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History of Neurology

The landmark contributions of Paul Blocq, Georges Marinesco, and Édouard Brissaud in Parkinson's disease

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INFO ARTICLE

Article history:
Received 21 January 2021
Accepted 9 February 2021
Available online xxx

Keywords:
History of neurology
Parkinson's disease
Locus niger
Substantia nigra
Paul Blocq
Georges Marinesco
Édouard Brissaud
Jean-Martin Charcot

ABSTRACT

Two students of Jean-Martin Charcot, Paul Blocq and Georges Marinesco, presented a case of hemi-parkinsonism to the Société de Biologie on 27 May 1893. A tuberculoma was found at post-mortem in the cerebral peduncle contralateral to the side of the body affected by Parkinson's disease. A year later, in one of his lessons, Édouard Brissaud suggested that damage to the substantia nigra caused by the granuloma might have been responsible for the physical signs. This article provides brief biographical accounts of both Blocq and Marinesco and a detailed review of their seminal paper before going on to discuss how the substantia nigra was eventually established as the most consistent pathological substrate for Parkinson's disease and its role in the dopamine miracle which led to striatal dopamine replacement therapy in 1967.

At the 27 May 1893 session of the *Société de biologie*, Paul Blocq (1860–1896) and Georges Marinesco (Gheorghe Marinescu, 1863–1938) delivered a paper entitled *Sur un cas de tremblement parkinsonien hémiplégique symptomatique d'une tumeur du pédoncule cérébral* (on a case of hemiplegic parkinsonian tremor symptomatic of a tumour in the cerebral peduncle) [1] (Fig. 1). At that time, no consistent pathological lesion had been found to explain the symptoms of Parkinson's disease and Jean-Martin Charcot (1825–1893) had included it with epilepsy and chorea as a neurosis i.e. "insofar as it [had] no specific lesion of its own" [2]. Nearly a century after the seminal publication by James Parkinson (1755–1824) [3], Édouard Brissaud (1852–1909) formulated a novel hypothesis in 1895, in which he suggested that the tuberculoma 'noisette' described by Blocq and Marinesco had damaged the substantia nigra on the side contralateral to the parkinsonian tremor.

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https://doi.org/10.1016/j.neurol.2021.02.386
0035-3787/

Please cite this article in press as: Fénelon G, Walusinski O. The landmark contributions of Paul Blocq, Georges Marinesco, and Édouard Brissaud in Parkinson's disease. Revue neurologique (2021), https://doi.org/10.1016/j.neurol.2021.02.386

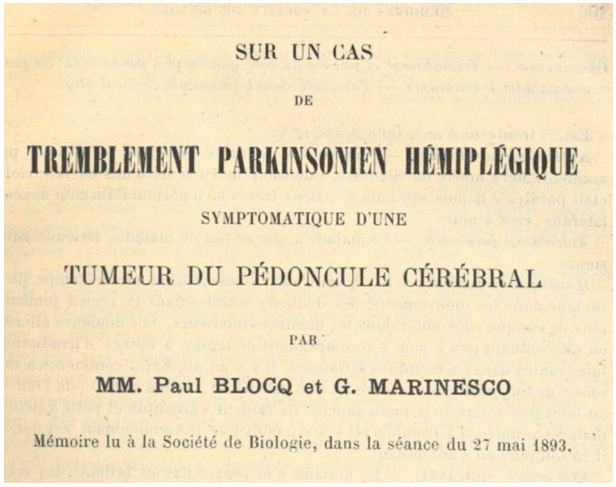
SUR UN CAS
DE
TREMBLEMENT PARKINSONIEN HÉMIPLÉGIQUE
SYMPTOMATIQUE D'UNE
TUMEUR DU PÉDONCULE CÉRÉBRAL
PAR
MM. Paul BLOCQ et G. MARINESCO
Mémoire lu à la Société de Biologie, dans la séance du 27 mai 1893.

Fig. 1 – Title of the article published in the *Bulletin de la société de biologie* (OW collection).

