

## SHORT HISTORICAL REVIEW



## George Gershwin (1898–1937) – genius composer, malignant brain tumor patient. Malignant glioma: an irritating/stimulating element in triggering geniality?

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### Abstract

George Gershwin (1898–1937) was one of the most influential American composers of the 20<sup>th</sup> century. Likewise his swift, comet-like, career progress from a high school dropout to an iconic composer of the 20<sup>th</sup> century: “*The man who said he had more notes in his head than he could write down in a hundred years died suddenly ... in Hollywood*”. His malignant glioma presented symptoms only in his last year of life and even then, the symptoms were masked by other hectic events in his personal life, which typically accompany the life of a famous and handsome composer from Hollywood. Considering new, emerging studies regarding the relationship between gliomas and brain activity, the authors explore the following questions: (i) Is intense neuronal, intellectual activity a cause that can trigger the development of a malignant brain tumor, especially a glioblastoma? (ii) Is glioblastoma and its connections with normal nerve cells, with noble tissue (a fact demonstrated in recent years), a cause that can trigger geniality, a different thought process from most people with a normal-functioning brain?

**Keywords:** George Gershwin, genius, malignant brain tumors, glioblastoma.

### ☞ Early life

George Gershwin (born Jacob Gershowitz) was an iconic American composer of the 20<sup>th</sup> century. He rose to fame by composing popular soundtracks for movies, theater, and Broadway, as well as classical music (Figure 1).

Gershwin was born on September 26<sup>th</sup>, 1898, in Brooklyn, New York, in a family of Russian-Jewish immigrants. He began his musical career as early as 11 years old, when his family bought a second-hand piano for his older brother, Ira. From the first note played at this piano until their last grand composition together, the brothers’ careers were virtually inseparable.

A true prodigy, by the age of 15 he studied piano on a daily basis and was so enveloped by this passion that he dropped out of school. Filled with ambition and raw talent, Gershwin sought to improve his musical abilities and discover new styles from an early age. Eventually, he had the chance to study musical composition under the respected piano teacher, Charles Hambitzer (1878–1918), in New York. It seems that Hambitzer was impressed by his new student, as he wrote to his sister: “*I have a new pupil who will make his mark if anybody will. The boy is a genius.*” [1].



**Figure 1 – Portrait of George Gershwin (1898–1937) with autograph, c. 1935. This photograph is in the public domain.**

Throughout his comet-like musical career, Gershwin was continuously driven to diversify his musical composition styles. Among his many noted teachers, he was inspired

by the classical, avant-garde style of Henry Cowell (1897–1965), he learned how to compose grand, orchestral music from Wallingford Riegger (1885–1961), studied harmony under Edward Kilenyi Sr. (1884–1968), and music theory from Joseph Schillinger (1895–1943). As fate had it, all of those teachers outlived him.

### ☞ A prodigious talent

After three years of constantly composing music for demanding customers, he matured into an experienced and well-rounded composer. In 1916, at just 18 years old, he finally published one of his original compositions: “*When You Want ‘Em, You Can’t Get ‘Em; When You Have ‘Em, You Don’t Want ‘Em*”.

Gershwin composed for George White’s annual production for four years, 1920–1924. George White proposed to Gershwin to compose a jazz song that would further popularize this type of musical genre. The creation of this famous song is enveloped in a remarkable story that underlines the musical genius of Gershwin: “*Legend has it that Gershwin forgot about the request until he read a newspaper article announcing the fact that Whiteman’s latest concert would feature a new Gershwin composition. Writing at a manic pace to meet the deadline, Gershwin composed what is perhaps his best-known work « Rhapsody in Blue ».*” [1].

