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N140 Latency as a Novel Biomarker for the Evaluation of Somatosensory dysfunction in Patients with Spinocerebellar Ataxia Type 2

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Abstract

Introduction: The N140, a long latency component of the somatosensory evoked potentials (LL-SEPs) related to passive attention, could be a valuable complement to short latency evoked potentials (SL-SEPs) for the evaluation of somatosensory pathways in patients with spinocerebellar ataxia type 2 (SCA2). There are no studies of N140 in patients with SCA2. **Objective:** To characterize LL-SEPs and SL-SEPs in patients with SCA2 and healthy controls.

Methods: We enrolled 28 patients with SCA2 and 34 age-matched healthy controls. LL-SEPs (N140) were recorded from the Cz electrode referenced to linked mastoids (Cz-A1+A2) following cutaneous stimulation of the second finger. SL-SEPs (N20) were obtained using standard procedures. Clinical assessment in patients included the Scale for the Assessment and Rating of Ataxia (SARA) and measurement of CAG repeat length.

Results: Compared to controls, SCA2 patients exhibited significantly prolonged mean latencies for both the N140 and N20 components. While the mean amplitude of the N20 was significantly reduced in patients, the amplitude of the N140 did not differ between groups. Notably, both N140 and N20 latencies showed significant positive correlations with SARA scores. **Conclusion:** The N140 potential is a valuable complement to the N20 for evaluating somatosensory dysfunction in SCA2 for two reasons: (1) the relative ease of recording N140 presents a practical benefit, and (2) more importantly, N140 probe the function of higher-order cortical networks involved in the cognitive processing of somatosensory information—networks not assessed by N20. The prolonged N140 latency observed here likely reflects the defective thalamo-cortical and cerebello-cortical interactions that are characteristic of SCA2 pathology.

INTRODUCTION

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disorder resulting from a CAG trinucleotide repeat expansion within the *ATXN2* gene (1). Clinically, SCA2 manifests as a progressive cerebellar syndrome, characterized by ataxic gait, cerebellar dysarthria, dysmetria, and dysdiadochokinesia (2,3). Furthermore, over 90% of the patients exhibit slowing of saccadic eye movements, peripheral neuropathy, and cognitive deficits (4–7). Sensory abnormalities, including impaired proprioception, vibration sense, and tactile discrimination, are also prevalent in SCA2, attributable to degeneration of the posterior columns and peripheral sensory nerves (8,9). The quantification of these sensory deficits is essential for diagnostic confirmation and for monitoring disease progression in both clinical practice and research settings.

Electrophysiological assessments are instrumental in evaluating the involvement of both peripheral and central sensory pathways in SCA2. Nerve conduction studies (NCS) frequently reveal a sensory axonal neuropathy, characterized by reduced or absent sensory nerve action potentials (8). Concurrently, somatosensory evoked potentials (SEPs) demonstrate delayed central conduction, primarily attributable to dorsal column dysfunction (9–13). The evaluation of SEPs provides a non-invasive method for assessing sensory pathway integrity, enabling the detection of subclinical abnormalities, differentiation between peripheral and central involvement, monitoring of disease progression, and guidance of therapeutic interventions (2). Based on their latency, SEPs are classified into short-latency (SL-SEPs) and long-latency

components (LL-SEPs). SL-SEPs, which occur within 40 ms post-stimulation, are widely employed in clinical practice. In contrast, LL-SEPs, occurring after 40 ms, are primarily utilized in research settings (14,15). In the present study, the N20 and N140 components of the median nerve SEPs will be used as representatives of SL-SEPs and LL-SEPs, respectively.

Notwithstanding its established clinical utility, recording SL-SEPs is often technically challenging. These potentials constitute very low-amplitude responses (1–5 μV) embedded within background electroencephalographic (EEG) activity (14,16). Extracting them typically requires labor-intensive procedures, including the averaging of hundreds or thousands of stimuli, mitigation of electromagnetic interference, and the need for patients to remain virtually immobile for extended periods (17). The impact of these technical limitations is particularly pronounced in individuals with markedly attenuated SL-SEPs, such as patients with SCA2, in whom identifying reproducible waveforms is exceedingly difficult and responses are frequently reported as absent (9,18,19).

The analysis of certain long-latency SEP components, such as the N140, may mitigate these technical challenges. The N140 component exhibits a substantially larger amplitude (20–40 μV) compared to the N20 (2–4 μV) (14,20,21). N140 waveforms can be reliably identified with as few as 20–30 stimuli, demonstrate reduced vulnerability to interference, and can be elicited using various stimulus modalities (22). These characteristics suggest that, under specific conditions, LL-SEP components like the N140 are more readily recordable than their SL-SEP counterparts. This disparity is likely attributable to the distinct neuronal populations involved: LL-SEPs engage a large, distributed network across multiple brain regions, whereas SL-SEPs arise from a more circumscribed population primarily confined to the primary somatosensory cortex (20,23–26).

