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## EDITED BY

Andrew Lee,  
Houston Methodist Hospital, United States

## REVIEWED BY

Fabienne C. Fierz,  
University Hospital Zürich, Switzerland

## \*CORRESPONDENCE

Evangelos Anagnostou

✉ granavan@yahoo.com;

✉ eanagnost@eginitio.uoa.gr

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# Clinical utility of square-wave jerks in neurology and psychiatry

Athena Zachou, Georgios Armenis, Ioannis Stamelos, Eirini Stratigakou-Polychronaki, Fotios Athanasopoulos and Evangelos Anagnostou\*

Department of Neurology, University of Athens, Eginition Hospital, Athens, Greece

Human eye fixation is steadily interrupted by small, physiological or abnormal, eye movements. Square-wave jerks (SWJ) are the most common saccadic intrusion which can be readily seen at the bedside and also quantified using oculographic techniques. Various neurological, neuropsychiatric and psychiatric disorders display abnormal fixational eye movement patterns characterized by frequent SWJ. For the clinician, SWJ are particularly important because they can be readily observed at the bedside. Here, we will discuss the pathological conditions that present with SWJ and explore the expanding body of literature suggesting that SWJ may serve as a potential indicator for various clinical conditions.

## KEYWORDS

square-wave jerks, eye movements, fixation, saccadic intrusions, progressive supranuclear palsy, cerebellar ataxia

## 1 Introduction

Foveate animals, including humans, can look quietly at a target for prolonged periods of time. This ocular motor condition is called fixation and is based on an active and dynamic eye stabilization system (1). Early on, it became clear that maintained fixation is steadily interrupted by a variety of small, fast and slow, eye displacements (2, 3). Traditionally, these eye movements are divided into two categories: a repertoire of physiological idiosyncratic miniature movements (microsaccades, ocular drift and ocular microtremor) collectively called fixational eye movements (4) and a group of larger, and therefore clinically visible, fixational intrusions comprising SWJ, ocular flutter, opsoclonus, saccadic pulses and macrosaccadic oscillations (5). The distinction of normal fixational eye movements versus abnormal saccadic intrusions, however, might prove to be more of a working hypothesis than an empirical reality. This is particularly true for microsaccades and SWJ, which likely represent different magnitudes across a saccadic continuum extending from fixation to exploration (6). Being easy to assess at the bedside, SWJ are certainly the best-studied saccadic

intrusion. Here, we review the measurement methods of SWJ using quantitative oculography and discuss the various neurological and psychiatric conditions that affect the occurrence of SWJ.

## 2 Characteristics, recording and quantification of SWJ

SWJ can be defined as a pair of small (<5 deg) saccades, each of them conjugate. The first one moves the eye away from the fixation point, whereas the second one returns the eye toward the target (corrective saccade), after a short time interval (usually less than 300 ms). SWJ seem to have a strong horizontal preference in humans, something that does not apply to non-human foveate animals, which may show a greater vertical predisposition (7). Macro-SWJ display amplitudes of up to 30 deg and are less commonly observed in clinical practice. Bursts or prolonged series of repetitive, nearly continuous disruptions of fixation are categorized as saccadic oscillations. These may manifest either as SWJ-oscillations or as back-to-back saccadic oscillations without intersaccadic intervals. In the latter case, ocular oscillations are classified as opsoclonus or ocular flutter, depending on whether the oscillations occur in all directions or are restricted to the horizontal plane, respectively.

The genesis of SWJ is still uncertain. A dysfunction of a brainstem oculomotor network is assumed, where the inhibition exerted by the inhibitory burst neurons (IBNs) on the omnipause neurons (OPNs) overcomes the inhibition of the OPNs on the IBNs. Subsequently a short burst of activity appears in the excitatory burst neurons that produces a small saccade. In turn, this produces a small retinal error that is detected in the superior colliculus (SC) which results in a second saccade in the opposite direction, completing a SWJ (8). The cerebellum, basal ganglia, and cortical regions are directly and indirectly interconnected within this network, thereby influencing its functionality (9).