1. Paul-Oscar Blocq

Paul-Oscar Blocq (Fig. 2), born on 4 January 1860, spent his last year of his medical training in Paris working under Charcot. On 24 February 1888, he defended his thesis: ''*Des contractures, contractures en général, la contracture spasmodique, les pseudo-contractures*'' (on contractions: general contractions, spasmodic contractions, and pseudo-contractions). Charcot presided over the jury and Brissaud then an associate professor also sat on the examination committee. With the help of Pierre Marie (1853–1940), head of the laboratory, and Joseph Babiński (1857–1932), senior resident, Blocq demonstrated the clinical and anatomopathological differences between permanent contractures in hemiplegia and multiple sclerosis, and contractions that he defined as spasmodic and hysterical on the other. After the successful defense of his thesis, Charcot put him in charge of anatomo-pathological laboratory research in his department. Blocq is now often best remembered for his seminal description of astasia-abasia: ''This term designates a morbid state in which the impossibility of standing upright and walking normally contrasts with the integrity of sensation and muscular force and the coordination of other movements of the lower limbs'' [4]. Blocq wrote several medical texts, the most original and historically remarkable of which is entitled ''*Anatomie pathologique de la moelle épinière*'' (pathological anatomy of the spinal cord), illustrated with photographs taken by Albert Londe (1858–1917) [5]. Londe, the head of medical illustration in Charcot's department, had devised a camera obscura that could be fitted on a microscope [6]. With Victor Babès (1854–1926), Blocq published ''Atlas der pathologischen Histologie des Nervensystem'' in Berlin in 1892. He also published three books for practitioners ''*Sémiologie et diagnostic des maladies nerveuses*'' (semiology and diagnosis of nervous diseases) in 1892, ''*Les troubles de la marche dans les maladies nerveuses*'' (gait problems in nervous diseases) in 1893, and ''*Études sur les maladies nerveuses*'' (studies on nervous diseases) in 1894. Working with Marinesco, he performed the anatomopathological examination of the brains of nine epileptics who had died in Charcot's department [7]. They discovered ''little cortical nodules'' that would later be called ''senile plaques'', though they failed to make the connection with either ageing or dementia [8]. Paul Blocq died aged 36 years old, on 20 May 1896 at the ''*Maison de santé du docteur Belhomme*'' (the asylum of Dr. Jacques-Étienne Belhomme, 1800–1880) in the 11th district of Paris, raising the possibility he died either from the consequences of general paralysis of the insane or a depressive psychosis [9].

Fig. 2 – Paul Oscar Blocq in 1887 (OW collection).

2. Georges Marinesco

Georges Marinesco (Gheorghe Marinescu) (Fig. 3) was born in Bucharest on 23 February 1863. He studied medicine at

Fig. 3 – Gheorghe Marinescu around 1935 (public domain).

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Brâcoveanu Hospital in his native city, eventually becoming an assistant to Victor Babès at the Institute of Bacteriology. After defending his thesis in Romania in 1889, he spent nine years in Paris first with Charcot, then under Pierre Marie. During this time, he visited several other neurology departments in order to perfect his skills. On 23 March 1897, he defended a thesis in Paris, ''*Main succulente et atrophie musculaire dans la syringomyélie*'' (oedema of the hand and muscular atrophy in syringomelia), with Fulgence Raymond (1844–1910) presiding over the jury. Marinesco published mainly in French, and his exile in Paris during World War I while his country was occupied by the armies of the Central Powers, bears witness to his affection for France. During this time, he resided with Henry Meige (1866–1940) and assisted Pierre Marie in caring for French soldiers at La Salpêtrière [10]. When he returned to Romania, Marinesco directed the neurology department at Colentina Hospital and held a personal chair in nervous diseases at the medical school. An esteemed teacher, he had numerous students. The most well-known in France is Jean Nicolesco (1885–1957), famous for the book he wrote with Charles Foix (1882–1927): ''*Les noyaux gris centraux et la région mésencéphalique sous optique, suivie d'un appendice sur l'anatomie pathologique de la maladie de Parkinson*'' (basal ganglia and the mesencephalic region, followed by an appendix on the pathological anatomy of Parkinson's disease). After meeting Étienne-Jules Marey (1830–1904) in Paris, Marinesco became interested in film-making for teaching purposes. Unfortunately, most of his films have been lost [8].

