

An internationally standardised antisaccade protocol

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ABSTRACT

Detailed measurements of saccadic latency – the time taken to make an eye movement to a suddenly presented visual target – have proved a valuable source of detailed and quantitative information in a wide range of neurological conditions, as well as shedding light on the mechanisms of decision, currently of intense interest to cognitive neuroscientists. However, there is no doubt that more complex oculomotor tasks, and in particular the antisaccade task in which a participant must make a saccade in the opposite direction to the target, are potentially more sensitive indicators of neurological dysfunction, particularly in neurodegenerative conditions. But two obstacles currently hinder their widespread adoption for this purpose. First, that much of the potential information from antisaccade experiments, notably about latency distribution and amplitude, is typically thrown away. Second, that there is no standardised protocol for carrying out antisaccade experiments, so that results from one laboratory cannot easily be compared with those from another. This paper, the outcome of a recent international meeting of oculomotor scientists and clinicians with an unusually wide experience of such measurements, sets out a proposed protocol for clinical antisaccade trials: its adoption will greatly enhance the clinical and scientific benefits of making these kinds of measurements.

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1. Introduction

Almost uniquely amongst clinical disciplines, neurology and psychiatry suffer from a lack of genuinely quantitative methods. We cannot send to the lab for detailed blood counts, or precise measures of pulmonary function; with the exception of certain tests of peripheral nerve function, and of the sense organs, we occupy, in effect, a number-free zone. To be sure, we have the rating scales used for Parkinson and Huntington patients, extensively used in drugs trials: but they are subjective, and virtually impossible to compare reliably from one clinic to another. And while our various kinds of brain scan are obviously clinically important in localising the cerebral focus of certain kinds of disorders, and for evaluating progression in degenerative conditions, from a scientific

point of view they do not in themselves enlighten us much about function: *where is not how*. Progress in neurological sciences requires quantitative methodologies.

One technique that *does* yield numbers has been gaining in popularity over the last decade: the measurement of eye movements. In particular, a task that might at first sight not seem very promising is to present a subject with a visual target that jumps unexpectedly from a central position a little to the right or left, and measure the time it takes a subject to make a saccade to the new target – the rapid conjugate response called a saccade. Though commonly, and misleadingly, called ‘reflexive’, the long latency of the saccade in this step task – some 150–200 ms – reflects the fact that its initiation is the culmination of a prolonged neural process of decision-making (Schall, 2003a), a topic currently a focus of intense interest amongst cognitive neuroscientists. Saccades are easy to elicit, measure and quantify, and amenable to the rigour of mathematical and computational approaches. With modern miniaturised and automated equipment, one can measure a couple

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of hundred such responses in a few minutes in the clinic, non-invasively and without noticeable fatigue (since we normally make two or three saccades every second of our waking life anyway). Because saccades are largely automatic and stereotyped, the quantity of data supplied by this kind of approach (which can be called saccadometry) can provide much information to the clinical neurologist (Leigh & Kennard, 2004). In addition, the functionality of the saccadic system is well understood and saccades have been divided into a recognisable hierarchy with specific physiological properties and anatomical substrates (Leigh & Zee, 2006).

In one respect saccades are not at all stereotyped: a feature of saccadic latencies – indeed of all reaction times – is that however simple the stimulus or the task, they vary dramatically and randomly from one trial to the next, even when separated by only a few seconds. The resultant statistical data concerning the distribution of reaction time provide a wealth of precise information about the underlying decision mechanisms, a window onto the operation of the very highest levels of cerebral function. Consequently, measurements of saccadic latency distributions are increasingly being used by neuroscientists to study these mechanisms, and have resulted in quantitative models that can be used to summarise a subject's behaviour in ways that can be related to the underlying neural processes (Carpenter, Reddi, & Anderson, 2009; Carpenter & Williams, 1995; Gold & Shadlen, 2007; Noorani & Carpenter, 2011; Schall, 2003b; Shadlen & Gold, 2004). As a result, distributional analysis of reaction time has also found an increasingly wide range of applications in clinical neurology: especially in neurodegenerative diseases such as Parkinson's and Huntington's disease, but also in a wide range of other conditions, from hepatic encephalopathy and phenylketonuria to migraine and frontotemporal dementia (Antoniades et al., 2010; Burrell et al., 2012; Chandna et al., 2012; Dawson et al., 2011; Krismer et al., 2010; Michell et al., 2006; Perneczky et al., 2011; Temel, Visser-Vandewalle, & Carpenter, 2008). The protocol is both simple and standardised, so data can be obtained under essentially identical conditions in a clinic in San Francisco or a laboratory in Beijing.

