Cerebral atrophy as a cause of aphasia: From Pick to the modern era

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ABSTRACT

In his epoch-making monograph, Wernicke (1874) claimed that atrophy of the brain cannot cause aphasia. Refuting this claim, Pick (1892, 1898, 1901, 1904a) documented in increasing detail several cases of aphasia with circumscribed atrophy of the left temporal lobe, frontal lobe, or both, which persuaded Wernicke (1906). To explain why the atrophy is circumscribed and leads to focal symptoms, Pick (1908a) advanced a functional network account. Behavioral, neuroanatomical, and histopathological studies by Dejerine and Sérisieux, Fischer, Alzheimer, Altman, Gans, Onari and Spatz, and Stertz further illuminated the clinical syndromes, the exact spatial distributions of the atrophy, the underlying disease, and its laminar specificity. Unaware of these seminal studies, research from the 1970s until now has independently rediscovered all key findings, and also supports Pick's forgotten functional account of the distribution of atrophy and the focal symptoms. His frontal and temporal forms of aphasia foreshadowed what are now called the nonfluent/agrammatic and semantic variants of primary progressive aphasia. Moreover, aphasic symptoms may occur with frontal degeneration (what used to be called “Pick’s disease”) that yields personality changes and behavioral disturbances, now called the behavioral variant of frontotemporal dementia.

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1. Introduction

A forgotten chapter in the history of the neurosciences, but highly relevant today, concerns the work of Arnold Pick (1851–1924) on aphasia caused by circumscribed brain atrophy (e.g., Pick, 1892, 1901, 1904a, 1908a). To mark the centenary of Pick’s death, I describe his empirical and theoretical work and the further discoveries to which it led. Important contributions were made by Dejerine and Sérisieux, Alzheimer, Fischer, Onari and Spatz, and others. Although basic facts about clinical presentation and relation to circumscribed frontotemporal atrophy were documented in German- and French-language journals between 1892 and 1926, they lay dormant for half a century, and were discovered again in the 1970s (Warrington, 1975) and later (e.g., Hodges et al., 1992; Ohm et al., 2022; Snowden et al., 1989; Zhou et al., 2012). Also soon forgotten was Pick’s (1908a) explanation of why the atrophy is circumscribed and leads to focal symptoms. Unaware of Pick’s proposal, the account has been independently proposed again in the modern literature (e.g., Mesulam, 2007; Seeley et al., 2009), which is now one of the best explanations around.

The story begins 150 years ago in Breslau, with Carl Wernicke’s dismissal of the idea that circumscribed atrophy may...
cause aphasia (Wernicke, 1874). Three decades later, the work of Pick had convinced Wernicke (1906) that he was wrong and led to further investigations detailing the clinical, neuroanatomical, and histopathological characteristics of progressive aphasias. Nowadays, two main types of aphasia due to frontotemporal degeneration are distinguished, called the non-fluent/agrammatic and semantic variants of primary progressive aphasia (e.g., Gorno-Tempini et al., 2011; Kemmerer, 2022). The first variant is characterized by slow, labored, and halting speech with sound errors and/or agrammatism, and atrophy of the left inferior frontal gyrus. The second variant is characterized by word retrieval and comprehension problems, loss of conceptual knowledge (across categories and modalities), spared repetition and episodic memory, and atrophy of the anterior temporal lobes, most prominent in the left hemisphere and sparing Wernicke’s area and the hippocampus. Over time, patients typically become mute in both variants and their comprehension is severely impaired. Also, they become demented (e.g., Kertesz, 2007). Pick saw most of his patients at an advanced stage of the disease, demented but not mute yet. A third type of primary progressive aphasia that is nowadays distinguished, called the logopenic variant, is characterized by word retrieval and sentence repetition deficits, and associated with left temporoparietal junction atrophy and Alzheimer’s disease (e.g., Gorno-Tempini et al., 2008).

During the past century, Pick’s name primarily has become attached to a type of dementia (“Pick’s disease”) caused by neurodegeneration of the frontal lobes (e.g., Berrios & Girling, 1994), now called the behavioral variant of frontotemporal dementia (e.g., Rascovsky et al., 2011). Afflicted individuals present with personality changes and behavioral problems, like apathy and disinhibition, but language problems are also often present (e.g., Geraudie et al., 2021; Staffaroni et al., 2021). Although Pick (1904b) gave the first clinical description of this type of disorder, he did not discover the underlying pathology (Alzheimer did). Importantly, with his work, Pick did not intend to define a new disease, but he wanted to demonstrate “that various focal phenomena can develop on the basis of a circumscribed, more pronounced, senile cerebral atrophy” (Pick, 1901, p. 403). In particular, he responded to Wernicke’s (1874, 1893) claim that stroke but not atrophy may cause aphasic symptoms. Moreover, Pick (1908a) expected that circumscribed atrophy, much more than the stroke lesions studied by Wernicke and others, would help identify functional systems. He argued that, different from stroke, atrophy of the brain specifically affects functional systems, and therefore the spatial distribution of atrophy and behavioral deficits should provide precise information about language systems in the brain. Evidence from atrophy has indeed yielded new insights about language in the brain, requiring modification of traditional models (e.g., Mesulam et al., 2021).

In the remainder, I first describe Wernicke’s (1874) rejection of cerebral atrophy as a cause of aphasia, which helped save his first autopsy case of sensorial aphasia, later given his name. Next, I describe the findings of Pick and others that provided evidence against Wernicke’s claim. The histopathological studies of Alzheimer and Fischer indicated that the underlying disease was different from the disease named after Alzheimer in 1910. Pick’s functional account was rejected by Alzheimer, but received support from later research by Onari and Spatz and others. Then, I describe how the key seminal findings were independently discovered in modern research, and how they support Pick’s account and modern versions of it (e.g., Roelofs, 2022, 2023a, 2023b). Throughout my review of history, I indicate how modern research using new methodological advances and large data sets from health and disease has confirmed and expanded upon the seminal historical findings.

1.1. Wernicke’s (1874) rejection of cerebral atrophy as a cause of aphasia

In his classic monograph on aphasia, Wernicke (1874) described two cases with sensory aphasia. The aphasic symptoms of the first case, 59-year-old Susanne Adam, were described extensively, but she recovered from her aphasia. She was still alive at the time Wernicke wrote his text, so autopsy results were not available. The symptoms of the second case, 75-year-old Susanne Rother, were described only very briefly. Autopsy was done, providing, for the first time, evidence on the lesion location of sensory aphasia. According to Wernicke, “the gyri of both hemispheres and both insular regions are wrinkled and atrophied throughout.” Moreover, because of obstruction by a blood clot of the artery under the left Sylvian fissure, “the whole first (closest to the Sylvian fissure) temporal gyrus” has been “transformed into a white-yellow paste” (Wernicke, 1874, p. 45).

