Research Aticle

Pursuit, Salience, and an Urge to Turn Left: A Review of the Frontal Eye Fields

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Abstract

In 2016 a patient was referred urgently to the regional neurosurgical service with a newly diagnosed primary brain tumour. The patient's presentation had been both striking and unusual: she had developed a progressive and irresistible urge to turn to the left. This proved to be due to a lesion neatly confined to the right frontal eye field. Its irritative properties were causing an unusual seizure variant manifesting itself in this movement disorder. The patient went on to have a successful craniotomy and remains well two years later. The episode prompted a review of this relatively unknown region of the frontal lobes. This review not only explains the unusual episode but demonstrates widespread implications for many fields of medical practice.

Introduction

The frontal eye fields represent a small but fascinating region of the frontal lobes of the brain. Although there is a host of published literature focussed on the region, it remains relatively esoteric. For example, in day to day neurosurgical practice, such individual regions tend to become subsumed in the general, greater mass of the frontal lobes anterior to the motor strip. When planning neurosurgical access to the ventricles or deep ganglia, the transcortical route often involves a corticotomy through this very region. In a similar vein, it is not uncommon to encounter patients with disease processes that have extensively damaged this region, yet who appear to be functionally near normal. Such experiences easily lead to the misconception that this region is relatively "forgiving", or non-eloquent.

Our unit recently treated a patient with a lesion neatly confined to one frontal eye field. Her striking and unusual presentation and symptoms prompted us to review the literature and current theories regarding the frontal eye fields. Although the majority of the published work to date concerns neurobiologists and neuroscientists, the findings have implications for neurosurgeons, neurologists, physicians, and perhaps even philosophers.

Patient study

The patient was a woman in her 60s who was fit and well except for a history of gastritis. Her GP duly referred her for an endoscopy. The results were reassuringly normal. However, after the procedure she was found wandering in the hospital grounds in what initially appeared to be an erratic pattern.

This post-procedural episode was unusual enough to prompt a referral to the neurologists. At the time of her initial review, she had returned to her normal self and was at a loss to explain the episode. Neurological examination was normal, as was an EEG and CT scan of the brain. A diagnosis of transient global amnesia was made, and routine follow up was arranged.

Further unexplained episodes then began to occur. As time progressed, these happened with greater frequency and intensity. By the time of her follow up six months later, these episodes had effectively taken over her life. It had also become clear that a distinct pattern was emerging. Following a brief prodrome, her gaze was involuntarily pulled to the left. This gaze preference dragged her head to the left, then forced her torso and ultimately her entire body to follow suit. She began to have mishaps whilst driving. After veering into the signage for a car wash on the left side of the street, she voluntarily (and sensibly) stopped driving. She vividly described having an attack whilst leaving a friend's house. Despite planning to walk straight down the path towards her home, an episode forced her to take an inadvertent tour of her friend's garden through a series of left turns before regaining control and walking home.

The neurologist recognised these as complex partial seizures, commenced her on anti-epileptic medications and arranged an MRI scan of the brain. This now revealed a lesion within the right frontal eye field with patchy enhancement (Figure 1).

By the time of her urgent review with our neurosurgical team the anti-epileptics had helped control the condition, but she was still experiencing several attacks a day. She had learned to recognise the prodrome. On sensing an episode coming on she would sit in the nearest chair and grip the sides. Despite this technique she would still experience this inexorable, irresistible impulse to turn to the left.

She went on to have wake craniotomy for the resection of what proved to be a grade III glioma. The benefit of an awake craniotomy is that it allows continual testing of the patient throughout the procedure, with electrical stimulation causing temporary muting of the region about to be resected. If the patient develops a deficit due to the temporary muting, that region is left intact. In short, the awake craniotomy permitted maximal resection of the tumour without incurring any neurological deficits. After the operation she was able to stop her anti-epileptic medication and she remains seizure free two years later.