Marinesco wrote more than 1500 publications covering all aspects of neurology. An illustration of his output is the book ''*La cellule nerveuse*'', published in 1909. In it, Marinesco describes two phenomena based on his experimental work: 1) central and peripheral chromatolysis, i.e. the structural modifications of a neuron following axotomy; and 2) neuronophagia, i.e. the destruction of a nerve by phagocytosis (microglia). In 1914, Marinesco confirmed the discovery of Hideyo Noguchi (1876–1928) and Joseph Waldron Moore (1879–?), who had isolated treponemal spirochaetes in nervous tissue in general paralysis of the insane. Marinesco–Sjögren syndrome, described in 1931 by Marinesco [11] and in 1950 by Karl Sjögren (1896–1974) [12], is characterised by ataxia due to cerebellar atrophy and by muscular hypotonia associated with mental retardation, congenital cataract, and nystagmus. It is now recognised as an autosomal recessive disorder involving chromosomes 5 and 18. On 15 May 1938, Marinesco died at the height of his intellectual powers after a full day's work in the hospital.

3. History of the description of the substantia nigra

The substantia nigra (SN) was described for the first time in 1786 by Félix Vicq d'Azyr (1748–1794), who called it the ''*tache noirâtre*'' (blackish spot) or ''locus niger crurum cerebri'' [13]. This discovery was erroneously attributed to Samuel Thomas von Sömmerring (1755–1830), who described the region six years later in 1792 [14,15]. In 1865, Jules Luys (1828–1897) described pigmented neurons [16], and in 1889, Giovanni Mingazzini (1859–1929) distinguished the ventral and dorsal parts [17], that would not be named zona compacta and zona reticulata until 1910, by Torata Sano [18]. The SN's histological resemblance to the pallidum was noted in 1896 by Domenico Mirto [14,15,19,20].

4. Observation of Blocq and Marinesco

Blocq and Marinesco hoped to ''shine some light on a controversial subject, the pathogenesis of tremor'' [1] by adding a discussion of Blocq's histological examination to the clinical observation of Jean-Baptiste Charcot (1867–1936). The alienist Eugène Béchet (1862–1939) first reported this observation as case 19 [21] in his thesis defended on 28 July 1892 before a jury presided by Jean-Martin Charcot.

A 38-year-old man, without any relevant medical antecedents, had presented with a 2 years history of pain in his spine and lower limbs, then ''numbness in the left side of his face, around the eye, and at the tip of the left hand. The stiffness had gradually increased, and the patient had started to shake''. Jean-Baptiste Charcot, at that time a resident under his father at La Salpêtrière, examined the man in June 1891 and observed ''a regular rhythmic tremor in the right hand with few oscillations when the patient is resting. The amplitude increases when the patient holds up his hand as if to take an oath''. The characteristics of the tremor were recorded: ''Marey's device made it possible to determine the modifications in the tremor under various influences and to time the oscillations, hardly five per second'' [1] (Fig. 4).

The tremor also affected the left leg, though less intensely. In addition, ''during walking, the patient is curved forward and stiff. He feels pulled forward, and there is a greater tendency to move to the left, i.e. to the side where he shakes''. The hand's posture was abnormal: ''The fingers are half-flexed and held side by side, with the thumb extended across the index finger'' [1]. The patient feels pins and needles in his hand, though no sensory disturbance is observed. Also noted were ''transient diplopia'' and ''an exaggerated left patellar reflex. There is no spinal tremor.'' The patient had a chronic cough and auscultation revealed ''unambiguous signs of pulmonary tuberculosis'' [1]. The diagnosis is ''unilateral Parkinson's disease''. The date of death of this unfortunate patient is not mentioned.

The autopsy confirmed miliary tuberculosis, with pulmonary and epididymal lesions, lesions in the first two lumbar vertebrates associated with pachymeningitis, and ''in the thickness of the right peduncle, a tumour slightly larger than a hazelnut'', in which Blocq identified tuberculous follicles on light microscopy. The authors noted that the lesion was bordered ''in front by the foot of the peduncle, in the back by the upper cerebellar peduncle, on the inside by the fibres of the oculomotor nerve, and on the outside by the elements of the Reil ribbon [lemniscus]. Overall, the tumour mainly involved Sömmerring's substance [substantia nigra]'' [1].