Although both atrophy and softening were observed, Wernicke was convinced that the aphasic symptoms were only caused by the softening of the left superior temporal gyrus. He stated:

> Simple atrophy, which as part of general atrophy has affected a single gyrus region, never causes a failure of its functions, causes no focal symptoms. We can regard this principle of experience, which must find its explanation in the nature of the pathological process, as one of the fixed points of cerebral pathology. ... We can therefore assert with certainty: the softening of the left first temporal gyrus in Rother was the only disease of the brain, which throughout the entire course could bring about focal symptoms of aphasia, and the general atrophy of the gyri was either biological aging, or, which is far more probable, a consequence of the circumscribed focal disease. (Wernicke, 1874, p. 46)

Twenty years later, Wernicke’s 1874 monograph was reprinted as the first chapter of a collection of his written works on the pathology of the nervous system (Wernicke, 1893). He had added a footnote on the first page stating that copies of his original 1874 book were still available (“das Original ist noch in einigen Exemplaren vorrätig”). However, the 1893 reprint was not identical to the 1874 original but had implemented several corrections. Whereas the 1874 original projected Wernicke’s functional model on the right hemisphere, the 1893 reprint showed the model in the left hemisphere, together with some
changes of localization. For example, whereas tactile images were shown in the right angular gyrus in 1874, they were in the postcentral gyrus in 1893. However, nowhere did Wernicke indicate to have changed his mind regarding brain atrophy. Clearly, cases of aphasia caused by cerebral atrophy were not attracting notice. For example, Exner (1881) created a quantitative lesion-overlap map for 31 patients with aphasia reported in the literature, none of which was said to have atrophy as cause. Between 1892 and 1904, Pick published several articles that managed to convince Wernicke that he was wrong in maintaining that simple atrophy cannot lead to focal aphasic symptoms.

1.2. Neuropsychiatry under Pick in Prague

As part of his medical training, Pick had been a student assistant to Theodor Meynert in Vienna (also a teacher of Wernicke) and a student of Carl Westphal in Berlin, where he had met Wernicke. From 1886 until his retirement in 1921, Pick was professor and chairman of the Department of Psychiatry of the German University of Prague. His clinic was in the Katerinky, a former military educational building erected on the site of a demolished medieval monastery of which only the church tower was left. Fig. 1 shows the building (still housing the neurological clinic), which served as the Asylum of Prague from 1822 onward (for a brief history, see Kertesz & Kalvach, 1996).

A few buildings further down the street from the clinic was the pathological-anatomical institute, where autopsies were performed on the brains of Pick’s patients by Hans Chiari and other pathologists. Among these patients were those who presented with aphasic symptoms and revealed circumscribed atrophy at autopsy. In the Katerinky, Pick saw the patients and documented their clinical presentation while his collaborator Oskar Fischer performed histopathological analyses. Fig. 2 shows photographs of Pick, Fischer, and Chiari. For short biographies of them, I refer to, respectively, Kertesz and Kalvach (1996), Goedert (2009), and Tubbs and Cohen-Gadol (2010). Pick’s student Sittig (1925) wrote an obituary for Pick, which includes a list of his publications.

2. The early symptom-to-atrophy mappings

Between 1892 and 1904, Pick published a series of articles reporting in increasing detail cases of aphasia caused by circumscribed atrophy. The aphasia was fluent or nonfluent, and the atrophy was in the temporal lobe, the frontal lobe, or in both.

2.1. Pick’s (1892) seminal case of aphasia with left temporal lobe atrophy

In his 1892 article, published in the Prager Medicinische Wochenschrift (see Fig. 3 for the front page), Pick reported on 71-year-old August H., who presented with progressive aphasia as part of a global dementing process. At autopsy, circumscribed left temporal lobe atrophy was observed, alongside more general atrophy of the brain. The aphasic symptoms consisted of word finding difficulty and impaired comprehension, while repetition was partly spared. Pick wrote:

The comprehension of speech is considerably but not totally impaired; he understands simpler questions, about his background, about conditions familiar to him through practice, but he does not understand other things at all. … Speaking: The patient has a considerable vocabulary and also speaks a lot; but although the sentences are sometimes correct when it comes to the simplest things, they
are mostly incomprehensible... He recognizes some of the objects that are shown, often gives them wrong names. ...

Repetition is done correctly, as long as one speaks to him slowly. (Pick, 1892, pp. 165-166)

As concerns the type of aphasia, Pick (1892) surmised, with reference to Wernicke (1874) and Lichtheim (1885), that “in essence it coincides with that form which Wernicke-Lichtheim call transcortical sensory aphasia, inasmuch as we find that loss of comprehension of speech and writing, paraphasia, and partially retained repeating of words, are the prominent symptoms of the language disorder” (p. 166). The autopsy performed by Chiari revealed that the gyri in the domain of the cerebrum are clearly narrowed, with atrophy of the gyrus in the left hemisphere and especially in the left temporal lobe being clearly stronger than at the corresponding places on the right” (p. 166). The article contained no pictures of the atrophied brain.

To explain the focal progressive disorder of language, Pick (1892) held “that simple progressive cerebral atrophy can occasionally also, and perhaps through greater local intensity of the diffuse process, lead to the symptoms of a focal affection” (p. 167).
546). Schoene, in a book edited by Rottenberg and Hochberg (Pick, 1977, p. 167), included the mechanism by translating the statement as “simple progressive brain atrophy can lead to symptoms of local disturbance through local accentuation of the diffuse process.”

2.2. The case of word deafness of Sérieux (1893) and Dejerine and Sérieux (1897)

A year later, converging evidence on atrophy as causal factor came from Paris. Sérieux (1893) reported on a case of progressive word deafness. He documented the declining language performance of patient B as it had occurred over a period of six years. In describing the initial symptoms, he stated: “The understanding of spoken language is, if not completely abolished, at least very seriously compromised”. As concerns spontaneous speech, she “speaks with fluency: there is neither motor aphasia, nor hampered speech, nor articulation difficulty: note only a slight degree of paraphasia and verbal amnesia”. Also, some words can be repeated while others “despite her efforts, she cannot repeat, even when they are articulated slowly several times.” Moreover, the patient presented with auditory agnosia, in particular, an “inability to recognize and sing certain musical tunes” and “difficulty distinguishing whistling, the songs of birds, of the human voice” (Sérieux, 1893, pp. 733–739). The seminal behavioral descriptions by Sérieux match subsequent single-case reports on word deafness (for a review of 100 years of studies, see Buchman et al., 1986).