However, there is one way in which this approach could be made very much more effective. Although the step task can generate highly significant latency effects when analysed in this way, they are often small: undoubtedly, more complex tasks can in many cases be more sensitive indicators of pathological dysfunction. Examples of such tasks include *go/no-go* (Noorani et al., 2011), in which responses must be made to some stimuli and not others, *countermanaging* (Boucher et al., 2007; Emeric et al., 2007; Hanes & Carpenter, 1999; Hanes & Schall, 1995), in which a delayed stop signal tells the subject to withhold the response, and in particular *antisaccades* (Butler et al., 2009; Condy et al., 2004; Cutsuridis et al., 2007; Everling & Fischer, 1998; Feng, 2012; Hutton & Ettinger, 2006; Katsanis et al., 1997; Kristjánsson, 2007; Peitsch et al., 2008; Pierrot-Deseilligny et al., 2002; Pouget et al., 2010; Smyrnis, 2008), in which the saccade must be made in a direction opposite to that of the stimulus. Specific deficits in antisaccades seem first to have been noticed by Guitton, Buchtel, and Douglas (1985), as a consequence of frontal lobe lesions.

A virtue of the antisaccade task is that it is cognitively demanding, so errors are made (a *prosaccade* to the target): consequently there are two separate populations – the correct antisaccades and the incorrect prosaccades – from which latency and other statistical measures can be obtained. It also lends itself to more complex tasks still, in which the subject must switch from one mode of response to another (Cameron et al., 2010; Evens & Ludwig, 2010; Olk & Jin, 2011). The growing importance of antisaccades in clinical investigation is reflected by an article and associated editorial that appeared while this paper was in the final stages of preparation (Hellmuth et al., 2012; Kaufer, 2012), that underline the utility of antisaccades in quantifying the effects of both aging and neurolog-

ical disease; their increasing use in psychiatric disorders has been the subject of another useful set of reviews (Gooding & Basso, 2008; Klein & Ettinger, 2008; Rommelse, van der Stigchel, & Sergeant, 2008).

Unfortunately there are currently two major obstacles to a wider adoption of the antisaccade in clinical practice. The first is that at present much of the kind of data that has proved so useful in saccadometry is simply thrown away: a very large number of studies report error rates and nothing else. It would therefore be highly desirable to extend the saccadometric approach to antisaccade tasks, by reporting full data about latency distributions. Some have already started doing this (Cutsuridis et al., 2007; Feng, 2012; Meeter, van der Stigchel, & Theeuwes, 2010), and have also been developing quantitative models from which descriptive parameters could be extracted, in the way that has proved so useful for ordinary saccadometry using the step task, and could be related to measurements of brain activity (Papadopoulou et al., 2010).

The second problem is that with a complex task of this kind, the huge number of different possible protocols presents an *embarras de richesses*: each investigator has their own favourite procedure, so that even if more detailed data were to be published it would be difficult to compare them. As a result, we find large variations in findings across studies – even error rates vary from 2% to 30% (Smyrnis, 2008) – which are likely to be almost entirely due to differences of protocol: indeed with sufficient manipulation of the task it is possible to eliminate latency differences between pro- and antisaccades completely (Chiau et al., 2011; Liu et al., 2010). Of course, in the early, investigative, stages of research, it is essential that people do things in different ways, and find out which factors are important and which are not. But once the technique has matured, and one wants to apply it clinically as an actually useful test, it is clearly essential that results can be compared from one lab to another.