The N140 is a long-latency SEP component that peaks 120–140 milliseconds following stimulation of the cutaneous territory innervated by the median nerve. This component reflects higher-order processing of sensory input features (24) and is generated within a distributed network including the bilateral secondary somatosensory cortices (SII) (15,27), the frontal lobes (20), and the pre-central, posterior parietal, insular, cingulate, and temporal cortices (28–30). Additionally, subcortical structures such as the thalamus (31) and the cerebellum (32,33) may modulate N140 responses through recurrent interactions with somatosensory and association cortices.

The N140 potential has been extensively employed in experimental contexts to investigate cognitive functions, including stimulus detection (27,34), attention to somatosensory input (23,31,35–37), and pain processing (22,29,38,39). Its application in clinical research, while less frequent, has been explored in conditions such as major depressive disorder (40), Parkinson's disease (41), and stroke (42). Although recording N140 potentials involves minimal technical demands, it yields valuable insights into the central processing of complex sensory features. Such information may complement data obtained from SL-SEPs, thereby enhancing the comprehensive assessment of somatosensory function (21,25).

While SL-SEPs serve as robust biomarkers of structural sensory pathway integrity in SCA2, evaluating the N140 component may offer novel insights into the abnormalities of higher order cognitive processing of somatosensory information. This approach could help to support the hypothesis that SCA2 not only results in delayed sensory afference (prolonged N13-N20 interval) but also leads to a fundamental impairment in the

subsequent cortical cognitive integration of that sensory input, as reflected by abnormal N140 responses. Such a finding could help to establish a neurophysiological link between the wide spread brain and cerebellar degeneration and the cognitive dysfunction observed in this population, thereby enabling a more comprehensive assessment of patients' neurological status. The principal novelty of this study lies in its focus on the N140 component: whereas SL-SEPs have been extensively investigated in SCA2, this represents the first evaluation of N140 responses in this patient population.

Subjects and methods

Subjects: 28 individuals with genetically confirmed SCA2 and 34 healthy controls participated in the study. Patients were recruited from the outpatient clinics of the Cuban Institute of Neurology and Neurosurgery (INN) and the Centre for Research and Rehabilitation of Hereditary Ataxias (CIRAH) from Holguin City. Healthy controls were selected among the staff and accompanying persons to the patients.

To be eligible for inclusion, subjects had to be between 18 and 80 years of age, with at least one expanded *ATXN2* allele (≥ 32 CAG repeats), and present with a definite cerebellar syndrome as confirmed by a SARA score ≥ 3. Exclusion criteria included individuals unable to walk independently, those with chronic conditions impacting the nervous system, psychiatric disorders, pregnancy, chronic alcohol abuse, severe visual or hearing impairments and significant cognitive impairment and individuals taking medications with probable effects on the nervous system. Disease duration, the SARA scale scores (43,44) and the number or CAG repeats were quantified in the patients.

Ethical considerations: Written informed consent was obtained from all participants prior to inclusion to the study. The study received approval from the Ethics Committees of Scientific Research of the INN and the CIRAH and was carried out in compliance with the Declaration of Helsinki.

Short latency somatosensory evoked potentials (N20): SL-SEPs were recorded in a quiet and dark room, following standardized procedures (17), with the subjects lying on supine position. Only cortical components were analyzed. To record the N20 component, surface disk electrodes (10 mm in diameter) were attached to the scalp. The active electrode was placed at C3’ and Fz was used as a reference. Impedance was maintained at less than 5 Kohms. Signals were filtered with a bandwidth from 20-3000 Hz. The analysis time was set to 50 ms. The electrical stimulus was a constant current square wave pulse (duration: 0.2 ms), delivered transcutaneously to the right median nerve at the wrist with an intensity enough to produce a weak twitch of the median innervated muscles at the thenar eminence. Three replicas, each averaging 300 stimuli, were recorded and superimposed. The N20 component was visually identified. N20 peak latency and N20-P25 peak-peak amplitude were measured with cursors manually placed on the N20 and P25 components. The upper limit of normality of N20 latency was established as the mean+2SD from the healthy subjects.