Four years later, Dejerine and Sérieux (1897) reported on the autopsy of B’s brain, but presented no pictures of the cerebral atrophy. They observed spatial gradients of cell loss, not only across the cortex but also across its layers, decreasing from the upper to the lower layers. They wrote:

The temporal lobes are massively atrophied on both sides. Their atrophy is symmetrical, and each lobe is diminished by almost half. ... The atrophy of these convolutions decreases from top to bottom, the 1st being more affected than the 2nd and this one more than the 3rd. ... All the rest of the hemispheres — frontal lobe, ascending frontal and parietal convolutions, superior parietal lobe, insula, occipital and temporo-sphenoidal lobes, medial face of the frontal lobe — are absolutely intact. ... The lesion of the convolutions is here an exclusively cellular lesion and is that of chronic poliencephalitis; it decreases in intensity from the periphery to the center of the cortex. (Dejerine & Sérieux, 1897, pp. 1075–1076)

2.3. Pick’s (1898) cases of frontal lobe atrophy

The cases of Pick (1892) and Dejerine and Sérieux (1897) had temporal lobe atrophy. A few years later, Pick (1898) reported on two patients with aphasic symptoms and circumscribed atrophy of both the left temporal and frontal lobes, or the frontal lobes only.

The first patient was 67-year-old Apollonia Fritsch, who presented with fluent speech, word retrieval difficulty, severely impaired word comprehension, and fully spared repetition. Pick (1898) reported that her brain at autopsy showed severe atrophy of Broca’s area and the left superior temporal gyrus. Fig. 4 shows drawings of the brain. The second patient was Karoline Euzicka, about 61 years old, presenting with fluent but reduced speech output, word retrieval difficulty, somewhat impaired word comprehension, and fully spared repetition. Her brain at autopsy was said to show severe atrophy of the frontal lobes. No drawings of the brain were shown.

Fig. 4 – Drawings of the brain of patient Apollonia Fritsch reported by Pick (1898): Side view (top) and coronal views (bottom) of the left and right hemispheres. Adapted from Pick.
2.4. **Pick’s (1901) case of nonfluent aphasia with phonemic paraphasias**

The two 1898 cases of Pick presented with fluent speech, despite frontal lobe atrophy. A few years later, Pick (1901) reported on a patient with nonfluent speech and left frontal lobe atrophy. The patient was 59-year-old Francisca Z. Relatives had said that she had become “monosyllabic” (“einsilbig”). Moreover, “the articulation (?) of the language became bad” [“die Articulation (?) der Sprache wurde schlecht”] (p. 403), Pick wrote, apparently surprised about the articulation problems, which none of his previous patients had. Francisca Z. made many phonemic paraphasias, and had severe word finding difficulty and impaired comprehension. In Pick’s words:

Brought to the examination, the most prominent symptom immediately appears as a severe aphasic disturbance of speech, which is characterized by two manifestations; first, the patient clearly does not understand most of the questions asked, and second the spontaneous speech presents itself as a severe form of aphasia. As concerns the speech understanding, it is evident that the patient understands simple questions, for example regarding her own background, but fails as soon as questions are asked that go beyond the very simplest, sometimes clearly in such a way that the main word of the question seems to be understood, but not the rest. (Pick, 1901, p. 403)

At autopsy, the “brain showed generalized atrophy, especially in the left hemisphere and particularly in the operculum, in the angular gyrus, in the superior temporal gyrus and inferior frontal gyrus, and in the gyri of the insula” (Pick, 1901, p. 404). Fig. 5 shows Pick’s article in the Wiener klinische Wochenschrift including drawings of the atrophied brain. The clinical presentation and anatomical findings resemble what may be observed in the nonfluent/agrammatic variant of primary progressive aphasia (e.g., Gorno-Tempini et al., 2006).

2.5. **Pick’s (1904a) cases of left temporal atrophy with sparing of Wernicke’s area**

A few years later, Pick (1904a) described three cases of aphasia with atrophy of the left temporal lobe sparing the superior temporal gyrus, now with photographs of side and coronal views of the brains. The first case, Josefa Valchar, 58 years old, presented with fluent speech but severe naming difficulty, moderate comprehension impairment, and spared repetition. The second case, 75-year-old Anna Jirinec, presented with fluent speech but word retrieval difficulty and severely impaired word comprehension, impaired conceptual knowledge, and seemingly spared episodic difficulty. The third case, Petronilla Vlasak, 38 years old, presented with motor speech disturbance and severe naming difficulty, but preserved object knowledge. In discussing the first case, Josefa Valchar, Pick wrote:
The absence of any severe word deafness, which can be demonstrated far into the later course, leads to the conclusion that the temporal lobe atrophy, in contrast to the other cases, did not begin in the first temporal convolution; the supposition that the amnestic aphasia of the case is to be brought into connection with the predominant involvement of the other sections of the temporal lobe, which can be inferred from this, receives a strong confirmation from the other facts known from the localization of the latter. (Pick, 1904a, p. 380)

Pick was somewhat at a loss in interpreting the second case, Anna Jirinec, whose aphasic symptoms seemed to be largely due to a loss of conceptual knowledge. Pick wrote:

The assessment of the language disorder in the above [second] case, just as it was at the time of the clinical observation, also now, when it is completed before us, presents very special difficulties which, of course, do not seem to be eliminated or reduced in any way by knowing the autopsy findings; from the beginning of the clinical observation, it must be admitted that a part, and not a small one, is related to the deterioration of the content of ideas; ... further in the process, the deterioration of the content of ideas comes more and more to the fore, through the absorption of which the other phenomena gradually become completely masked. (Pick, 1904a, p. 384)

Fig. 6 shows photographs of side and coronal views of the brain of Anna Jirinec, illustrating that the anterior part of left temporal cortex is predominantly affected, while the superior temporal gyrus and the hippocampus seem to be spared. These observations agree with what is typical for semantic dementia (e.g., Patterson et al., 2007). The photographs of the brains of the three patients were not reproduced in the English translation of Pick’s article by Girling and Berrios (Pick et al., 1997). Also, they were not scanned for the digitalized archive of the original journal. Still, the photographs reveal important information. The observation that especially the anterior part of the left temporal lobe was atrophied, while Wernicke’s area and the hippocampi were less affected, was also made in other cases by Altman (1923) and Onari and Spatz (1926) using macroscopic and histopathological methods. Moreover, the observation has been confirmed by a modern case series study (Mesulam et al., 2015) and by a quantitative meta-analysis of gray matter volume reductions in semantic dementia (Yang et al., 2012). In the English translation by Girling and Berrios, the impairment of Anna Jirinec was said to include a “significant destruction of her mental functions”, whereas Pick (1904a) talked more specifically about a “Verödung des Vorstellungsinhaltes” (p. 384), which literally means a “destruction of ideational content”. Spatt (2003) translated Pick’s words as “a devastation of concepts”. Pick’s assignment of Jirinec’s problems to a loss of concepts is important in light of the later finding that this is the key impairment in semantic dementia (e.g., Patterson et al., 2007). At the time, it was generally assumed that concepts only consist of sensory and motor images, as did Wernicke (1874). The general opinion later changed mainly due to the work on “imageless thought” by experimental psychologists at the University of Würzburg (e.g., Küpe, 1922; Watt, 1904; see Woodworth, 1938, for a review).