The Frontal Eye Fields

Despite being comparatively small, the frontal eye fields have been recognised since the 19th century. David Ferrier was one of Britain's pre-eminent neurologists. Born in Scotland, he went on to study and combine influences from psychology, neurophysiology, and medicine. He performed seminal work using faradic stimulation to specific regions of the brains of macaque monkeys. He was able to deduce that influencing a specific region within the frontal lobes affected the gaze

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and attention of the monkeys studied. More specifically, stimulating the region now known as the frontal eye fields drove the animal's gaze to the contralateral side. A lesion of the region led to the inability of the animal to direct gaze to the contralateral side, though interestingly this effect was often temporary[1]. He presented his findings to the Royal Society of Medicine in a series of lectures.

It is remarkable to reflect that this work predates modern brain imaging by over a century. Furthermore, it was not until the 1960s that there was any degree of resurgence of research into the field [1,2].

The fields correspond to Brodmann area 8 in primates. By various means, including transcortical magnetic stimulation, transcortical electrical stimulation, and MR Imaging, the region has been accurately mapped. In humans, however, the region becomes more nebulous [2]. This would appear to be due to the various functions that it performs spreading to neighbouring sulci depending on the specific task. Its immediate neighbours are the supplemental eye fields and the pre-supplementary eye field, causing some authors to suggest that the territory also includes Brodmann area 6 [2].

They are a component of the complex mechanism of visualisation. The frontal eye fields respond to and direct components of visual tasks. Microscopic analysis has revealed that the neurones fall into three classes that reflect this role. There are purely sensory neurones, motor neurones, and neurones that have both sensory and motor components [1].

A superficial study of the process of seeing suggests that the information received by the retina is passively transmitted via the optic nerves, chiasm, and tracts to the visual cortex spread along the calcarine fissure of the occipital lobe, where it is then processed. Such an overly simplified approach ignores the vast interconnecting network of centres throughout the brain that respond to and influence this process.

The process of visualisation and attention includes input from centres within the frontal eye fields, the parapontine gaze centres, the superior colliculi, the vestibular apparatus and the cerebellum. The raw data received by the occipital lobe itself is then transmitted to the parietal lobes, the temporal lobes, and the frontal lobes for further processing.

The information from the occipital lobes is transmitted to the parietal lobes, specifically the lateral interparietal sulcus but also to the remainder of the lobe in general. Here, details of spatial orientation are interpreted, answering the question of *where* things are. Transmission to the temporal lobes accesses memory, comparing the current stimulus to learned information and laying down new information. This helps us to interpret *what* things are. Transmission to the frontal lobes addresses the importance of what is seen often referred to as salience.

The reader will surmise that salience itself is influenced by memory, demonstrating another important interconnection between regions of the brain invoked in the process of seeing. Indeed, anatomical studies have demonstrated that the frontal eye fields have connections to all of the regions mentioned above[2]. Memory, spatial awareness, and learned motor patterns inform the frontal eye fields, allowing them to govern pursuit, saccadic and vergence movements. These movements occur on the subconscious level, with the frontal eye fields predicting movement through learned patterns allowing for smooth, uninterrupted gaze fixed on moving items of interest. Another example is reading.

Along with pursuit movements, a chief role of the frontal eye fields is to constantly analyse the visual field and to direct attention to objects of importance. The frontal eye fields superimpose a "salience map" on the visible world[2].This enables the gazelle to locate the lion amidst the grass of the savannah, the cat to see the mouse hiding in the shadows, or the child to find the four leafed clover in the field.

The strength and rapidity of the connection between the frontal eye fields and the remainder of the visual network is such that actions can occur prior to conscious recognition. As above, the complex network directing visual gaze employs reflexes and programmed motor patterns learned from previous experience [3]. The reader may recognise this pattern wherein the body moves even before the conscious mind has realised why. Examples include suddenly reaching for a found object or leaping away from a threatening shadow. As mentioned above, hunting mechanisms in some animals occur largely on this level, demonstrating almost reflexive behaviour. Pertinent to our case history, the patient's unusual focal seizures were triggering such a sequence of events, dragging visual attention and then ultimately the entire body to the imagined focus of interest on a pre-conscious level.

As alluded to above, Ferrier noted that lessoning of a frontal eye field appeared to have an only temporary effect on visual attention. Although it would be an exaggeration to state that there are redundancies in the cortical pathways, it appears that the ability to recover is due to the multiple inputs into the process of vision. The superior colliculi of the quadrigeminal plate are arranged in a somatotopic fashion. Provided that these remain intact, the brain seems able to compensate for the loss of one frontal eye field. Lesioning both the field and the colliculus results in permanent loss of visual attention [4].