Blocq and Marinesco discussed similar observations recorded in the literature. Emanuel Mendel (1839–1907) had described a 4-year-old child with an ''intentional tremor in the right arm'', weakness in the right leg, and damage to the cranial nerves, including the oculomotor nerve on the other side [22]. The autopsy had revealed ''a tubercle in the middle

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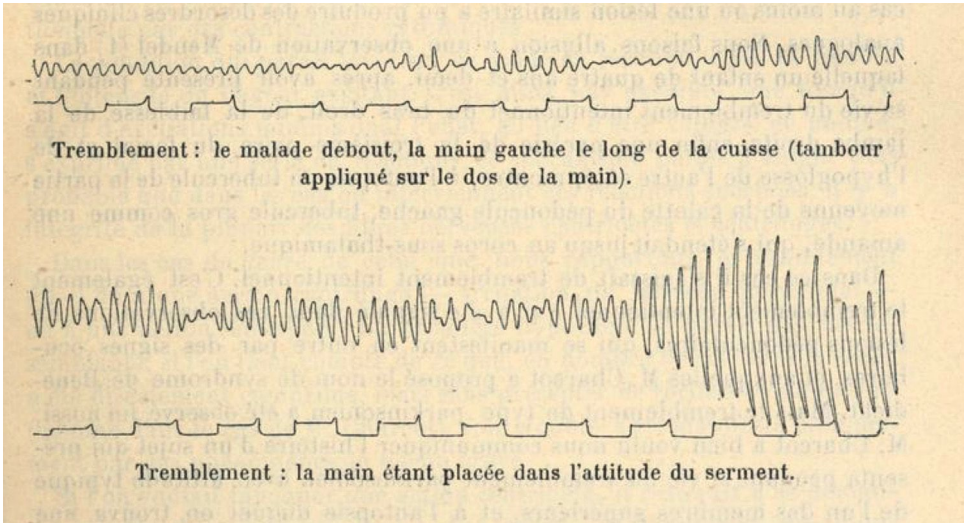

Fig. 4 – Recording of tremor using the device of Étienne-Jules Marey (1830–1904) (OW Collection).

part of the top of the left peduncle''. Blocq and Marinesco reminded readers that the unilateral tremor, previously observed in association with ocular damage, was an intentional action tremor; Charcot had named this clinical picture ''Benedikt syndrome'' in 1893 [23]. In an 1889 lecture, translated into French [24], the Austrian neurologist Moritz Benedikt (1835–1920) had reported three cases that combined damage to one oculomotor nerve with hemiparesis and ''tremor'' in the contralateral limbs. In the first case of a child, the nature of the abnormal movement was uncertain. There was ''jerking that [resembled] tremor'' in the left hand, while the left leg was ''almost constantly in motion''. Post-mortem examination had revealed multiple tuberculous lesions, including one ''the size of a pigeon's egg'', on the inner surface of the right cerebral peduncle. No autopsy had been performed in the other two cases. One of them involved a woman with damage to the third cranial nerve since the age of three, then ''paralysis on the left side, with tremor that was violent in the arm and weaker in the leg''. The tremor ''considerably increased with voluntary movement''. Blocq and Marinesco also discussed an observation Charcot had shared with them, involving ''a subject who, while alive, had parkinsonian tremor with a typical posture in one of the upper limbs and at autopsy a tumor had been found that had compressed one of the cerebral peduncles''. They also commented that ''lesions to the top of the peduncle would normally lead to ataxia''. Henri Claude (1869–1945) did not describe the eponymous crossed brainstem syndrome (damage to the third and fourth cranial nerves and contralateral ataxia) until 1912 [25].

In summary, the main clinical features of the case described by Blocq and Marinesco was a mixed tremor, existing at rest but also during held postures, accompanied by a few axial parkinsonian signs and possible dystonia in the hand. The end of the article examines the mechanisms of tremor. The authors propose both ''minimum excitation'' of the pyramidal tract, but cannot exclude the possibility of ''excitation of sensitive fibres that project to the internal capsule''.