Throughout the years, Gershwin composed many other songs for theater and screenplay. Like most of his compositions, they quickly became classics of the 20<sup>th</sup> century, such as “*Oh, Lady Be Good*”, “*Someone to Watch over Me*”, “*Strike Up the Band*”, “*Embraceable You*”, “*Let’s Call the Whole Thing Off*”, and “*They Can’t Take That Away from Me*”. From the first piano lesson and until his death, his older brother Ira was by his side. The two brothers were inseparable and collaborated with ease. Their bond in personal life continued in their careers: Gershwin would compose the musical part and Ira would complete it with unforgettable, witty lyrics. The duo was equally acclaimed for their songs.

### ☞ The symptoms

#### Nausea and gastric dysfunctions – “composer’s stomach”

At first, Gershwin’s symptoms were mild and had a slow debut. Although he was “*a trim, energetic bachelor who developed unusual physical stamina from exercising in a gymnasium in his apartment*” [2], he suffered for many years of occasional attacks of nausea and vague gastric dysfunctions. From 1923, he began consulting multiple doctors in search of a diagnosis and treatment, but to no avail. Considering his stressful career, a psychosomatic manifestation was considered so he was advised to seek a psychiatrist’s help instead. In consequence, from 1934 he began regular psychoanalysis five times a week with Dr. Gregory Zilboorg (1890–1959) [2].

With no definitive diagnosis or treatment from the medical and psychiatric specialists, Gershwin was left on his own to search for a cure to his increasingly irritating symptoms. He started a very well-kept journal of his diet, detailing every diet and regimen that he tried. It was all in vain.

For the following years, until his death, he was continuously affected by those symptoms. The doctors suspected an organic origin of his illness, but the general consensus between both doctors and his friends remained that his affliction was psychosomatic: “*Various diagnoses were made of his condition, including spastic colitis, chronic neurosis, and composer’s stomach.*” [3].

#### The year 1936 marked the beginning of new symptoms: emotional changes

When he moved from New York to Hollywood, Gershwin was surrounded by his friends. He would constantly express his great satisfaction with his new life in Hollywood. Even though he was surrounded by his friends, as he was always an extrovert and loved the life that he lived, he suddenly began to feel depressed and lonely.

While previously he avoided marriage by any means, now Gershwin was often heard talking about getting married, as one of his friends said: “*Once he sat down and wrote letters to old flames, inviting them to come see him in California. When none of them came, his feeling of loneliness grew even more pronounced.*” [3].

In 1936, at a large gala, Gershwin met Paulette Goddard, the wife of Charlie Chaplin. For the first time in his life, he was convinced that he must get married: “*When he came home from this party, he felt convinced that this was the woman he wanted to marry.*” [4]. The following weeks he was completely focused on winning the affection of Paulette Goddard. When Paulette refused to leave her husband for him, Gershwin was shocked, and his emotional state profoundly changed. He felt even more lonely and “*began to grow irritable and touchy about matters to which previously he would not have attached the slightest importance*” [3].

This new situation was even more reason for his friends and doctors to believe that he was just melancholic and nothing organic was at fault for his mood swings.

The following period, he started worrying about a new issue that never bothered him before: going bald. In consequence, he bought a device that promised to cure the baldness: “*... it consisted of a metal cap connected by a flexible tube to a motor-driven pump. The cap was placed over the scalp, and the pump was then started to produce a suction effect on the scalp.*” [3].

Ironically, this anti-balding device was considered the reason for his severe headaches. While this new situation did not alleviate his baldness or depression, it masked the reason for his severe headaches and pushed him further away from his true diagnosis.

By the following year, he started to feel depressed and would often sink into melancholy. He complained about this feeling to one of his close friends in January 1937: “*I am 38 years old, wealthy and famous, but I’m still deeply unhappy. How come?*”.

While those symptoms and changes in his personality were known to his friends and doctors, to the outside world everything was business as usual. Gershwin continued to compose and play in various concerts, as the same musical genius beloved by everyone. His physical state and his career were still in perfect condition.

