theories on catatonia. From these reports, it became very clear that the vast majority of historical authors also mentioned autopsies in their articles or book chapters on catatonia. For instance, Wilhelm Andreas Haase (1784–1837) was a German physician who suggested in 1817 that catalepsy is based on a disorder of the brain and

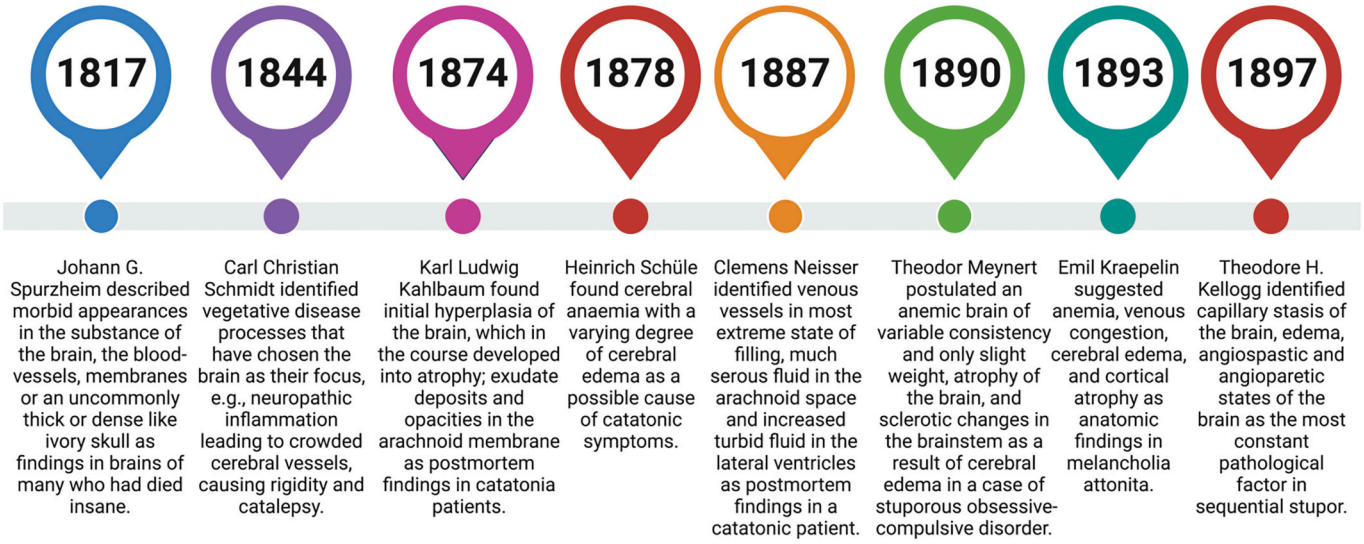

Fig. 2. Timeline of important findings in the historical postmortem research on catatonia between 1800 and 1900.

nerves with their origin in the spinal cord (Haase, 1817). He stated:

> "*Obviously, in catalepsy the irritability and activity of the brain and those nerves that go to the sense organs rest conspicuously, but not at all, or only in a lower degree, in those nerves that take their origin from the spinal cord, and especially the muscles of the outer body, so that one could perhaps regard catalepsy as a transitory paralysis of the brain, after which it would be nothing else in the brain than what paralysis is in the larger trunks of the nervous system.*"
>
> (Haase, 1817, p. 488)

In the same year, Johann Gaspar Spurzheim (1776–1832) (Spurzheim, 1817) postulated changes in brain volume and vessels as possible causes of catalepsy and rigidity. Similar to Spurzheim, also George Man Burrows (Burrows, 1828) (1771–1846), an English physician, suggested redundancy of blood in the vessels of the brain as a cause of catalepsy:

> "*There are various diseases with which insanity is commonly complicated, and which also appear to originate in derangement of the balance between the nervous and vascular systems, and thus prove their relationship. The most conspicuous of these affections are, 1, vertigo — 2, epilepsy — 3, convulsions — 4, apoplexy — 5, paralysis — 6, catalepsy — 7, hysteria — 8, hydropic effusions. (…) In all these maladies, as a general principle, the marks of increased circulation in the vessels of the encephalopathy are unequivocal. But the reciprocal, and sometimes the preponderating influence of the nervous power in some of them is also strongly marked.*"
>
> (Burrows, 1828, p. 152)

Burrows went even further and proposed a treatment option for catalepsy, i.e. violent nose bleed (=epistaxis). Overall, it is interesting to note that in the 19th-century neuroscience, the abnormalities of the blood vessels, especially overfill, distension, and enlargement of the blood vessels and their pressure on different brain regions were discussed by several clinicians and researchers as possible causes of catatonic symptomatology. The following historical authors have also supported this thesis: Gabriel Andral (1797–1876) (Andral, 1838), Carl Christian Schmidt (1793–1855) (Schmidt, 1844), Wiliam Alexander Hammond (1828–1900) (Hammond, 1876) (American military physician, and founder of the American Neurological Association), Clemens Neisser (1861–1940) (Neisser, 1887), Jules Seglas and Philippe Chaslin (Seglas and Chaslin, 1889), and Theodor Meynert (Meynert, 1890), respectively. Interestingly, Theodor Meynert, a German-Austrian psychiatrist, was one of the main representatives (together with Carl Westphal and Carl Wernicke) of the so-called "*epoch of brain psychiatry*".