2.6. Pick’s (1904b) case of personality change and behavioral disturbance

In the same year, Pick (1904b) published a case of personality change and behavioral disturbance, but without an autopsy report. This patient, 41-year-old Anna H., is considered to be the first described case of clinical Pick’s disease (Kertesz, 2007), now called the behavioral variant of frontotemporal dementia. Although the behavioral disturbance stood out from the other symptoms, the patient also showed language problems in the pragmatic domain. Modern research has shown that word retrieval and comprehension problems are also present in about half the cases of the behavioral variant of

Fig. 6 – Photographs of the brain of patient Anna Jirinec reported by Pick (1904a): Side view (top) and coronal views (bottom) of the left and right hemispheres. Adapted from Pick.
frontotemporal dementia (Geraudie et al., 2021; Staffaroni et al., 2021), discussed later.

2.7. Wernicke’s (1906) acceptance of atrophy as a cause of aphasia

Pick’s findings had convinced Wernicke. In a review of the literature on aphasia, Wernicke (1906) accepted the evidence of Pick that focal aphasic syndromes may be due to circumscribed brain atrophy. Wernicke stated: “Pick has shown that within the framework of a general brain atrophy, there are more pronounced localized atrophies, which reveal themselves through focal symptoms that correspond with the locus” (p. 553).

It should be noted, however, that not everyone was convinced that the atrophy had to be locally intensified. Goldstein (1906), a former student of Wernicke, stated:

We had findings similar to those, e.g., described by A. Pick: general atrophy of the cerebral convolutions with particular involvement of certain sites. Perhaps this last assumption is not even necessary, since uniform atrophy probably means damage of varying degrees to the different functions of the brain. (p. 948)

Although Goldstein’s suggestion is a theoretical possibility, the empirical studies showed that atrophy actually always was locally enhanced. Wernicke (1906) discussed progressive transcortical sensory aphasia, occurring “always through circumscribed atrophy of the left superior temporal gyrus” (p. 554). Importantly, however, Pick’s studies documented several cases of circumscribed left temporal lobe atrophy in which the superior temporal gyrus was spared.

3. Pick’s (1908a) theoretical account

In September 1907, Pick travelled to Amsterdam to present two talks on his work. The occasion was the first International Congress of Psychiatry, Neurology, Psychology, and Nursing of the Insane. The conference attracted “a remarkable number of the best-known specialists of the time” (Müller, 2001, p. 90), including Santiago Ramón y Cajal, Constantin von Monakow, Hugo Liepmann, and Cécile and Oskar Vogt. The venue was the city’s famous concert hall, the Concertgebouw. Before the entrance of the Dutch Queen Wilhelmina and her husband Prince Hendrik, a choir sang the national hymn of the Netherlands, and “during the afternoon sang selections from Handel’s oratorios, Joshua and The Messiah”, according to a Special Correspondent in the Medical Record (New York) on September 21, 1907 (Correspondent, 1907). Music lover Pick must have liked it.

In a plenary address at the conference, Pick put forward an explanation of why the atrophy is circumscribed and leads to focal symptoms. The paper he read appeared as a chapter of a book on work from his clinic in Prague (Pick, 1908a), see Fig. 7, and it was also included in the conference proceedings (Pick, 1908b). Pick (1908a) wrote:

Under the certainly justified assumption that, just like the individual organ systems of the brain, the functionally similar neuron chains that make up such a system also have different degrees of viability, one can assume that such a systematically similar neuron group, i.e., a system in the older sense, occasionally succumbs earlier to atrophy than others, and as a result the function of this system fails completely in an isolated manner; this would have resulted, even if not roughly anatomically, but yet more significant, in a functionally circumscribed elimination, i.e., a focal affection in the purest sense of the word. (p. 24)

Pick used a drawing of Ramón y Cajal to illustrate how laminar-specific atrophy may occur. In support of his theoretical proposal, Pick (1908a) referred to work from his laboratory in Prague by Fischer, who had observed that atrophy may spread through particular layers of the cortex. In a footnote, Pick mentioned that he had just learned that Alzheimer had reported findings similar to those of Fischer.

In discussing the observation that atrophy typically affects the left temporal lobe, Pick (1908a) pointed to functional factors. He stated:
It is a fact confirmed by everyone who deals with it, that precisely the temporal lobe and apparently especially the left one, succumbs particularly early to the senile or presenile cerebral atrophy; the reasons for this have not yet been elucidated, but should not lie in any morphological factors, since this atrophy affects one lobe particularly early and intensively and nothing is known which would morphologically explain such a special position of this part; on the contrary, all that is known of the left hemisphere, applied to its temporal lobe, would give reason to ascribe to this latter a functional preference over that of the other side. If, despite this, or rather because of this, the left temporal lobe atrophies earlier and more severely than the right one, then there is every reason to look for the cause in functional factors. From this point of view, we shall certainly be justified in relating one of the earliest manifestations of the onset of senescence, word amnesia, to this early-onset temporal atrophy. (p. 27)

Pick (1908a) had high hopes that circumscribed atrophy, more than stroke lesions, would help identify functional systems. He wrote:

I would like to express the opinion that for the time being we can expect more detailed information from the atrophy method, as practiced by nature to such a large extent, than even from the study of spatially smaller, differently constituted foci; only this method signifies the progression from circumscribed locality to circumscribed function. (p. 26)

4. The early anatomical-pathological discoveries

After Pick's series of articles on circumscribed atrophy, the time was ripe for more detailed investigations of the underlying anatomical pathology. These investigations were done in the context of another important discovery. In 1907, two articles appeared on the neuropathology of what later came to be called Alzheimer's disease. One article was by Alois Alzheimer working in the laboratory of Emil Kraepelin in Munich and the other by Oskar Fischer working in the laboratory of Pick in Prague. Alzheimer (1907) described plaques and tangles in the brain of one patient, Auguste Deter. Fischer (1907) described the plaques in 12 out of 16 patients clinically presenting with senile dementia and he reported the absence of plaques in 65 controls, which included patients with other clinical presentations and healthy controls. In a new edition of his handbook on psychiatry, Kraepelin (1910) was quick to announce the new disease, which he named after Alzheimer: “Alzheimerschen Krankheit” (p. 627). A year later, in 1911, Alzheimer discovered another disease, complementing Fischer's (1910, 1911) histopathological findings on circumscribed atrophy.

4.1. Fischer's (1910, 1911) histopathological findings

In 1910, Fischer reported on an examination of the brains of 275 patients, 58 with plaques and 10 of them additionally with tangles (Fischer, 1910). Pick's patient Anna Jirinec described above was not among the patients who showed plaques and tangles, indicating that she was afflicted with a different disease. Moreover, Fischer (1911) described in detail the features of the circumscribed atrophy in 12 patients, which he characterized as spongiform. The spongiform cortical wasting had thinned the cortex of Jirinec's left temporal lobe by 75%.