In order to detect and quantify SWJ, precise eye position data has to be obtained. Out of various eye tracking methods, two are the most commonly used for these purposes: Magnetic Field/Scleral Search Coil (SSC) and Video-Oculography (VOG). The former, albeit more invasive and not as well tolerated, is considered more precise and accurate than the latter. However, they have both shown adequate performance in detecting saccades of small magnitude. Temporal resolution is highest for SSC (500+ Hz), but high-end VOG systems can reach frequencies of 400 Hz. Other recording methods, such as Infrared Reflection and DC-electrooculography, are no longer widely used for SWJ detection (10).

Experiments typically consist of subjects viewing a small target on a screen and being asked to maintain fixation for 10-120 seconds. The head is restrained by a forehead-chin headrest. Fixation duration, target shape and size, screen-to-cornea distance and other environmental conditions at the time of the experiment (e.g. lighting) may differ according to the goals of the respective study. In order to detect SWJ from large amounts of data, automated and objective algorithms have been developed. A common approach is to first detect all saccades, using methods reliant on eye movement velocity (11). Saccades are then filtered

based on amplitude. Subsequently, pairs of consecutive saccades that are separated by an appropriate intersaccadic interval and display approximately opposite directions and similar magnitudes are classified as SWJ (12). Another approach that has been used is the creation of an SWJ index, incorporating the above metrics in a continuous variable between 0 and 1, and then comparing it to the "ideal SWJ". Index values above a specified threshold are considered to be SWJ (7).

## 3 SWJ in neurological and psychiatric disorders

### 3.1 SWJ in cerebellar, brainstem and basal ganglia disorders

Progressive supranuclear palsy (PSP) and cerebellar ataxias are perhaps the most widely recognized neurological disorders in which SWJ play a prominent role in their phenotype (Figure 1A). Early on, Troost et al. recognized that SWJ were the second most prevalent ocular motor disorder in PSP after saccadic slowing (14). Subsequently, several clinical and oculographic studies have confirmed and quantified the presence of SWJ in PSP (9, 15–20)]. The occurrence of >10 SWJ/min with amplitudes up to 4 deg, have been recently included in the clinical diagnostic criteria of PSP by the Movement Disorder Society (21). While more prevalent in PSP, SWJ also occur, albeit less consistently, in various other movement disorders (22–28), with Parkinson's disease being the most characteristic among them (9, 29–31).

Among cerebellar disorders, Friedreich's ataxia (FA) is the most thoroughly studied with regard to SWJ (32). Ribai et al. followed 37 FA patients prospectively for 7 years using eye movement recordings. These authors found a high frequency of SWJ in all of them at the beginning of the study, with a further increased rate at the end of it (33). In 2008, Fahey et al. investigated SWJ in 15 Friedreich's ataxia (FA) patients under target-on and target-off conditions. They observed longer and larger SWJ in the target-off condition. Younger patients exhibited more fixation instability with more frequent and shorter SWJ in both conditions; no differences in the total number of SWJ between ambulant and non-ambulant participants were found, but the latter group exhibited significantly more macro-SWJ. Interestingly, in almost half of the patients, oblique SWJ with a prominent vertical component, as well as occasional pure vertical SWJ, were recorded (34).