Earlier this year, a small international meeting was held in Cambridge at which a number of people with an interest in facilitating this kind of co-operation met to see whether, despite the variety of protocols currently in use, some agreement could be reached on a common, harmonised protocol that could be recommended for use both as diagnostic aids and for scientific investigation. They were able to bring to the discussion a very wide range of experience of measuring prosaccades as well as antisaccades, with a variety of different protocols and techniques, and in a wide range of settings, from specialised laboratories to ordinary clinics. One might have expected that individual experimenters would be too firmly wedded to their particular procedures to be willing to change, but this proved not to be the case. Although the members of the committee came to the meeting with entirely different favourite ways of carrying out these experiments, it soon became clear that these were not adopted because of passionately-held beliefs: with an ease that would not perhaps have been anticipated beforehand we arrived at a general agreement for the standardised protocol that follows.

2. The recommended protocol

It may be helpful to present (Fig. 1) a generalised antisaccade task, and the notation we shall be using to refer to its components. It can be seen that there are many potential parameters that need to be considered; fortunately they fall into four essentially independent categories:

1. *Stimulus parameters*, such as position and colour.
2. *Trial parameters*, that concern the timing of the stimuli to be used in any particular trial.
3. *Run parameters*, to do with how individual trials are arranged into runs or blocks.
4. *Outcome measures*, the variables that are actually measured and reported.

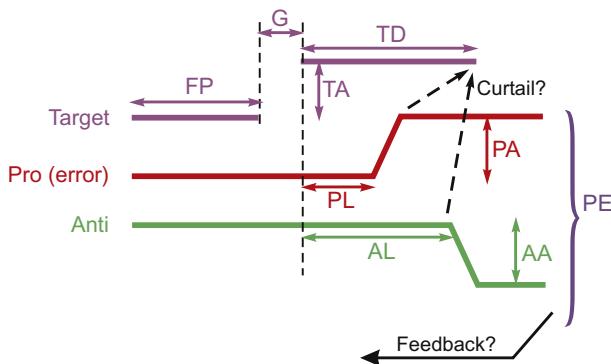


Fig. 1. Schematic representation of a generic antisaccade trial. Above (purple), step-like movement of the target from its initial fixational position; below, a correct antisaccade (green) and incorrect prosaccade (red). FP = foreperiod; G = gap duration; TA, TD = target amplitude and duration; PL, AL = pro- and antisaccade latency; PA, AA = pro- and antisaccade amplitude; PE = proportion of error (prosaccade) responses.

In each case we mention some of the relevant considerations in making a particular recommendation, and our final conclusion; we start with the general guiding principles that informed our approach.

2.1. General principles

- 1. Timing.** For clinical use, a paramount consideration is that the test should not be unduly tiring for the subject. We believe that it is appropriate to aim for a maximum duration of 20 min overall, and that this requirement must constrain the choice of run and trial parameters.
- 2. Classes of stimuli.** Whilst for scientific research much may be learnt by using a variety of different stimulus types, given the time constraints in a clinical setting, we believe it is better to get comprehensive and good-quality data about one specific stimulus, rather than poorer quality data about several.
- 3. Incidence of errors.** Some have argued that it is desirable to use a test that increases the average number of errors made. We believe this view to be false: with a very difficult task, an impaired patient will produce a saturatingly (and thus uninformatively) large number of errors; conversely, if the task is too easy, some may make very few errors indeed, so that the effects of therapeutic intervention cannot be measured. Either way, the potential amount of information is limited. We therefore need a task generating neither too few nor too many errors.
- 4. Prosaccades.** Data should be obtained in the conventional prosaccadic step task as well as in the antisaccade task; the parameters derived from the prosaccade task are helpful in trying to model the antisaccades.

2.2. Stimulus parameters

Direction. On the principle of reducing the number of classes of stimuli, we recommend that only horizontally-arranged stimuli should be presented (they are in any case easier to record than vertical).

Amplitude. Similarly, we do not recommend using more than one target amplitude (TA). Since amplitudes of less than 5 deg may be responsible for 'square waves' (see Leigh & Zee, 2006) in some subjects, and amplitudes of more than 10 deg are accompanied by head movements under natural conditions, we recommend an amplitude of 8–10 deg, with stimuli presented in equal numbers to left and right.

Contrast. Targets should be of high contrast (>50%). If presented on a lab-based display, it is better practice for them to be dark on a light background, so as to minimise issues related to light-adaptation level. If they are presented as laser projections, then the background should be as uniform as possible and at the ordinary ambient level of illumination, neither so bright as to reduce contrast, nor so dark as to cause adaptation transients. Size and shape of target are probably not very important: on screen displays we recommend a diameter of 0.5 deg, but laser-projected targets of much smaller diameter are also acceptable, and may in fact be better from the point of view of discouraging microsaccades during the fixation period.