4.2. Alzheimer's (1911) study of two cases of circumscribed temporal atrophy

Following up on Pick (1904a) and the work by Fischer (1910) on circumscribed atrophy, Alzheimer (1911) reported on a histopathological study of two cases of circumscribed left temporal cortex atrophy. The report occurred at the end of an article that described the case of Auguste Deter in more detail and it provided an extensive documentation of a second case with Alzheimer's disease, Johann Feigl. In these examinations, Alzheimer had used silver staining (i.e., Bielschowsky stain), which he used again for the cases of left temporal lobe atrophy. But now he did not observe the plaques and tangles found a few years earlier in the brain of Deter and the plaques observed in the brain of Feigl. Instead, he observed round silver-stained inclusions ('silver bullets') in the cytoplasm of nerve cells and ballooned neurons, suggesting a different disease, later given Pick's name. Fig. 8 shows a coronal slice of the left temporal lobe of one of the patients (Therese Mühlich) and drawings by Alzheimer of the round inclusions found in the neurons. Alzheimer (1911) was unsure about the cause of the pathology. He speculated about a vascular origin: “Perhaps such circumscribed atrophies of larger gyral areas occur due to faulty nourishment of the atrophic area following severe arteriosclerotic alterations of a larger artery supplying the whole area” (p. 383). As concerns the distribution of atrophy, Alzheimer stated:

![Image](https://example.com/image.png)

**Fig. 8** – Photograph of a coronal slice of the left temporal lobe of Therese Mühlich (left) and drawings by Alzheimer (1911) of the round inclusions and ballooned cells that he found (right). The coronal slice is from Onari and Spatz (1926). Reproduced with permission from Springer Nature.
However, against the assumption that the localized atrophy of the left temporal lobe is caused by functional factors, as Pick suggests, speaks in my view the fact that in both cases the first temporal convolution was least affected, and the second and third were much more severely atrophied and the cornu ammonis was no less damaged than the second and third temporal convolutions. In any case, the cornu ammonis belongs to a completely different functional area. But perhaps this arrangement of the atrophy could also be related to the blood vessel supply of the temporal lobe. (p. 384)

Thus, Alzheimer rejected Pick’s (1908a) functional account. Modern research has confirmed the functional difference between lateral temporal cortex and the hippocampus, with the cornu ammonis as a part. An important functional distinction regarding memory is between storage and consolidation of knowledge (e.g., Eichenbaum, 2012). Whereas lateral temporal cortex stores factual knowledge about concepts and words (semantic memory) as well as knowledge about personal events (episodic memory), together called declarative memory, the hippocampus plays a critical role in learning new declarative knowledge and consolidating it in cortical areas. Patients with semantic dementia present with a loss of conceptual knowledge and atrophy of the anterior temporal lobes (see Lombardi et al., 2021, for a large-scale study), while patients with Alzheimer’s dementia have a consolidation disturbance (most evident from their impaired episodic memory) and atrophy of medial temporal regions, predominantly in the hippocampus. Alzheimer’s disease starts in the entorhinal cortex, then spreads into the hippocampal formation, and later further progresses to the lateral temporal cortex and other brain regions (e.g., Braak & Braak, 1991; Josephs et al., 2020).

In 1912, Alzheimer exchanged Munich for Breslau to take the chair of Psychiatry that had been occupied for almost 20 years by Wernicke (who had died in 1905). The brains with circumscribed temporal lobe atrophy that had been studied by Alzheimer were left behind in Munich. In Breslau, Alzheimer’s eldest daughter Anna met a young psychiatrist named Georg Stertz, and they married shortly afterwards. A few years later, Stertz accepted an invitation by Kraepelin to work in his clinic in Munich (Hippius et al., 2008). In the early 1920s, Stertz revisited the clinical descriptions by Alzheimer of his cases of circumscribed temporal atrophy, and Onari and Spatz reexamined the cerebral slices. This led to new insights, discussed later.

5. Pick’s final manuscript in 1924

After the acceptance by Wernicke (1906) of atrophy as a cause of aphasia and publishing his theoretical account (Pick, 1908a), the issue seemed settled for Pick. A major effort in the following years was his book on agrammatism (Pick, 1913), for which he is perhaps best known in psycholinguistics and aphasiology (e.g., Levelt, 2013; Tesak & Code, 2008). Shortly before his death in 1924, Pick completed a manuscript providing an overview of aphasia, posthumously made ready for publication by his student Otto Sittig. The work appeared in print in 1931 as a chapter of a handbook on normal and pathological physiology (Pick, 1931), 40 years later translated into English (Pick, 1973).

In a discussion of pathological phenomena, Pick (1931) stressed the importance of a distinction “between actual degradation, for example through simple atrophying processes, and focal affections that destroy structure and function in a quite irregular manner” (p. 1443). Whereas stroke does not respect functional borders, atrophy causes a deterioration of specific functional systems, something he also had stressed in his earlier theoretical account (Pick, 1908a). Although earlier he was unsure about what function is affected by atrophy of the left temporal lobe, he now came with a concrete proposal, with reference to Goldstein (1906, 1911). Pick (1931) stated that it has been shown that their foci are based in the 2nd and 3rd temporal convolutions, usually on the left side ... This suggests that ... through ... involvement of a so-called “concept field” (Goldstein) the temporal lobe plays the leading role. (p. 1467)

In his early works, Goldstein had taken the concept field to be the location in the brain where concepts are stored, separate from their sensory and motor features (for a discussion of Goldstein’s evolving view on localization, see Geschwind, 1964). Goldstein (1913) stated:

While the purely sensory components of experience are represented in the sensory fields, we have to place everything else in an area of the brain that I call the concept field in relation to the sensory fields. The exactness of this concept field is necessary for the normal formation of ideas and concepts. ... Every concept owes its origin to a judgement, it is the result of a judgement, the summary of elements previously isolated in our thinking into a higher unity from the point of view of the categories of judgements, which all lawfully combine the content given by perceptions or ideas. (pp. 542–543)

Earlier, Pick (1908c) had accepted the distinction between thought with images and without (“unanschaulich”), thereby taking a stance in the debate on imageless thought initiated by the Würzburg psychologists. The view of Pick (1931) that the temporal lobes represent a ‘concept field’, separate from sensory and motor features, resembles what is now called the hub-and-spoke view of meaning (e.g., Patterson et al., 2007). This view holds that supramodal concepts are stored in the anterior temporal lobes, connecting modality-specific features stored in wide-spread sensory and motor areas of the brain. In semantic dementia, the semantic hub deteriorates.