### ☐ The first sign of serious illness appeared on February 11<sup>th</sup>, 1937

“Gershwin was playing his *Concerto in F* with the Los Angeles Symphony Orchestra in February 1937 when the first alarm symptom appeared, **absence crises: suddenly his mind went blank**. He missed several bars, then recovered sufficiently from the fit to continue playing. After the performance, the composer complained of a sensation of smelling burned rubber. Two months later **the sensation of the pungent odor** recurred while having his hair cut.” [2].

This epileptic episode marked the appearance of new symptoms, that would affect him every day:

“For several weeks, Mr. Gershwin experienced **severe, pounding headaches** in the front and temple areas that were worse in the morning, sometimes waking him up at 6 o'clock in the morning. Occasionally they were accompanied by nausea, dizziness and the foul-odor hallucinations.” [2].

This new development prompted him to consult with his psychiatrist, Dr. Zilboorg. In late February, he had a medical checkup, but nothing was detected. While this was encouraging for the people who believed that all those symptoms were just some forms of neurosis, his situation began to steadily worsen. Throughout the day, but especially in the morning, he experienced moments of nervousness or tensions, olfactory hallucinations, headaches, and dizziness. Even more so, in April he had another blackout while having his hair cut.

On June 9<sup>th</sup>, he was consulted by an internist, Dr. Gabriel Segall, who ran an electrocardiogram, urine analysis, blood examinations and other tests, but to no avail. Dr. Segall recommended he consult a neurologist as well, Dr. Eugene Ziskind. On June 20<sup>th</sup>, his neurological examination revealed right hyposmia and photophobia, no papilledema or visual field defect was detected.

In search for a diagnosis and treatment, Gershwin was admitted to Cedars of Lebanon Hospital, on June 23<sup>rd</sup>. Some further evaluations were conducted: X-rays, a funduscopy, a Wassermann test, a craniocerebral X-ray, but no pathology was observed. All noninvasive investigations were used, so the recommendation was to perform a lumbar puncture, that could have detected a brain tumor (increased amounts of proteins or increased cerebrospinal fluid pressure). Gershwin rejected this procedure and was released from the hospital on June 26<sup>th</sup> with the same diagnosis as before: “*most likely hysteria*”.

### ☐ The final phase – rapid degradation and loss of functions

After the discharge from the hospital, Gershwin returned home, his physical and mental state getting progressively worse, though he was under daily medical care. By now, his motor functions were considerably worse. He struggled to use the stairs, had trouble using utensils while eating and could not play the piano anymore. Even more, due to the administration of Phenobarbital (used to relieve his severe headaches), he grew increasingly apathetic. “[...] *the knife with which he was eating fell from his hand. At another meal, he lost control and was unable to bring his fork to his mouth, and he also spilled water out of his glass when trying to drink.*” [3].

After one week, on July 4<sup>th</sup>, he was relocated to a nursing home. Around this time, he experienced another two epileptic seizures. He tried to push his friend, who was driving him to the psychiatrist, out of the moving car and smeared a box of chocolates (a gift from his brother's wife, Leonore) on his body [1].

### ☐ Coma, diagnosis, and operation – Walter Dandy is recruited from the other side of the continent

July 9<sup>th</sup> was finally the day Gershwin's pathology could no longer be misinterpreted. On this day, he woke up at five in the afternoon and was in such a bad state that even with the nurse's help he collapsed on his way to the bathroom. At this moment, he lost his consciousness immediately. By the time he arrived at the hospital, he was in a deep coma. He presented “*left sided hemiparesis and there was also papilledema with severe protrusion.*” [3].

Finally, a lumbar puncture was performed which showed: “*... an initial pressure of 400 mmH<sub>2</sub>O which quickly fell to 220 mmH<sub>2</sub>O after 6 mL of cerebrospinal fluid was obtained. The cerebrospinal fluid was clear with just one leukocyte and 30 mg of protein.*” [5].