SWJ have been described in many spinocerebellar ataxias (SCA), including SCA1, SCA2, SCA8, SCA10, SCA14, SCA20, SCA21, SCA25, SCA27, SCA29, SCA37, SCA46, and DRLPA, although they are more noticeable in SCA3 and SCA6 (35, 36). Bürk et al. detected SWJ in 30% of SCA3 patients (37), whereas another study reported a percentage of approximately 55% for SCA3 patients; SCA1, SCA2, and SCA6 percentages were found lower, around 20% (38). Similarly, Moscovich et al. found SWJ in 23% of SCA3 patients and 17% of SCA6 patients (39). In 2017, Wu et al. investigated ocular movements in SCA3 and found a high frequency of SWJ in both symptomatic patients (n=44) and SCA3

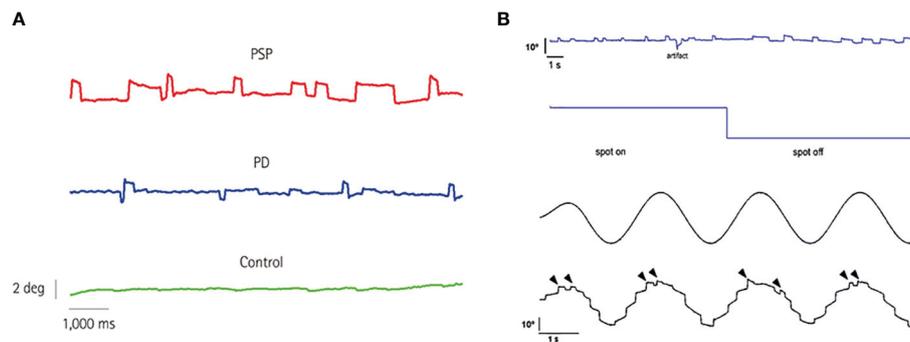


FIGURE 1

(A) Eye position while fixating an LED straight ahead for 10 s in three subjects of the same age (69 years): a PSP patient, a PD patient, and a control subject. Note the increased rate of square-wave jerks in the PSP patient. PD, Parkinson's disease; PSP, progressive supranuclear palsy. From Anagnostou et al. (9), with permission by the "Korean Neurological Association". This figure is published in "Anagnostou E, Karavasilis E, Potiri I, Constantinides V, Efstathopoulos E, Kapaki E, Potagas C. A Cortical Substrate for Square-Wave Jerks in Progressive Supranuclear Palsy. *J Clin Neurol* 2020;16: 37–45", Copyright Korean Neurological Association. (B) 60-year-old man with Langerhans' cell histiocytosis and cerebellar involvement. Continuous SWJ during straight ahead fixation as well as after removal of visual fixation (upper panel). The average frequency of occurrence was  $40.8 \text{ min}^{-1}$  and remained unchanged after turning the fixation spot off. In the latter case, however, prolonged off-center fixation periods were demonstrated making square-wave intrusions appear wider. Typical pathological staircase appearance of smooth eye tracking in the same subject due to numerous catch-up saccades (lower panel). Notably, SWJ continue to occur during smooth pursuit (arrowheads). From Anagnostou et al. (13), with permission by "Elsevier". This figure is published in "Anagnostou E, Papageorgiou SG, Potagas C, Alexakis T, Kalfakis N, Anastasopoulos D. Square-wave jerks and smooth pursuit impairment as subtle early signs of brain involvement in Langerhans' cell histiocytosis. *Clin Neurol Neurosurg* 2008;110: 286–290.", Copyright Elsevier.

carriers ( $n=12$ ) (40). Additionally, Bour et al. recorded downbeat nystagmus accompanied by horizontal SWJ (bow-tie nystagmus) in the majority of SCA6 patients they recruited ( $n=4/6$ ). Similar oculomotor findings (bow-tie nystagmus) were also observed in patients with familial cortical myoclonic tremor with epilepsy (FCMTE) ( $n=4/6$ ) (41).

SWJ along with gaze-evoked and/or spontaneous nystagmus are common features of Ataxia-Telangiectasia (42). High SWJ frequency and amplitude have been also found in patients with Ataxia with Oculomotor apraxia type 2 (43). Pronounced oculomotor abnormalities with frequent SWJ have been observed in patients with chorea-acanthocytosis, who have heterozygous VPS13A mutations and basal ganglia degeneration, when compared to normal controls (25). Likewise, SWJ have been reported in adult-onset Alexander disease (44) and X-linked ataxia (45).