Today, the tremor described by Blocq and Marinesco would be classified as a Holmes tremor [26] rather than a classical pill rolling rest tremor. This type of tremor, described in 1904 by Gordon Holmes (1876–1965) [27] typically occurs at rest and increases in held postures and even more so with gestures. Its frequency is slow, generally below 4.5 Hz. and it is associated with a peduncular or thalamic lesion in more than 80% of cases [26]. Classically, this type of tremor is considered the result of a lesion interrupting the nigrostriatal dopaminergic pathway and the cerebello-thalamo-cortical pathway [28], but the former is not involved in every case [29]. In a series of 29 patients, Holmes tremor was only associated with bradykinesia and rigidity in two cases [26].

In his thesis on contractions, Blocq defended the possibility that parkinsonian rigidity could be muscular in origin, citing certain clinical characteristics and muscle damage observed in the histological examination for one case [30]. Observing no lesions in the central nervous system, Blocq remained cautious: ''This does not mean we have any doubt that Parkinson's disease is a condition of the nervous centres. We simply think that rigidity, one of the morbid clinical modifications may result from a muscular lesion''. Despite these cautions, Blocq was later often cited unfairly as promoting a ''myopathic theory'' of PD [31].

Léopold Ordenstein (1835–1902) distinguished between PD and multiple sclerosis in his famous thesis, inspired by his jury president, Charcot, and defended on 17 December 1867. At the autopsy of his second case of PD, he noted, ''The two cerebral peduncles are softened and atrophied. The softening especially affects the black substance which appears macerated'' [32]. This accurate observation appears to have gone unnoticed.

5. From the observation of Blocq and Marinesco to the role of the substantia nigra in Parkinson's disease

After Charcot died on 16 August 1893, Brissaud spent a year as the interim professor holding the Chair of Nervous System

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Diseases [33]. The first volume of his ''*Leçons sur les maladies nerveuses*'' (lessons on nervous diseases), compiled by Henry Meige (1866–1940) and published in 1895, reported the lessons he gave in 1893 and 1894 [34]. Lessons XXII and XXIII deal with Parkinson's disease and the second is entitled ''*Nature et pathogénie de la maladie de Parkinson*'' (nature and pathogenesis of Parkinson's disease).

Brissaud explicitly stated that in his view Parkinson's disease was not a neurosis, even though he accepted the idea that a violent emotion could permanently trigger the symptoms (''you can die of fear''). He also rejected the idea that it was simply a reflection of premature aging and not a disease at all. He also conceded that the lesions so far described were ''disparate and in some cases contradictory''. Brissaud then referred to a ''mixed theory based on the theory of neurosis as well as anatomical theory; this might be the theory of muscle tone''. He assumed that exaggerated muscle tone ''[caused] the rigidity, which [was] the key element of Parkinson's disease''. This exaggeration could depend on an ''upper tonic centre in the brain'', which remained to be localised. This would either eliminate inhibition or ''excite'' the spinal cord and muscles and it was in this way that the substantia nigra came into play:

> ''Allow me, sirs, to remind you that the history of unilateral diseases provides the explanation for many unknown nervous localisations. This is because in diseases, such as hemiplegia, half the subject's body remains an experimental control that is easily compared to the other half.
> In the case of Monsieurs Blocq and Marinesco (1893), a tuberculous tumor, which is circumscribed with distinct borders and thus incapable of diffusion phenomena, was compressing the lower portion of the cerebral peduncle, with very little effect on the upper portion. It had completely destroyed the substantia nigra, and in this case, a parkinsonian hemiplegia was observed on the side opposite the lesion.
> This region of the substantia nigra remains poorly understood [the French word Brissaud used is 'obscure' or dark, creating a play on words he was probably unaware of]. We know little about its normal structure, and even less about its lesions.
> Is it, by chance, in this territory at the confines of voluntary movement fibres and automatic movement fibres that we should look for the centre of muscle tone?
> In other words, a lesion in the substantia nigra could well be the anatomical substratum of Parkinson's disease.
> The type of lesion is not important, but everything suggests that repeated ischaemic softening is more frequent than any other destructive changes.'' [34]

Brissaud thus reasoned from Blocq and Marinesco's single case report that lesions of the substantia nigra might cause PD, but he failed to convince his contemporaries. Raymond, Charcot's successor after Brissaud's interim appointment, reviewed the data and concluded: ''Such is the assessment of pathological anatomy. When all is said and done, we have made no progress since Charcot's time'' [35].

