The Saccadic System: A Neurological Microcosm

Familiarity can breed contempt: perhaps it is precisely because the saccade is the commonest movement we make – about three every second of our waking lives – that we rather take it for granted. Yet, apart from being a movement of extraordinary speed and elegant precision (fig. 1), it not only determines absolutely what we are allowed to see, but precedes and prepares for nearly every directed action that we make. Research over the last couple of decades has demonstrated in detail the involvement in saccadic control of nearly every level of the brain, from the simple neural circuits in the brainstem reticular formation that ensure the saccade's remarkable technical performance, to neurons in frontal eye fields that help decide whether to look at one thing or another. As a result we have a more detailed understanding of the saccadic system, in the sense of being able to relate structure and disorder of structure to quantitative measurements of function, than of any other sub-system of the brain. Because saccades are stereotyped movements, small deviations may carry immense clinical significance. As a result, recent technical advances (in making micro-miniatuised oculometers that store data for subsequent analysis by lap-top) have begun to turn this neurophysiological knowledge into clinical utility, inaugurating what may perhaps turn out to be a new era of genuinely quantitative neurology.

The saccadic hierarchy
There is an intrinsic three-fold hierarchy in any motor act, that can be summarised as what, where, how: recognition of a target, and decision; localisation and proprioception; and creation of the detailed patterns of forces needed for execution. This general principle of motor organisation is particularly clearly seen in the saccadic system (fig. 2). At the lowest level are the neural circuits in the prefrontal and mesencephalic reticular formation, close to the oculomotor nuclei, that generate the highly specific temporal patterns of firing by which the oculomotor neurons move the eye so precisely and rapidly to their new position. Above them, the colliculus primarily has the task of converting information about the visual location of an object into an appropriate command to the brainstem that will move the gaze to the same location; in this it is supplemented by the cerebellum and has assistance from the cortex. But in the real world we are seldom presented with just a single potential target: we must choose between many, and some will have more significance than others. This choice – deciding what to look at – is a function that culminates specifically in the frontal eye fields. All of these hierarchical levels have immense diagnostic potential; for instance, saccadic slowing characteristic of disorder at the lowest level may be a very early indicator of neurodegeneration. But in this review there is only space to concentrate on the highest level, where recent work has used the stereotyped precision of saccades to discover a great deal about how cortical areas make saccadic decisions.

Latency: the measurement of decision
The two lowest levels of the saccadic hierarchy are in principle all that is needed to generate a saccade that lands accurately and swiftly on a visual target. In a laboratory situation, with single targets presented in the dark, that would be fine. But the real world is full of interesting stimuli competing for our attention. While the collicular level can localise visual targets, what it cannot do is recognise them, or evaluate their behavioural significance, for which the cortex appears to be necessary. Consequently, we find that the collicular mechanisms are tonically switched off by descending, ultimately cortical, inhibition, and only permitted to carry out their function when the higher processes of decision are complete. As a result, we have procrastination. The time between presenting a stimulus and starting to make a response – the saccadic latency – is far longer than would be expected from the speed of visual transduction, nerve conduction and synaptic action. Reaction time is decision time, and studies of how this latency varies with changing stimuli and circumstances – and in neurological disorder – have yielded much information about how these decision mechanisms work. The result is something called the LATER model: as well as recalling the procrastination the name stands for Linear Approach to Threshold with Ergodic Rate. This succinct but perhaps cryptic expression implies the existence of decision units, whose activity represents the system's degree of belief in different possible targets; at rest, their activity represents prior probability or expectation, and as sensory evidence comes that supports the belief, their activity increases linearly until it reaches a threshold, the point where it is so overwhelm-
UK ABBREVIATED PRESCRIBING INFORMATION: PROVIGIL 100 mg/200 mg Tablets.

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Figure 3. a miniature, non-invasive saccadometer in use. In this prototype the three miniature lasers are projected on to a convenient surface from a single morning dose according to response. Elderly: Treatment should start at about 100 mg daily, which may be increased subsequently to the maximum adult daily dose of 400 mg in the absence of renal or hepatic impairment. Severe renal or hepatic impairment: Reduce dose by half (100–200 mg daily). Children: See SmPC. Warnings and precautions: Patients with major anxiety should only receive Provigil treatment in a specialist unit. Sexually active women of child-bearing potential should be advised on a contraceptive programme before taking Provigil. Blood pressure and heart rate should be monitored in hypertensive patients in patients with obstructive sleep apnoea, the underlying condition and any associated cardiovascular pathology should be monitored. Provigil is not recommended in patients with a history of left ventricular hypertrophy nor in patients who have experienced intracranial vaso proliferative syndromes when previously treated with other modafinil. Side effects may present with ischaemic ECG changes, chest pain or arrhythmia. Studies of modafinil have demonstrated a low frequency of nervousness and an increase in the capacity of this occurring with long-term use cannot be entirely excluded. Drug Interactions: Modafinil is known to induce CYP3A4/5 and to a lesser extent, other enzymes and so may cause clinically significant effects on other drugs metabolised by the same pathways. The effectiveness of oral contraceptives may be impaired through this mechanism. When used for contraception, a product containing at least 50 mcg ethinyl oestradiol should be taken. Certain tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 2% of the population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil is also metabolised by CYP2C19, some patients with antidepressants may be required in such patients. Care should therefore be taken to monitor for symptoms of other drugs with a narrow therapeutic window, such as anti-convulsant or anti-anginal drugs. Side effects: Very common (>10%): Headache, Common (1–10%): Nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, asthenia, chest pain, abdominal pain and blurred vision. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. See SmPC for uncommon side effects. Basic NS: Full blood count, ECG and routine blood biochemistry at baseline and at regular intervals of 3 months.


Future developments
An attractive aspect of LEATER is that the performance of the eye in terms of latency can be summarised essentially by just two numbers, which are in turn directly related to the parameters of the model itself. They represent the fundamental parameters that must be defined for any decision system: for example, whether speed is more important than accuracy, the relative weight to be attached to present rather than past information, and the degree of creativity (randomness). In the brain, these parameters clearly need to be regulated in some way, and an exciting possibility is that they might possibly be related to the several ascending systems – noradrenergic, serotonergic, histaminergic - that innervate cortex relatively diffusely from below. The reason for having so many has always been a puzzle: if all they do is cause ‘arousal’ one would surely be enough. We hope soon to be able to establish whether these defects in systems do indeed cause the quantitative changes that LATER would predict. If so, the fact that miniature non-invasive devices for measuring eye movements (fig. 3), requiring practically no skill in setting up, will very soon be available at little cost and could revolutionise the diagnosis and monitoring of neurological impairment.

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For a case report on vertical supranuclear gaze palsy, see http://acnr.oxfordjournals.org/cgi/content/first/2003/abstract+

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Review Article