Paraneoplastic cerebellar degeneration is associated with a frequent occurrence of SWJ as described in cases of anti-Hu and anti-CV2/CRMP5 cerebellar ataxia associated with Small-Cell Lung Cancer (SCLC) (46, 47). Additionally, SWJ are observed in paraneoplastic Stiff-person syndrome with anti-amphiphysin antibodies, which can be linked to malignancies like SCLC, breast cancer, and Hodgkin's Lymphoma (47). Similarly, frequent SWJ can be found in cerebellar ataxia due to autoimmune mechanisms, whether or not autoantibodies are detected in serum or cerebrospinal fluid (CSF). This includes conditions like anti-GAD Stiff-person syndrome (47) or anti-Sj/ITPR1 and anti-NMDA cerebellar ataxia (48). High frequency SWJ ("square wave oscillations") have been reported in a case of anti-GAD cerebellar ataxia accompanied by autoimmune thyroiditis (49). They have also been described in a patient with steroid-responsive encephalopathy with autoimmune thyroiditis presenting with pure cerebellar ataxia

(50) and in a case of a SCLC patient with pembrolizumab therapy-induced encephalitis (51).

A high occurrence of SWJs was found in a case of Langerhans' cell histiocytosis (LCH) with central nervous system involvement (13) (Figure 1B) and has also been described in Creutzfeldt-Jacob disease, presenting with progressive cerebellar ataxia, oculomotor abnormalities, mental impairment and hyper-intensities in the basal ganglia and thalami (52). In Arnold-Chiari malformation type 1, SWJ along with downbeat nystagmus have been described, but only after strabismus surgery (53). In contrast, Chiari type 2 malformation is not associated with an increased SWJ rate (54).

Finally, oculomotor recordings in patients with essential tremor have revealed an increased rate of SWJs, along with increased saccade latency and decreased saccade peak velocity when compared with normal controls. These findings appear to be unrelated to the duration, severity, or treatment of the disease (55).

### 3.2 SWJ in dementias

It has long been reported that SWJ occur in patients with acute or chronic focal cerebral lesions, regardless of the lesion's location. The amplitude of these SWJ is typically lower than that observed in cerebellar diseases (56).

Typically, SWJ are generated during visual fixation (VF) and suppressed in darkness. However, in Alzheimer's disease (AD), SWJ occur more frequently in low-light conditions than during VF. These SWJ without VF are associated with increased cortical dysfunction (57).

Nonetheless, it has been reported that patients with AD and control subjects do not differ in the rate of intrusive saccades during VF at baseline. Only AD patients exhibit a progressive increase over

an 18-month follow-up period, and this increase correlates with heightened dementia severity. However, it is not specified whether this phenomenon holds true for SWJ, which are paired intrusive saccades characterized by equal amplitude and opposite direction (58).

In another publication, healthy controls and young onset Alzheimer's disease patients (YOAD) also showed no significant difference in the average number of SWJ. However, YOAD patients exhibited a higher frequency of large intrusive saccades and had shorter periods of fixation compared to healthy controls (59).

A slightly different scenario is presented in a study by Shakespeare et al. (60). Patients with typical AD demonstrated an elevated rate of SWJ during attempted VF in comparison to healthy controls. Furthermore, the SWJ rate was found to be associated with a decrease in cerebellar grey matter volume. On the other hand, patients with posterior cortical atrophy, a variant of AD, exhibited increased occurrence of large unpaired saccadic intrusions, which correlated with reduction in cortical thickness.

Small SWJ are defined as paired microsaccades with equal amplitude and opposite directions. Microsaccades in individuals with AD or mild cognitive impairment tend to exhibit a more oblique trajectory when compared to those in healthy controls (61). A high frequency of small SWJ has also been observed in the behavioral variant frontotemporal dementia group compared to age-matched controls. Neural correlates were identified in the orbitofrontal and ventromedial prefrontal cortices, as well as the striatum.