In 1919, Pierre Marie presided over the jury for the thesis defended by a young Russian refugee, Konstantin Tretiakoff (1892–1958). Tretiakoff had worked under Marie and been appointed the head of the Salpêtrière laboratory. His thesis was entitled ''*Contribution à l'étude de l'anatomie pathologique du Locus niger de Sœmmering, avec quelques déductions relatives à la pathogénie des troubles du tonus musculaire et de la maladie de Parkinson*'' (contribution to the study of the pathological anatomy of Sömmering's locus niger, with some deductions on the pathogenesis of muscle tone problems and Parkinson's disease) [36]. The idea for his research was suggested by Marinesco who also assisted Tretiakoff and they first set about comparing the lesion of paralysis agitans with that of post-encephalitic Parkinsonism [37]. In his thesis, Tretiakoff reported on the histological examination of fifty-four brains including nine with PD and three post-encephalitics. Using a matched comparison based on age, he observed the rarefaction of pigmented neurons in the SN, a ''lumpy'' degeneration, and, in the surviving neurons, inclusions that had been described in 1912 by Friedrich Lewy (1885–1950) in the dorsal vagal nucleus [38]. In his 1919 thesis, Tretiakoff referred to these inclusions as ''Lewy bodies'' [39], a name already proposed in 1913 by the Spanish neurologist Gonzalo Rodriguez Lafora (1886–1971) [40]. Tretiakoff observed neuronal depopulation and inflammatory lesions in the SN of two patients who had suffered from lethargic encephalitis. He noted that a case of unilateral PD was accompanied by lesions in the contralateral SN. He also observed SN lesions in other pathological conditions such as ''Brissaud's mental torticollis'' (dystonia in current terms), Sydenham's chorea, and amyotrophic lateral sclerosis, all considered to be disorders of muscle tone. These observations led Tretiakoff to the following conclusion: ''The lesions of the substantia nigra and symptoms of Parkinson's disease are very closely related. This relationship is probably one of cause and effect.''

We might assume that the case was then closed, but during the ''yearly neurological meeting'' of the *Société de neurologie* de Paris on 3 and 4 June 1921, no consensus was reached between the proponents of the nigral, pallidal, striatal, or mixed localisations. And it is worth mentioning that these were only some of the possible sites for the lesion that were discussed. Achille Souques (1860–1944), who reported on this meeting, concluded: ''If we limit ourselves to positive facts, the lesion appears to be situated in the striatal and sub-optic regions, but it has not yet been precisely localised'' [31]. As for Charles Foix (1882–1927), he clearly agreed with Tretiakoff's observations: ''The substantia nigra lesions exist in every case. Macroscopically, the substantia nigra already appears small, discoloured, or at least irregularly pigmented with points of discolouration. The histological examination shows that the cells are damaged with a tendency to disappear'' [41].

The emergence of post-encephalitic parkinsonian syndrome (von Economo's disease) intensified the debate over the nosography of Parkinson's disease: was there an ''authentic'' or ''legitimate'' PD as well as secondary Parkinsonian syndromes due to specific causes such as infection and toxins [42], or was Souques correct in seeing PD not as ''a morbid entity'', but rather ''a common syndrome having different causes'' [31]? Concerning the lesions associated with PD and/or parkinsonian syndromes, the divergence was not limited to lesion localisation, as mentioned above; they also involved type, characteristics, and cause.