6. Later anatomical-pathological discoveries

Pick’s work had led to a rather coherent account of aphasia caused by circumscribed atrophy of the brain. However, two issues were still lingering, both raised by Alzheimer (1911). In the 1920s, the issues were resolved.
6.1. The studies of Altman (1923) and Gans (1923)

From the laboratory of Alfons Jakob (who co-discovered Creutzfeldt-Jakob disease) in Hamburg, Emil Altman reported two cases of “circumscribed cerebral atrophy of later age” [umschriebene Gehirnatrophie des späten Alters] (Altman, 1923, p. 610), both presenting with dementia and ending in complete muteness. The patients were said to be aphasic, but no examples of their speech were given. Atrophy was most pronounced in the frontal lobes in the first case and in the temporal lobes in the second case. Layers III and V of the cortex were most affected, with plaques and tangles being absent but silver bullets present in both cases. Altman noted that the hippocampus was spared and that the distribution of atrophy had no relation to the vascular system, but drew no theoretical consequences (which Onari & Spatz, 1926, would do). In the same year, Abraham Gans (a psychiatrist in Santpoort and later in Leyden, the Netherlands) reported a case of dementia and nonfluent aphasia (examples of disturbed speech were given) with circumscribed left inferior frontal atrophy, which he referred to as “Pickian atrophy” [Pickscher Atrophie] (Gans, 1923, p. 10). In an article in Dutch published in 1925, Gans compared “the diseases of Pick and Alzheimer” [De ziekten van Pick en van Alzheimer], thereby coining the term “Pick's disease”.

6.2. The complementary studies of Onari and Spatz (1926) and Stertz (1926)

Whereas Pick (1908a) argued that the atrophy in the temporal lobes concerns degeneration of a specific functional system, explaining why the atrophy is circumscribed, Alzheimer (1911) maintained that the atrophy crosses functional boundaries. Recall that he maintained that the atrophy was present in the left middle and inferior temporal gyri as well as in the cornu ammonis of the hippocampus, which are part of different functional systems. Moreover, Alzheimer had suggested that the atrophy may have a vascular origin. Both these remaining issues were addressed by Onari and Spatz (1926). Kimuri Onari was a visiting neurologist from Japan staying at the Munich laboratory in 1923 (Kreutzberg, 1990), where Hugo Spatz (who studied with Franz Nissl) worked as a neuropathologist. Spatz would later become director of the Kaiser Wilhelm Institute for Brain Research in Berlin, succeeding Oskar Vogt in 1937.

Alzheimer (1911) had not given the names or initials of the two patients with circumscribed atrophy that he had examined. Working in Munich as Alzheimer did, Onari and Spatz identified one of the patients as Therese Mühlich and Alzheimer’s son-in-law Stertz recovered her clinical record. Onari and Spatz (1926) reported on a reexamination of the cerebral slices of Mühlich and an investigation of the brains of Anna Bradt (who had been a patient of Stertz in Breslau) and Maria Ruge (a patient of Stertz and Kraepelin in Munich), while Stertz (1926) described the clinical symptoms. Mühlich and Bradt presented with prominent aphasic symptoms and circumscribed temporal lobe atrophy, while Ruge presented with severe dementia (i.e., apathy, inertia, emotional blunting) and circumscribed frontal lobe atrophy. “In R.’s case I was able to rightly relate the cessation of every form of drive to the atrophy of the frontal lobes” (Stertz, 1926, p. 746).

6.2.1. Resolving the functional issue

The reexamination of the brain preparations of patient Therese Mühlich led Onari and Spatz (1926) to contest Alzheimer’s original description of the spatial distribution of the atrophy. This settled the functional issue. They stated:

In one point we have to contradict the presentation of Alzheimer. Alzheimer has already pointed out the relative integrity of the first temporal gyrus, but he says the cornu ammonis is no less damaged than the 2nd and 3rd temporal gyri. The cornu ammonis has probably suffered somewhat more than in Bradt’s case, but it is incomparably better preserved than the 2nd and 3rd temporal gyri. (p. 489)

Moreover, Onari and Spatz (1926) also found in Anna Bradt’s brain that atrophy was most prominent in the left temporal pole and fusiform gyrus, while sparing Wernicke’s area and the hippocampi. The left panel of Fig. 9 illustrates the key findings. Summarizing their anatomical findings on the brain of Bradt, they stated:

The highly atrophic area thus includes, taken from medial to lateral: Gyrus hippocampi (after the subiculum), gyrus fusiformis (= collateralis), second and third temporal convolution. In the sagittal direction, the change increases in intensity towards the temporal pole, and gradually

Fig. 9 – Photograph of a coronal slice of the left temporal lobe (left) and microphotograph of cortical layers of the temporal pole (right) of the brain of Anna Bradt reported by Onari and Spatz (1926). Reproduced with permission from Springer Nature.
decreases in intensity towards the gyrus supramarginalis and angularis, as well as towards the occipital area. (pp. 487–488)

Thus, the atrophy in the brain of Mühlich did not cross functional boundaries, different from what Alzheimer (1911) had suggested. In the brains of both Mühlich and Bradt, there was circumscribed atrophy in the left middle and inferior temporal gyri, sparing the posterior superior temporal gyrus (Wernicke’s area) and the hippocampus. This has appeared to be typical for semantic dementia (e.g., Gorno-Tempini et al., 2011). The brain of Maria Ruge revealed circumscribed atrophy in the anterior insula and gyrus fornicatus, including the anterior cingulate cortex. This has appeared to be typical for the behavioral variant of frontotemporal dementia (e.g., Seeley, 2008; Seeley et al., 2009). The insular-cingulate regions make up the brain’s salience network, further discussed below.

As concerns the functional factors at work, Gans (1923) stated: “The fact that the function plays a role in explaining the development of Pick’s atrophy is proven by the fact that cytoarchitecturally definable areas, which nevertheless represent functionally related parts of the brain, are affected by it” (p. 27). And Onari and Spatz (1926) wrote: “One thing is probably certain, the spread of Pick’s atrophy is not random; in at least a number of cases, there are remarkable relationships to tectonic, genetic, and functional systems” (p. 506). Based on published cases (listed were 9 patients with temporal lobe atrophy and 12 with frontal lobe atrophy), they summarized the literature by stating:

The local disease prefers to affect certain systems while leaving others free. According to the nature of the changes, we can assume a regressive process that progresses at a very slow pace. This is in good agreement with the slow creeping progression of the clinical course. The systematic spread seems to correspond to the “systematic impact” of dementia and aphasia, of which Stertz speaks. (p. 472)

Modern research has shown that neurodegenerative diseases target specific functional networks, starting in regions with heavy network traffic and propagating along strong functional and anatomical connections (e.g., Mandelli et al., 2016; Seeley et al., 2009; Zhou et al., 2012). Employing network-sensitive neuroimaging methods, Seeley et al. showed that five different neurodegenerative syndromes (i.e., Alzheimer’s disease, behavioral variant frontotemporal dementia, semantic dementia, progressive nonfluent aphasia, and corticobasal syndrome) cause circumscribed atrophy of five distinct functional and structural networks, as determined in healthy human brains. They concluded that “neurodegenerative diseases are not diffuse, random, or confluent, but instead target specific large-scale distributed networks. In the healthy brain, these networks feature convergent intrinsic functional and structural covariance” (Seeley et al., 2009, p. 49). Mandelli et al. showed that an epicenter in the left inferior frontal gyrus disrupts the network that is concerned with phonological encoding, giving rise to symptoms of the nonfluent/agrammatic variant of primary progressive aphasia. Zhou et al. showed that an epicenter in the anterior temporal lobes disrupts the network underlying semantic memory, giving rise to symptoms of semantic dementia (e.g., Patterson et al., 2007). Seeley and colleagues (Seeley, 2008; Seeley et al., 2009) showed that an epicenter in the anterior insula and dorsal anterior cingulate cortex disrupts the insular-cingulate salience network. This network is involved in the detection of salient stimuli and the recruitment of other relevant functional systems, such as the lateral frontotemporal executive control system. Disruption gives rise to symptoms of the behavioral variant of frontotemporal dementia.