2.3. Trial parameters

The *foreperiod* FP during which the central fixation target is displayed should be of random duration in order to avoid temporal predictability of peripheral target onset. Though it is not yet universal practice, it was agreed that the duration should be non-ageing: that is, that the probability of it terminating per unit time should be constant (see for instance (Oswal, Ogden, & Carpenter, 2007)). If this is not done, and the FP is ageing (in other words, uniformly distributed within its range), expectation rises steadily throughout the foreperiod. Consequently in those trials for which the FP happens to be long the subject's expectation of the target will be higher, and vice versa when it happens to be short, and these differences in expectation will translate into an unwanted variability of the reaction times and error rate. The random part of the foreperiod needs to be preceded by a component of fixed duration to ensure that subjects are never taken completely by surprise, and the non-ageing algorithm needs to be curtailed to avoid occasional extremely long durations: we recommend a total range of $FP = 1\text{--}3.5$ s, with a mean of 1.5 s.

Some experimenters routinely use a *gap* (a small time interval, often 100–200 ms, between central fixation offset and target onset: G in Fig. 1), which undoubtedly has an effect on subsequent behaviour and may increase errors. Nevertheless, in the interest of simplicity and of reducing the time of each trial, we recommend that gaps are not used in routine clinical testing; thus $G = 0$.

There appears to be no evidence that *target duration* TD significantly affects performance. We recommend that the target should remain on for 1 s, which allows sufficient time to record any correcting saccade if a prosaccade has been made.

Feedback has not been shown to influence performance, and should not be provided during a block, but given during the practice runs (see below). However, if a subject makes four errors or no-responses in a row in the antisaccade task they should be reminded of the task in order to ensure that they understand the instructions.

2.4. Run parameters

Block size. Reliability of data appears to be high with blocks of antisaccade trials of around 45 trials for most subjects: we recommend a block size of 40 for antisaccades. Prosaccades are less fatiguing, and it was considered that 60 sequential prosaccade trials could be performed comfortably without significant fatigue effects. The aim here is to achieve an optimum trade-off between having enough trials to enable reliable and informative analysis, and time and patient comfort.

Direction. Targets to the left and right should be randomly interleaved within a block. 'Randomly' with replacement (so that the expectation of left and right before each trial is constant) or without replacement, so that the total frequency *overall* is identical. The former is probably to be preferred, but we are not aware of any evidence that it makes a significant difference in runs of this length.

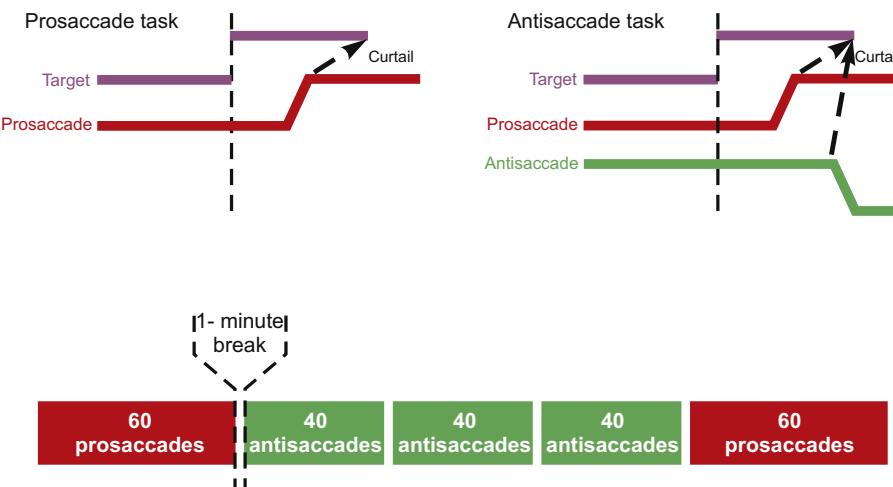


Fig. 2. Summary of the recommended protocol. Above, typical prosaccade (left) and antisaccade (right) trials. Below, the format of a single run.