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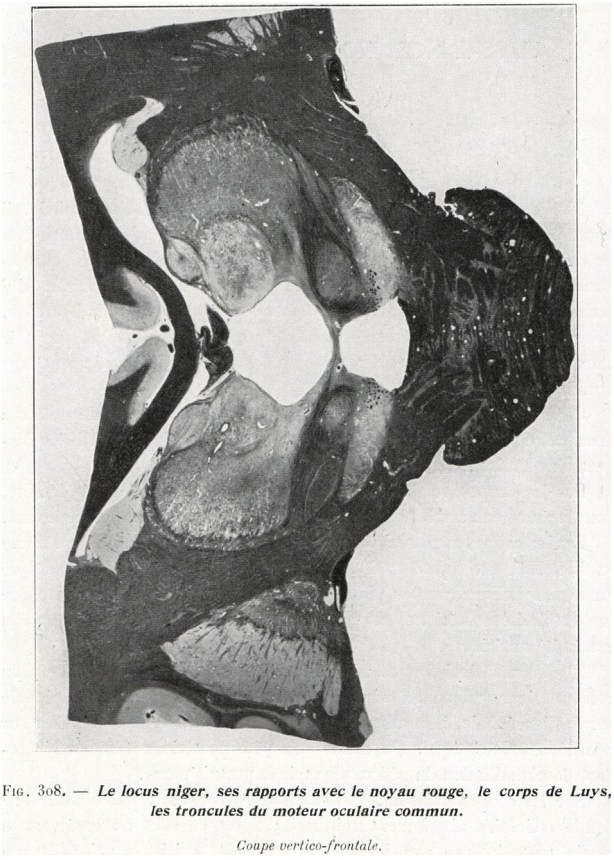

FIG. 308. — *Le locus niger, ses rapports avec le noyau rouge, le corps de Luys, les troncules du moteur oculaire commun.*

Coupe vertico-frontale.

Fig. 5 – Sömmering's locus niger, p 462, Atlas des noyaux gris centraux by Foix and Nicolesco, 1925 (OW Collection).

There were many influential proponents of concomitant damage to the SN and other regions of the basal ganglia. In 1938, Rolf Hassler (1914–1984) focused interest on the SN, in particular its ventral part (pars compacta). He was notably followed in 1953 by Joseph G. Greenfield (1884–1958) and Frances D. Bosanquet (1916–2004) [43], who also confirmed damage to other pigmented structures in the brainstem, previously observed by Foix and Nicolesco (1895–1957) in 1925 (Fig. 5) [44]. Despite this, the proponents of the pallidal hypothesis such as the Vogts did not back down, Derek Denny–Brown (1901–1981) in 1962 who dedicated a section of his book to ''the enigma of parkinsonism'' wrote in 1962 ''There is still no agreement as to the essential change in anatomical structure'' [45]. Arvid Carlsson (1923–2018) discovered dopamine as a neurotransmitter in 1957 [46], and the nigrostriatal dopaminergic pathway was brought to light in the 1960s, as well as the deficit of dopamine in the striatum in PD [47]. Then in 1967, the therapeutic effect of levodopa was demonstrated [48] and the substantia nigra as the pathological substratum for bradykinesia and rigidity firmly established.

6. Conclusion

The discovery of the SN's role and the deficit of dopamine during PD is often presented as a linear progression of contributions leading up to the therapeutic revolution of L-DOPA therapy. In reality, since the time of the fortuitous observation by Blocq and Marinesco (unrelated to PD for the authors) and Brissaud's prescience in 1895, until the 1960s, the evolution of ideas might best referred to as ''multifarious branched''. The notion of a preponderant lesion specific to the SN existed alongside other hypotheses, now considered dead branches in the tree of Parkinson's disease discovery. The reductive re-writing after the fact of how the ideas evolved is reminiscent of certain erroneous histories of the evolution of species, as described by Stephen Jay Gould (1941–2002). Gould proposed to ''write the history of a system (group, institution, evolutionary lineage) by documenting the changes in all components of its diversity, rather than by identifying the system as an illusory entity progressing in a linear fashion'' (translated from the French) [49]. This observation is made all the more apposite by the fact that history is in constant motion, and that the SN's role, without being doubted has in recent years been extended by new hypotheses implicating other sites of damage far more diverse than those postulated by earlier authors ranging from the intestinal mucosa and olfactory bulbs to the cerebral cortex and to a consideration of the pathophysiology in terms of systems and circuits [50,51].

Statement of ethics

This work required no approval from an institutional review board and was prepared in accordance with ethical guidelines of the journal.

Funding

No funding was obtained for this work.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

Many thanks to Andrew Lees and Yves Agid for their proofreading and to Anna Fitzgerald for her translation.

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Please cite this article in press as: Fénelon G, Walusinski O. The landmark contributions of Paul Blocq, Georges Marinesco, and Édouard Brissaud in Parkinson's disease. Revue neurologique (2021), https://doi.org/10.1016/j.neurol.2021.02.386