In addition to the above-mentioned pronounced vascular changes, pathophysiological processes such as anemia, inflammation, edema, and softening of the brain tissue have also been suggested as possible causes of catatonic phenomena. In line with this, nutritive-toxic influences on the brain were discussed as well, especially by Theodore H. Kellogg (1841–1931) (Kellogg, 1897), John Thompson Dickson (1841–1874) (Dickson, 1869), George H. Rohe (1851–1899) (Rohe, 1899), and Friedrich Scholz (1831–1907) (Scholz, 1892). In particular, Theodore H. Kellogg was an American psychiatrist who believed that patients who recovered very quickly from stupor must have a nutritive-toxic or circulatory origin of stupor (Kellogg, 1897). According to his theory, the brains of patients with stupor were most often in an angiospastic or angioparetic state at autopsy. He stated:

> "*The fact that recovery from stupor may be sudden points not to organic lesions, but to functional disturbance of cortical regions, either from circulatory or nutritive disorder. The pathology which best accords with the clinical manifestations is vasomotor disorder. The same capillary stasis evident in the general surface of the body probably exists in cerebral tissues, which have been found oedematous post-mortem in some cases.*"
>
> (Kellogg, 1897, p. 743)

John Thompson Dickson, a British physician, held a similar opinion and wrote that the underlying pathology of catalepsy was anemia and resulting malnutrition of the brain lobes (Dickson, 1869). However, Dickson went even further and assumed that catalepsy was merely a subtype of epilepsy. George Henry Rohe (1851–1899) was an American physician who first made a name for himself in the field of dermatology before specializing in psychiatry. He believed in a nutritive-toxic cause of catatonia and therefore listed it among psychoses due to nutritional structural changes in the brain (Rohe, 1899). Furthermore, according to Rohe, the macroscopic appearances of the brains of catatonics resembled those of general paresis of the insane (GIP):

> "*IV. Psychoses due to microscopial structural alterations in the brain. These are primarily probably nutritional or toxic. In this class are included general paresis, catatonia, consecutive dementia, senile dementia, and epileptic dementia. In a majority of the brains of those dying insane, macroscopial examination shows a milky opacity of the arachnopia, closely associated with underlying morbid processes in a space which can be covered with the two hands placed together, the lower ends of the hypothenar eminences covering the spot where the fissures of Rolando meet. The giant pyramids are the first to show markedly-altered structure.*"
>
> (Rohe, 1899, p. 49)

This is interesting because Kahlbaum also saw a number of clinical similarities between catatonia and GIP. Unlike Kahlbaum, William Julius Mickle (unknown–1917), a Canadian physician who mainly performed scientific work on the influences of syphilis on insanity, also examined catalepsy (Mickle, 1891) and postulated that it was not curable:

> "*For it is essentially somewhat cyclical in nature; shows a great tendency to change from phase to phase,* (…)*; is not so curable as supposed by Kahlbaum; the subjects of it often are members of families showing hereditary psychic degeneration; and, should death follow, the brain-atrophy, anemia and marked basal meningeal changes (or the passive hyperemia and edema of meninges) indicate a preceding profound alteration of nutrition of brain, and that in comparatively young subjects, for katatonie chiefly affects the relatively young.*"
>
> (Mickle, 1890, p. 507

Furthermore, Mickle assumed that post-mortem findings in patients with catatonia such as cerebral atrophy, anemia, or meningeal changes were actually indicative of preceding profound nutritional disturbances of the brain (Mickle, 1890, 1891).

While many earlier authors used the term cerebral anemia, we could not find an exact definition of cerebral anemia in the identified historical texts. In Kahlbaum's monograph, the term anemia is mentioned in only three paragraphs (pp. 58 and 88 in Kahlbaum, 1874), but he does not offer a clear definition. Not only Kahlbaum but also the other historical authors have not provided the reader with an explanation of how to understand the term cerebral anemia. They use this term either as a clinical phenomenon (e.g. drowsiness, mydriasis, headache restricted to a small space; headache and vertigo) or as an autopsy finding, which most likely means reduced blood volume in brain vessels.

Another representative of the nutritive-toxic theory of catatonic symptoms was Friedrich Scholz (1831–1907) (Scholz, 1892). Scholz was a German physician and clinical director of the Bremen asylum. In his work "*Lehrbuch der Irrenheilkunde*" (Scholz, 1892), he postulated that nutritional disturbances of the brain should be regarded as the anatomical cause of melancholia attonita. According to Scholz, these nutritional disturbances are caused by initial vasoconstriction, which is then followed by vasodilatation in the further course:

> "*The anatomical basis* [*of melancholia attonita*] *is thought to be nutritional disturbances of the brain, presumably caused by vasoconstriction, followed later by vasodilatation.*"
>
> (Scholz, 1892, p. 90)

Taken together, the above-mentioned authors shared a commitment to autopsy research on catatonic symptoms. All authors mentioned in this paper have provided autopsy reports and attempted to define catatonia (similar to GIP) as an organic brain disease. Although there were skeptics among the historical authors (e.g. Kahlbaum, Hecker, and Kraepelin) of the new brain-based approach to understanding psychiatric disorders, neuropathological research by other historical scientists such as Franz Nissl, Alois Alzheimer, and Korbinian Brodmann rapidly progressed leading to some of the most revolutionary findings (Kendler and Engstrom, 2017).