Only now everything was being done to bring the experts to his aid. Dr. Walter Dandy (at the time, the best neurosurgeon in the USA) was contacted in a desperate effort to bring him from Baltimore to the other side of the continent, in California. Unfortunately, he was at sea on a private yacht. Still the efforts continued, and a telegram was sent to the White House which recruited two U.S. Navy destroyers to localize Dr. Dandy's yacht. Once found, a special motorcycle escort was provided to bring him to the nearest airport where a private plane would take him to Newark where another private plane was prepared to finally bring him to Los Angeles [3].

It was obvious that while this desperate attempt would bring the country's foremost neurosurgeon to help Gershwin, there was still the issue of time. With this in mind, the help of another famous neurosurgeon from California, Dr. Howard Nafziger, was requested.

Now, all available investigations were used: a ventriculography showed a midline shift in the brain. It was clear that the intraventricular pressure was extremely high and that a tumor was present in the right temporal region.

By this time, Dr. Dandy reached Newark and was ready to embark the plane which would bring him to Los Angeles but was stopped by Dr. Nafziger. The two conferred over the phone and reached the conclusion that Gershwin must be operated immediately and by the time Dandy could arrive the operation would be over.

In the late evening of July 10<sup>th</sup>, Gershwin was operated by Dr. Nafziger who performed a subtotal resection on a partially cystic glioma. Histopathology examination revealed a “*spongioblastoma multiforme*” (which today is regarded as a malignant glioma). Without regaining consciousness after the operation, Gershwin died on the morning of July 11<sup>th</sup>, 1937 [3].

After the surgery, Dr. Walter Dandy wrote to Gershwin's internist: “*I do not see what more could have been done for Mr. Gershwin. It was just one of those fulminant tumors. There are not many tumors that are removable. I think the*

*outcome is much best for himself, for a man as brilliant as he with a recurring tumor, it would have been terrible; it would have been a slow death.*" [6].

*"Announcing his death on the radio, the commentator stated: « The man who said he had more notes in his head than he could write down in a hundred years died suddenly today in Hollywood »."* [3].

While retrospectively it may seem obvious that a neurosis alone could not explain all his symptoms (emotional distress, headache, hyposmia, photophobia, olfactory hallucinations, loss of motor functions and coordination and even loss of consciousness) it is important to consider the historical context:

(i) *"Hollywood encouraged a psychological explanation for all physical ills, according to Behrman, who wrote, « Hollywood was so preempted by the psychoanalysts that it was inconceivable that any ailment could on occasion be physical... Whatever was wrong with you must be a mental aberration due to some disappointment connected with the film industry »."* [4].

(ii) Computed tomography (CT) and magnetic resonance imaging (MRI) investigations were not available in 1936–1937. All neurosurgical cases were discussed on neurological examinations alone. If there was a suspicion of a brain tumor and the patient denied the only three paraclinical examinations available for neurosurgical diagnosis, which were invasive and had a low sensibility (lumbar puncture, ventriculography and angiography), like in Gershwin's case, nothing else could be done.

(iii) In most cases, the patient was referred to psychiatric evaluations and palliative medication, which also had reduced options compared to the modern options (the first neuroleptic drug, Chlorpromazine, was discovered in the 1950s).

## ☞ New scientific advancements

Venkatesh *et al.* (2019) discovered for the first time that severe brain cancers integrate with the healthy parenchyma by forming new synapses. In their study, high-grade gliomas form synapses that steal electrical signals from healthy neurons to promote their own growth [7].

The hypothesis supported by the authors is based on the new ideas debated in the scientific community that postulates the appearance of Scherner structures (discovered since 1930) in all high-grade gliomas. These structures connect the glioma cell and the nerve cell unaffected by the neoplasm. Through them, neural activity determines the establishment of bidirectional signals (electrical or chemical by using neurotransmitters) that determine tumor growth and progression. The discovery and study of this micro-circuit has so far led only to a one-way understanding of the effects of stimulating tumor cells by noble tissue but without highlighting the reverse effect, possibly of feedback given by glioblastoma to unaffected nerve cells [8].

The authors propose the assumption that this reverse direction of information transmission can lead to an accelerated development of perilesional glial cells and even a process of developing new synapses between perilesional neurons, unaffected by the neoplasm.