Regression analyses by Mesulam et al. (2021) of performance on tests of grammar, repetition, and semantics by patients with primary progressive aphasia (N = 62) revealed three nonoverlapping left hemisphere clusters where atrophy was related to impaired performance: A morphosyntactic cluster related to impaired sentence construction located in middle and inferior frontal gyri; a phonological cluster related to impaired repetition in the temporoparietal junction; and a lexicosemantic cluster related to impaired object naming and single word comprehension in the middle and anterior parts of the temporal lobe. For a neurocognitive computational model of how these clusters relate to single word production, comprehension, and repetition in the three variants of primary progressive aphasia and behavioral variant frontotemporal degeneration, I refer to Roelofs (2022, 2023a, 2023b).

6.2.2. Resolving the vascular issue

Onari and Spatz (1926) documented in much detail that the atrophy was not related to the vascular system, refuting Alzheimer’s (1911) conjecture of a vascular origin. They wrote:

Alzheimer conjectured that arteriosclerosis should be considered as the cause of Pick’s atrophy. Against this possibility speak however the following reasons: In the cases which we were able to examine, arteriosclerotic changes in the cerebral vessels played only a very minor part. … Particularly speaking against this possibility is the fact that the atrophy affects very specific parts of the temporal lobe, which in no way correspond to the area supplied by a larger vessel, just as the atrophic frontal regions in case I of Gans are not identical to the area supplied by a larger vessel. (Onari & Spatz, 1926, pp. 496–497)

6.2.3. Laminar characteristics

In their histopathological investigation of the brain of Anna Bradt with temporal lobe atrophy and the brain of Maria Ruge with frontal lobe atrophy, Onari and Spatz (1926) observed that atrophy was predominantly present in the upper three layers of the cortex. The right panel of Fig. 9 illustrates the key findings for Bradt. They wrote:

Just as the spread in the surface chooses a particular cortical area of the temporal lobe, so does the spread in the depth involve a choice. Microscopic examination revealed that the reduction in size of certain gyri corresponds to a high-grade loss of nervous elements, but the loss of nerve cells and nerve fibers is not equally intense in the cross-section of the cortex, but reaches its highest degree in the
upper cortical layers (I-IIIa), while the deeper cortical layers (especially the IV layer) are generally better preserved. (Onari & Spatz, 1926, p. 488)

Moreover, in the brain of Bradt, Onari and Spatz (1926) did not find plaques or tangles (found by Alzheimer in the brain of Deter, evidence of Alzheimer's disease) or round inclusions or ballooned cells (found by Alzheimer in the brain of Mühlich, evidence of Pick's disease). Apparently, the presence of round inclusions or ballooned cells was not necessary for the clinical manifestations of Pick's disease to occur. Stertz (1926) described Bradt as presenting with fluent speech but severe word retrieval difficulty, impaired word comprehension, and impaired conceptual knowledge, alongside seemingly spared episodic memory. He noted that these symptoms overlapped with those of Mühlich. But whereas Mühlich's brain showed the round inclusions, the brain of Bradt did not.

Ballooned cells come in two varieties (e.g., de León et al., 1986). Using Bielschowsky staining, Alzheimer (1911) observed Pick bodies and ballooned cells that included the bodies. Using Nissl staining, Onari and Spatz (1926) observed Pick cells without the bodies, which were seen as ballooned neurons with the cytoplasm having a pale appearance.

Modern examination of the laminar distributions of pathology in frontotemporal lobar degeneration has revealed that pathology predominantly occurs in the upper three cortical layers of the atrophied cortex or in the lower three layers (Ohm et al., 2022). The two most common disease proteins are pathologic TDP-43 and tau. TDP-43 pathology involves aggregation of diseased TAR DNA-binding protein 43 and tauopathy concerns the aggregation of hyperphosphorylated tau protein (Olney et al., 2017). TDP-43 pathology tends to be present in the upper three layers, and tau pathology in the lower three layers. Pick bodies mainly consist of 3 R tau. Ohm et al. (2022) stated that “tau burden may appear bilaminar due to frequent Pick body accumulation in upper layers and prominent Pick cells in lower layers” (p. 375), with the Pick cells including the bodies. Altman (1923) observed the bilaminar pattern of atrophy in his two patients with Pick bodies and cells, whereas Onari and Spatz (1926) observed the upper layers atrophy in their patients without Pick bodies. Onari and Spatz (1926) defined Pick's disease in terms of dementia or aphasia caused by circumscribed frontotemporal degeneration, independent of whether Pick bodies and cells were present. However, during the next half century, the frontal presentation was foregrounded and Pick pathology was deemed necessary for the diagnosis (e.g., Berrios & Girling, 1994; Delay et al., 1957).

7. Summary of the key discoveries

Between 1892 and 1926, several key discoveries were made. Fig. 10 displays a map of the historical milestones. Shown is Europe at the dawn of the twentieth century, dominated by the German and Austro-Hungarian empires. The boxes link the key contributions to the cities where they were made and the numbers indicate the succession in time.

8. Dormant period from the 1930s to the 1970s

The rise of the Nazi regime in the 1930s dissolved brain research in central Europe, where neurology had flourished in cities like Breslau, Munich, and Prague for over half a century. Several researchers (including Goldstein) fled Germany, while others took a wrong turn within the country. Hugo Spatz kept examining brains as a member of the Nazi party (Voges & Kupsch, 2021), and Oskar Fischer (as Pick belonging to the Jewish community of Prague) became one of its victims. His name is among the almost 80,000 ones on the inner walls of the Pinkas Synagogue in Prague, commemorating the Holocaust victims from the Czech lands.

Between the 1930s and 1970s, the work of the pioneers was largely forgotten: “Only a few groups continued Pick's work during this time” (Olney et al., 2017, p. 340). The language of...
science changed from German and French to English, which made the seminal articles inaccessible to many researchers (e.g., Levitt, 2013). As Norman Geschwind stated regarding the aphasia studies in German and French published before the mid-1920s: “Practically none of this literature was available in English, except occasionally in accounts by its detractors, and much of it is contained in old journals, many of which are no longer published, and often difficult to obtain” (Geschwind, 1964, p. 215).