### 3.3 SWJ in psychiatry

Eye movement studies in psychiatric diseases are more sparse than those in neurologic disorders. Impairments in different oculomotor paradigms have been reported in major depressive disorder (MDD) (62, 63), in bipolar disorder (BD) (62, 64), in obsessive compulsive disorder (OCD) (65), in anorexia nervosa (AN) (66) and especially in schizophrenia (SCZ) (67–69) with some researchers considering them as potential biomarkers (63, 70–72) while others remain more skeptical (68, 73).

SWJ in psychiatric diseases, however, have been less frequently studied, and this not always in dedicated visual fixation paradigms. Regarding SCZ most of the studies have found no differences between SCZ patients and health controls (HC) (67, 74–78). However, one study (79) reported increased frequency in SWJ during smooth pursuit eye movements, while others have even reported lower SWJ rates in patients (80, 81). Clearly, differences in methodological approaches account for these discrepancies. More recently, Levy et al. reported that SWJ frequency was one of the variables that discriminated between subjects with normal and subjects with abnormal smooth pursuit performance (in a mixed group of HC and schizophrenic patients). Hence, the presence of another ocular motor dysfunction (i.e. smooth pursuit) rather than SCZ itself appears critical with respect to the occurrence of SWJ (82).

Data on SWJ in affective disorders are not less contradictory. Sweeney et al. found that patients with BD presented higher rates of SWJ compared to SCZ patients but had no differences compared to

controls (81). Flechtner et al. compared the number of SWJ produced by SCZ patients, patients with affective disorders (both MDD and BP) and controls in a smooth pursuit paradigm and reported a trend for patients with affective disorders to perform more SWJ (77). On the other hand, Friedman et al. did not spot any differences between SCZ patients, patients with affective disorders and controls (76, 80). Finally, Sweeney et al. reported increased SWJ rates in MDD patients using a visual fixation task in contrast to the previous studies (83).

Concerning patients with OCD, Sweeney et al. reported increased frequency of SWJ during a smooth pursuit task (84). On the contrary, other studies (85–87) found no increase in the frequency of SWJ in OCD patients compared to controls. Moreover, Pallanti et al. observed SWJ in three anorectic patients while they were absent in controls (88). In a study by Phillipou et al. it was shown that AN patients made SWJ at a higher rate compared to controls which was also negatively correlated with anxiety. Also, 87.7% of AN subjects and 95.5% of healthy participants were properly classified based on SWJ and anxiety scores (89).

## 4 Discussion

Square Wave Jerks (SWJ) are an especially valuable ocular motor sign due to their ease of detection during bedside physical examinations. However, they often go unnoticed and receive far less attention compared to larger eye movements like saccades and smooth pursuit among general neurologists.

Dedicated studies on SWJ are still relatively scarce, but accumulating evidence underscores their significant relevance in the ocular motor characteristics of movement disorders and cerebellar ataxias. Certainly, PSP and cerebellar syndromes of various etiologies (degenerative, autoimmune, paraneoplastic) stand out as the most extensively studied and well-established central nervous system disorders associated with saccadic intrusions. When it comes to neurodegenerative dementias, there exist somewhat conflicting results. Most studies focus on patients with AD, with some demonstrating an increase in SWJ rates compared to age-matched controls, while others show normal rates. Clearly, methodological variations and, more importantly, diagnostic uncertainties may account for these discrepancies. The inclusion of more homogeneous diagnostic groups based on cerebrospinal fluid biomarkers rather than relying solely on the neuropsychological profile might enable more robust conclusions regarding the role of SWJ in dementia. The same applies to psychiatric disorders, where the concept of drug naivety may be of particular importance in designing methodologically robust studies.