*"In the adult brain, proliferation and differentiation of stem cells in the subgranular zone of the dentate gyrus is coupled to excitation of neighboring neurons."* [9].

Can this mechanism explain the onset of personality disorders, an avid intellectual advancement of patients diagnosed with this type of pathology?

Can a thorough understanding of this microenvironment lead to the discovery of a new predisposition to high-grade gliomas, especially glioblastoma? The intense intellectual activity of the patients before the appearance of glioblastoma, the proliferation of new synapses, the energetic effort of the brain and the acceleration of the mitoses in the glial cells necessary for this process, leads to a main enigma. Can these elements be a trigger in the appearance of the first mutation and implicitly of the first cancer cell?

At this time, we know for sure that the activity of neurons regulates the central nervous system glial precursor proliferation, a process called myelin plasticity. This process modulates the structures of the brain and implicitly the function it exerts on the intellect and body as a whole.

Neural activity promotes the normal proliferation of physiological glial cell precursors. These glial cell precursors represent the origin of high-grade gliomas. The translation of these two scientific demonstrations determines the understanding of an extremely complex process, represented by the direct influence of the neural activity toward the appearance and continuous evolution of high-grade glioblastomas, including glioblastoma. An *in vivo* study demonstrates that the optogenetic stimulation of the premotor cortex leads to increased proliferation of patient-derived pediatric cortical glioblastoma xenografts in the premotor circuit [10].

This stimulation is a specific circuit thus showing a complex but predictable mechanism of cause (stimulation of normal nerve cells) and effect (tumor proliferation) on a well-defined anatomical and physiological circuit.

Another study conducted in 2017 highlights a clear link between the activity of the Neurotrophin 3 neurotransmitter molecule and the neurotrophic factor of noble tissue in its interaction with the glial neoplastic cell [11].

*"One curious and potentially illuminating observation comes from a retrospective analysis demonstrating that patients with a history of long-term therapy with tricyclic antidepressants also display a reduced incidence of glioma."* [12].

These drugs are known to have broad effects but are thought to act primarily *via* reuptake inhibition of serotonin and norepinephrine. Limiting the development of new synapses and limiting stress on the central nervous system appear to have a protective effect and decrease the possibility of glioblastoma.

High-grade gliomas, especially glioblastoma, do not have gamma-aminobutyric acid (GABA) receptors, the main inhibitory neurotransmitter in the mature central nervous system. In contrast, small-grade gliomas and other brain neoplasms not as infiltrative and aggressive as glioblastoma, have a wide range of GABA receptors [13].

The authors conclude that glioblastoma is dependent on electrical and chemical stimulation by neurotransmitters given by adjacent nerve tissue. Glioma cells induce micro-environment remodeling that promotes hyperexcitability of perilesional circuits, resulting in stimulation of neural activity, which in turn contributes to numerous activity-dependent mechanisms of tumor growth and progression.

## ☞ Our questions

(i) Is intense neuronal, intellectual activity a **cause** that can trigger the development of a malignant brain tumor, especially a glioblastoma?

(ii) Is glioblastoma and its connections with normal nerve cells, with noble tissue (a fact demonstrated in recent years), a cause that can trigger genius, a different thought from most people with a physiological brain?

## ☞ Conclusions

In the case of the artist Gershwin, the intense intellectual activity, the stress of always making extraordinary compositions, the lack of sleep and the proper nutrition were predisposing factors for the appearance of an expansive intracerebral process. Also, the rapid evolution and rapid neurological degradation of this expansive process as well as subsequent histological studies advocate a diagnosis of high-grade glioma: glioblastoma.

The authors believe that the answer to these questions requires extremely detailed research, but we suppose that there is a high possibility that brain malignancies, especially glioblastoma with localization in the frontal lobe, can be both a cause and an effect of “genius”.

## Conflict of interests

The authors declare that they have no conflict of interests.

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