Discussion

The implications of a detailed study of the frontal eye fields range from amusing to more clinically pertinent. On the lighter end of the spectrum, one notes that the right frontal eye field is dominant [5]. As such, the vast majority of people have a slight gaze preference to the left, explaining why computer icons are grouped on the left side of the screen.

Perhaps more relevant to clinical practice is the reminder that seizure patterns can be complex and unusual. Although neurosurgeons encounter patient seizures on a daily basis, most often these fall into the broader categories defined by the presence or absence of consciousness (simple v complex), and whether part or all of the body is affected (focal v generalised). This presentation is a reminder to neurosurgeons and physicians in general that any stereotyped, repetitive and unusual behaviour may be due to seizure activity. Frontal lobe seizures in particular can have unusual presentations, including grunting, gesturing, sexualised behaviour, and complex automatisms [6].

Salience is another fascinating and clinically relevant concept. Salience drives a great deal of our behaviour, from the little things to

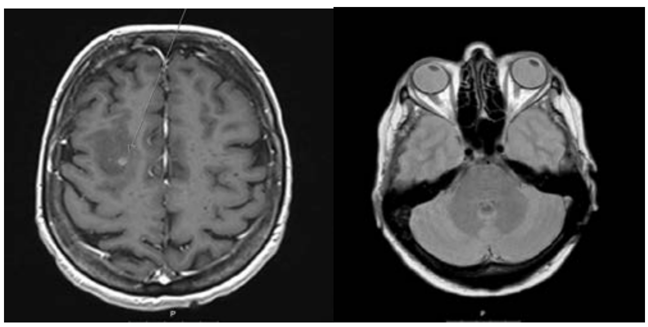

Figure 1: MRI scanning demonstrating the lesion in right frontal eye field.
Note that the images have been captured during an attack, demonstrating the characteristic eye deviation.

the bigger picture. Scanning the room at a party identifies old friends or new and interesting people to talk to. The drive to work harder to achieve a goal is recognition of the salience of that goal.

As with many of the reward and recognition pathways of the brain, a chief neurotransmitter of the frontal eye fields is dopamine. Blunting this pathway with, for example, anti-psychotic medication reduces the patient's sense of salience. This is at least part of the explanation as to why such patients engage so poorly with treatment and rehabilitation: the importance of the process simply fails to register.

At the very beginning of this article it is mentioned in passing that disease processes destroying this region often have surprisingly little in the way of clinical symptoms. It is rare that similar conditions have such a dramatic presentation as in this case. However, the signs of conditions affecting the frontal eye fields are significant if subtle. Poor performance on visual attention tasks are the first signs of various dementias and can even help discriminate between these conditions [7]. In this disease process this occurs before any other tests of cognitive function.

It goes without saying that there are many crossovers between the objective, clinical aspects of neuroscience and the more generalised, philosophical questions regarding what defines us as human beings. Often the microscopic analysis of the brain permits a glimpse of this bigger, macroscopic picture.

The frontal eye fields are a case in point. A question that has plagued philosophers and neuroscientists alike is that of consciousness. What defines the line between awareness and coma? Is the rough, mathematical approach of the Glasgow Coma Score enough? Work mimicking Ferrier's original treatise has demonstrated that the frontal eye fields can be "primed". A low dose of transcranial magnetic stimulation results in increased speed and accuracy on visio-spatial tasks [8]. However, increasing the stimulation to the level at which the frontal eye field ceases to function renders the individual oblivious to the contralateral half of the visual field.

Although this too is likely to be an oversimplification, this finding has led some authors to suggest that the frontal eye fields play a key role in the origin of consciousness. Although some may find this concept esoteric, its relevance is enough in the field of neuroscience to drive ongoing research [9].

Conclusion

There are many aphorisms regarding how we, as physicians learn from our patients. None is more fitting to this case than the words of Harvey Cushing, a founding father of neurosurgery. He wrote that "A physician is obligated to consider more than a diseased organ, more even than the whole man - he must view the man in his world [10]." For this patient, the insight given into the frontal eye fields has shown how we all view our worlds.

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