In the fourth chapter of his monograph, "*Pathological Anatomy*" (p. 62), Kahlbaum wrote: *"Like general progressive paralysis, catatonia is also a psychic form of illness, which in itself often leads to death without concurrent other illnesses, and it will therefore perhaps be most possible to find the anatomical genesis in it as in the latter. Of a large number of sections of patients who died from catatonia, which I had the opportunity to make in the East Prussian provincial hospital of Allenberg, I will first give some of them here, which are available to me in detailed reports."* Seen from a contemporary perspective, Kahlbaum's scientific approach had three major limitations. First, Kahlbaum studied his patients who died from somatic complications associated with severe catatonia. He did not examine patients with previous episodes of catatonia after their natural death. This fact relativizes the identified neuropathological correlates of catatonia considerably because the autopsied patients died mainly because of exhaustion, marasmus, peritonitis, infection, etc. In particular, Kahlbaum was aware of the important role of extracerebral organs in catatonia. For instance, he mentioned tuberculosis, because many of his catatonia patients had suffered from tuberculosis. Second, Kahlbaum's patients were of different ages, had different durations of illness, and died after varying periods of severe catatonia. This means that the anatomical findings are not exclusively due to catatonia, but are to some extent associated with other non-catatonic factors. Third, although Kahlbaum does not explicitly list the limitations of his approach, artifacts may have occurred in any case due to different cell autolysis times in the autopsied patients. Autolysis artifacts can be seen in the autopsy findings, such as tissue discoloration, tissue slippage, and the presence of bacteria or other organisms. We searched for the term "autolysis" in Kahlbaum's monograph but did not find a single entry. It can therefore be assumed that Kahlbaum may not have been aware of this process, or that he and other researchers back then may have had other terminological considerations. Still, Kahlbaum was aware of some limitations of his scientific methods because he stated that his histological examinations did not yield any useful findings: "*The microscopic examination of the cerebral cortex and other parts of the brain in catatonia patients has not yielded any useful results, although I have no doubt that the specificity of catatonia will also be proven histologically when normal and pathological brain histology has progressed further. Even for the long-known and much-studied picture of progressive general paralysis, no definitive result has yet been reached*" (p. 85).

For obvious reasons, our study has a number of limitations: First, we cannot claim to have covered the entire literature on the brain pathology of catatonia, because our search strategy was limited only to the previously identified historical texts. It may therefore be that other historical authors have also covered this topic, but we have not been able to identify them. Second, the authors often did not conduct the autopsies but referred to other colleagues. It was therefore often impossible to distinguish whether some reports stem from the author him-/herself or if a quotation came from another author. Third, historical authors often did not refer to specific brain regions because a uniform nomenclature and anatomical classification according to a unitary brain map was not available until 1909. Interestingly, in 1909, the German neuroanatomist, neurologist, and psychiatrist Korbinian Brodmann (1868–1918) published his studies on the cytoarchitecture of the cortex (Brodmann, 1909). Using Franz Nissl's (1860–1919) staining methods, he subdivided and mapped the human cortex into 52 parts with similar histological structures (Loukas et al., 2011). These fields are still known to us today as Brodmann areas. This was one possible reason why historical authors examining catatonia tended to focus their descriptions mainly on macroscopic brain tissue consistency rather than brain topographical findings. Fourth, one of the most serious problems of post-mortem studies is generally the structural changes that inevitably take place after the death of the patient. Fifth, historical authors have focused only on macroscopic changes because all the above-mentioned studies that were conducted until the end of the 19th century were only based on macroscopic examinations. Histological or histochemical studies only began at the beginning of the 20th century, especially with the creation of the Institute of Psychiatry in Munich, Germany. Finally, there was no apparent consensus regarding the pathophysiology of catatonic symptoms between 1800 and 1900. Interestingly, the authors did not really cite each other either. The reasons for this are manifold and require further research in this area.

5. Conclusion

Both Kahlbaum and other historical authors have postulated micro- and macroscopic brain tissue changes as possible causes of catatonia. However, the selection of patients, the autopsy methods, and the catatonia-related brain regions make a detailed comparison with current

neuroimaging studies and case reports difficult. Nevertheless, the historical neuropathological findings in catatonia, which seemed controversial in the 19th century, do not - in the main - indicate a single focal brain lesion, but rather may implicate a network dysfunction, similar to modern structural and functional imaging studies.

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CRediT authorship contribution statement

DH and MA: original idea and design of the study. DH and MA: literature search and close reading of the texts. DH, MA and RCW: first draft of the manuscript. DH, PG, KMK, FS, JRF, GN and RCW: discussion of the topic, writing and manuscript revision.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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