Some practice should be provided. We recommend 10 practice trials before the first prosaccade block, and 4 before the first antisaccade block, those data being discarded, and feedback being provided to the subject as necessary.

It is important to give standardised *instructions* to the subject, pointing at the screen to emphasise the target positions and the correct responses. For the prosaccades, '*Look at the central dot; as soon as a new dot appears on the left or right, look at it as fast as you can*'. For the antisaccades: '*Look at the central dot; as soon as a new dot appears look in the opposite direction, to here, as fast as you can. You will probably sometimes make mistakes, and this is perfectly normal*'. Note that we do not in general recommend asking the subjects to make 'mirror' saccades, i.e. to the exact opposite location on the display, since such an instruction is found not to affect the basic outcome measures of the task except the amplitude of the antisaccade (Evdokimidis, Tsekou, & Smyrnis, 2006), and may cause confusion. But if the amplitude is a desired outcome measure then the instruction should include the requirement for a mirror movement.

A suitable overall design, that starts with the simpler task and is symmetrical so that time-dependent effects can be detected, is: 60 Prosaccades; 40 antisaccades; 40 antisaccades; 40 antisaccades; 60 prosaccades.

There should be a break of 1 min between each block; with automated recording this total of 240 trials should take significantly less than the target of 20 min overall. This has been confirmed in practice in preliminary trials in Oxford with 10 PD patients and 10 age-matched controls: the subjects had no difficulty in following the instructions, and the time for a complete protocol was between 13 and 16 min.

These recommendations are summarised in Fig. 2.

2.5. Outcome measures

The following parameters should be measured for each prosaccade (control) trial:

1. Latency of first saccade, from appearance of the target to the start of the saccade.
2. Whether in the correct direction, or no response at all, or a misrecording (including blinks, head movements, etc.).
3. Peak saccadic velocity, if possible; duration might be added, but is perhaps less fundamental.

4. The gain of the first saccade (ratio of actual amplitude to correct amplitude), if desired: this is probably better than simply recording amplitude alone.

The following parameters should be recorded for each antisaccade trial:

1. Latency of first response, from appearance of the peripheral stimulus to the start of the saccade.
2. Whether it was an anti- or prosaccade, a non-response, or a mis-recording.
3. Latency of any correcting saccade, measured from the end of the previous saccade (to count, a correcting saccade must cross the midline).
4. Peak saccadic velocity of the first response and of any correction, if possible.
5. The gain of the first saccade and of any correction, if desired.

Summary statistics to be reported should include cumulative distributions of control latencies, and of correct and error antisaccade latencies; it may be convenient to use reciprobit plots for this purpose, and to plot correct and error responses 'defectively', i.e. as a cumulative proportion of the total number of trials (for an example, see Noorani et al., 2011). When median values are used, inter-quartile difference is more appropriate as a measure of dispersion than the standard deviation; also the ratio of interquartile difference to the median (the coefficient of variation) is another measure of variation that is independent of the central tendency of the distribution. All latencies greater than 50 ms should be included, since distributions of early saccades can themselves be of diagnostic or scientific significance (Antoniades et al., 2010; Halliday & Carpenter, 2010). Total error rates in the antisaccade task and median latencies in all tasks should be reported, as should mean peak velocity for each class of movement, with standard deviations.

These outcome measures imply certain minimum technical requirements for the recording and display equipment. For latency measurements, 100 Hz sampling is a minimum, and a higher rate may add a little to the precision (though this may not mean much, given the huge variability of the intertrial variation); for peak saccadic velocity the requirement is higher, perhaps a band-width of 250 Hz, based on a higher raw sampling rate. If a conventional display screen is used, it should have a frame rate of 100 Hz or more and be capable of synchronising with the oculometric data.

3. Conclusion

We have presented here a protocol for the clinical use of anti-saccades that is supported by a substantial number of practitioners in the field, from a wide range of countries. We hope that its adoption will encourage clinicians to get more out of the data than at present is commonly the case, that it will enable comparisons to be made between different laboratories and clinics, and – most important of all – between neurological and psychiatric conditions, and that it will provide a basis for parameterisation of the data, as has proved so successful for the simple saccadic step task.

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