A major issue in the dormant period from the 1930s to the 1970s concerned the clinical and anatomical distinction between Pick’s disease and Alzheimer’s disease. The clinical presentation of Pick’s disease was taken to consist of personality change and behavioral disturbance. In 1957, Delay and colleagues reported on an examination of 185 cases of Pick’s disease documented by previous researchers and 7 cases of their own (their article was in French, recently translated into English by Thibodeau & Miller, 2013). Delay et al. (1957) argued that Pick’s disease is always restricted to frontotemporal areas, whereas Alzheimer’s disease is characterized by diffuse cerebral atrophy. Delay et al. noted that researchers had insisted on the postmortem established presence of Pick bodies or cells for the diagnosis of Pick’s disease. However, following Onari and Spatz (1926), Constantinidis et al. (1974) stressed that the specific neuropathology is not necessary for the clinical symptoms to occur. The controversy was ultimately resolved in recent times by coining a new name and reserving the term Pick’s disease for cases with postmortem confirmed neuropathology.

9. The modern era from the 1970s onward

Since the 1970s, unaware of the seminal studies, research has rediscovered the key findings of Pick, Fischer, Alzheimer, Gans, Onari and Spatz, and Stertz, among others. Brun (1987, p. 193) reported on “frontal lobe degeneration of non-Alzheimer type”, stating that “we are faced with a hitherto not fully recognized if not a new type of dementia caused by ‘simple’ neuronal degeneration of mainly the frontal or frontal and temporal lobes.” Among the 158 patients with dementia that he had studied, there were 20 cases of frontotemporal degeneration, with 4 of them having Pick cells and 16 not having such cells and also not the plaques and tangles of Alzheimer (as observed by Onari & Spatz, 1926). Neary et al. (1988) reported on seven cases of “dementia of the frontal lobe type” presenting with personality changes and behavioral disturbances. “The designation of Pick’s disease in this paper has nevertheless been avoided, since it cannot be assumed that these patients meet the pathological criteria for that disease” (p. 360).

9.1. Behavioral and language variants

Later research (e.g., Gorno-Tempini et al., 2011; Rascovsky et al., 2011) rediscovered that frontotemporal degeneration may give rise to three syndromes, a behavioral one (as observed by Pick, 1904b) and two language ones (as observed by Pick, 1892, 1901, 1904a). Aphasia can be fluent or nonfluent (Pick, 1892, 1901, 1904a; Stertz, 1926). The distribution of atrophy across the cortex differs between syndromes (as observed by Onari & Spatz, 1926; Pick, 1901, 1904a). The pathology underlying the syndromes is different from Alzheimer’s disease (as observed by Fischer, 1910, and Alzheimer, 1911). Zhukareva et al. (2002) discovered that the silver bullets (Pick bodies) first observed by Alzheimer (1911) consist mainly of the 3 R tau protein. Also, TDP-43 was discovered to be a major disease protein (Neumann et al., 2006). The behavioral and nonfluent/agrammatic variants of frontotemporal dementia are associated with tau and TDP-43 pathology, whereas the semantic variant is predominantly associated with TDP-43 (see Olney et al., 2017, for a review). The pathology is laminar specific, with TDP-43 present in the upper three cortical layers (Onari & Spatz, 1926, observed upper-layer atrophy) or with tau in the lower ones. Tau pathology may appear bilaminar due to frequent Pick body accumulation in upper layers and prominent Pick cells in lower layers (Altman, 1923, observed the bilaminar pattern). The selective laminar distribution of pathology is observed in both the frontal and temporal lobes, independent of clinical presentation.

Since the 1930s, Pick’s name has been chiefly attached to the type of dementia (albeit with postmortem pathology confirmation) that is now referred to as the behavioral variant of frontotemporal dementia (e.g., Rascovsky et al., 2011). The new name and corresponding clinical criteria prevented the problem that the diagnosis could only be made after the patient’s death. Moreover, only a minority of cases appeared to have Pick’s pathology at autopsy (as noted by Brun, 1987). In introducing the translation into English of Pick’s seminal 1892 article, Berrios and Girling (1994) contested the appropriateness of the original eponym:

This paper has been quoted by generations as the locus classicus for what is now called ‘Pick’s disease’. ... It is difficult for the historian to establish a connection between the case of August H., who comes across as a patient with multi-infarct dementia, aphasia and delirium and what now is called ‘Pick’s disease’. Also quoted as a landmark in the history of the ‘disease’ is Pick’s report in 1901 of a woman of 59 with generalized cortical atrophy, affecting her left hemisphere. However, in neither case did Pick inculpate the frontal lobes. (pp. 539–540)

However, the woman described by Pick (1901) had atrophy of left frontal areas and she presented with nonfluent aphasia, resembling the nonfluent/agrammatic variant of primary progressive aphasia. Still, most of the other patients of Pick had pronounced left temporal lobe atrophy and a clinical presentation that resembles what is now called semantic dementia.

9.2. Semantic, nonfluent/agrammatic, and logopenic variants of aphasia

In the modern era, Warrington (1975) reported three cases of selective impairment of semantic memory, as evident from their impaired object recognition, word comprehension, and naming. Air encephalography revealed “generalized atrophy” in all three cases. Later postmortem investigation, reported by Warrington in a personal communication to Hodges et al.
10. Conclusions

In looking back on 25 years of studying primary progressive aphasia, Mesulam (2007) wrote that this type of aphasia “offers a unique experiment of nature for exploring the molecular fingerprints that make the language network a primary disease target and for probing the cognitive architecture of human language as it undergoes a slow but relentless dissolution” (p. 11). I have described how this insight originally arose from the patient studies of Pick in Prague between 1892 and 1904, and was further illuminated by examinations of Dejerine and Sériex, Alzheimer, Fischer, Altman, Gans, Onari and Spatz, and Stertz, among others. Although Wernicke originally rejected the idea, he ultimately was convinced by Pick’s reports. The seminal findings of the beginning of the twentieth century have been replicated and further detailed in research performed since the 1970s, mostly unaware of the early studies. Moreover, modern research employing network-sensitive neuroimaging methods has supported Pick’s forgotten functional account of the distribution of atrophy and the focal symptoms. In a letter to Wernicke commemorating the publication of his classic monograph 30 years earlier (i.e., Wernicke, 1874), Pick (1904c) wrote that he felt a great need to bring the historical significance of Wernicke’s work to the attention of the younger generation. The present article has described the historical significance of Pick’s own work on aphasia caused by circumscribed atrophy, and seminal behavioral, neuroanatomical, and histopathological studies by others, which have remained mostly unknown even to older generations.
Credit Author Statement

Ardi Roelofs: Conceptualization, Investigation, Writing – original draft, Writing - review & editing, Visualization.

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