Many clinicians consider SWJ to be rather nonspecific, as they can occur in otherwise healthy elderly individuals, particularly when the rest of the oculomotor examination is normal. The number of SWJ per minute might therefore be a critical parameter given the fact that the occurrence of SWJs is not a binary on-off phenomenon distinguishing health from disease but rather a continuum. To establish a valid clinical criterion, thresholding, particularly in terms of SWJ frequency, is essential. Table 1 offers an overview of SWJ rates as reported in the available literature. Only studies that

TABLE 1 Summary table of SWJ rates in neurological and psychiatric disorders.

Disorder	Study	Diagnosis	No. of Patients	Mean SWJ rate (SWJ/min)
Brainstem/Cerebellar/ Basal Ganglia	Rascol et al. (15),	PSP	7	54
	Otero-Millan et al. (8),	PSP	10	48
	Anagnostou et al. (9),	PSP	20	33.5 (fixation on) 22.5 (fixation off)
	Pagonabarraga et al. (19),	PSP	65	22.8
	Becker et al., (20)	PSP	50	31.2
	White et al. (29),	PD	14	52
	Rascol et al. (15),	PD	13	45
	Anagnostou et al. (9),	PD	12	10.3 (fixation on) 13.3 (fixation off)
	Pagonabarraga et al. (19),	PD	25	1.2
	Bonnet et al. (27),	Ephedrone-induced Parkinsonism	28	6.8
	Ribaï et al. (33),	Friedreich ataxia	37	36 (first assessment) 54 (7 years later)
	Salman et al. (54),	Chiari malformation type 2	21	3.5
	Gitchel et al. (55),	Essential Tremor	60	26.9
	Wu et al. (40),	SCA3	44 patients 12 pre-clinical carriers	47 32
Dementia	Nakamagoe et al. (57),	Alzheimer's Disease	15	10.4 (fixation on) 20 (fixation off)
	Pavisc et al. (59),	Alzheimer's Disease (young onset), Posterior Cortical Atrophy (young onset)	26, 10	6.2, 4.9
	Shakespeare et al. (60),	Alzheimer's Disease, Posterior Cortical Atrophy	17, 20	36, 18.9
	Kapoula et al. (61),	Alzheimer's Disease, Mild Cognitive Impairment	18, 15	2.0, 2.2
	Russell et al., 2021 (90),	Frontotemporal degeneration (behavioral variant)	19	18.4
Psychiatric	Nickoloff et al. (85),	Obsessive-compulsive disorder	8	3.4
	Sweeney et al. (84),	Obsessive-compulsive disorder	17	7.5
	Campion et al. (75),	Schizophrenia	46 (13 drug-naïve, 20 chronic, 13 residual)	12
	Friedman et al. (80),	Schizophrenia, Affectives	23, 16	7.2, 5.0
	Sweeney et al. (81),	Schizophrenia, Bipolar disorder, Major depressive disorder	101, 17, 13	2.8, 7.5, 3.5
	Friedman et al. (76),	Schizophrenia, Affectives	26, 14	19.8, 24.6
	Flehtner et al. (77),	Schizophrenia, Affectives	43, 34	9.6, 14.7
	Levy et al., (82)	Schizophrenia	43	6
	Phillipou et al. (89),	Anorexia nervosa	22	11.8

reported mean SWJ frequencies, which can be converted into rates per minute, were included, while single case reports were excluded.

There are still important questions awaiting answers concerning the neuronal mechanisms that govern fixation in humans. To gain a deeper understanding of the mechanisms underlying saccadic intrusions in neurological and psychiatric disorders, it would be beneficial to perform a more detailed oculographic categorization of SWJ waveforms, considering factors such as amplitude, direction, and intersaccadic intervals. Combining clinical assessments with quantitative oculographic analysis and both structural and functional neuroimaging approaches is expected to provide further insights into the pathophysiology and clinical significance of ocular oscillations in various disease categories.

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