Long latency somatosensory evoked potentials (N140): LL-SEPs were recorded also in a quiet and dark room with the subjects lying on supine position. Surface disk electrodes (10 mm in diameter) were attached to the scalp. The active electrode was placed at Cz. Linked earlobes (A1+A2) were used as a reference. Impedance was maintained at less than 5 Kohms. Signals were filtered with a bandwidth of 0,5-2000 Hz. The electrical stimulus was a constant current square wave pulse (duration: 0.5 ms). The stimuli were delivered

transcutaneously to the right index finger using conventional ring electrodes. The intensity of electrical stimulation was set from eight to ten times the threshold of sensory perception. In order to secure the stimulus salience necessary to elicit the N140 potential, single electrical pulses were delivered at long inter-stimulus intervals of 10 seconds. We used a deviant-alone paradigm of stimulation. Unlike the classical N140 oddball paradigm, in the deviant-alone paradigm all stimuli of the series had the same intensity and frequency and the subjects are not instructed to pay attention to the electrical stimulation. The analysis time was set to 500 ms with a negative delay of 100 ms. Three replicas, each averaging 30 stimuli, were recorded and superimposed. The N1 peak of the N140 component was defined as the main negative peak after the 120 ms. The P1 component was defined as the main positive deflection after the N1. Latency and peak-valley amplitude were measured with cursors manually placed on the visually identified N1/P1 components. The upper limit of normality of N140 latency was calculated as the mean+2SD from the values recorded in healthy subjects.

Molecular Assessment: The CAG-triplet repeats in the *ATXN2* gene were assessed by PCR amplification with the previously published oligonucleotide primers. Aliquots of the PCR products were sized by fragment analysis on an ALF Express II apparatus (Amersham Biosciences, Sweden) in comparison to internal and external size markers using Allele Links 1.0 software (Amersham Biosciences, Sweden). Quantification of CAG repeats was only available for 16 of the 28 cases; however, PCR analysis confirmed the expansion in the remaining cases where the repeat number could not be determined

Statistical analysis: Means, standard deviations and ranges were calculated for demographic, clinical and molecular variables. Normality of the distribution of quantitative variables was assessed by the Kolmogorov-Smirnov test. T-test was used to compare the latencies of LL-SEPs and SL-SEPs recorded in patients vs. healthy controls. To facilitate intergroup comparisons, the amplitudes of LL-SEPs and SL-SEPs responses was transformed to logarithmic units. The Manh-Withney test was used to compare the amplitudes of LL-SEPs and SL-SEPs recorded in patients vs. healthy controls. Multivariate statistical tests were used additionally to quantify the size and interactions of the effects in the intergroup comparisons. Pearson coefficient was used to evaluate the possible lineal correlation between SARA scores and CAG length repeats and the latencies of the electrophysiological responses. A P value less than 0.05 was considered significant.

Results

Clinical examination: All patients showed a cerebellar syndrome characterized by ataxic gait, cerebellar dysarthria, dysmethria, dysdiadochokinesia, abnormal tandem stance, slow saccadic eye movements and limited voluntary ocular movements. Facial atrophy, reduced or absent vibration sense and deep tendon reflexes, abnormal swallowing, cognitive disorders, peripheral neuropathy and autonomic disorders were also present in most patients. Table 1 summarizes the main clinical and electrophysiologic results of SEPs in each patient. Table 2 describes the average values of the main demographic, clinical, and molecular features of both groups. Patients were significantly older than normal controls ($p<0.05$) which prompted the development of additional multivariate statistical tests to ascertain the possible effects of age on the intergroup comparisons. Both groups had a similar gender distribution. It was not possible to retrieve data for the variables disease duration, SARA scores and number of CAG repeat from all the patients.

Electrophysiological data: SL-SEPs waveforms were well delineated and reproducible in normal subjects but were either absent (32.2%) or very difficult to identify in the SCA2 patients, due to considerably reduced amplitude and increased temporal dispersion of the N20 potential (table 1, Fig. 1A). Easily identifiable and very reproducible N140 waveforms were also recorded in all normal controls and in 96% of the patients (table 1, Fig. 1B).

Patients showed significantly increased latency of the N20 component, as compared to controls (21.5±1.2 vs. 18.6±1.7; p= 0.000) with an effect of F: 19.6 (p= 0.000). The mean N20 latency of the patients was increased 22.5% compared to normal controls. Both groups have a different distribution of the N20 latencies with most controls clustered around the mean value of 18 ms whereas half of the patients showed N20 latencies above 21 ms. (Fig. 2A). The upper limit of normality calculated for normal controls (mean + 2 SD) was 22 ms. According to this cutoff value, 63.3 % of the patients and 9% of controls presented abnormal N20 latencies (Fig. 2A).

On the other hand, patients with SCA2 showed also a mean N140 latency significantly increased as compared to normal controls (t-tests: 166.7±18.5 vs. 136±14.9 ms; p= 0.000). Multivariate analysis of variance showed significant effects for the factor group (F: 14.4, p= 0.000) and for the group-age interaction (F: 2427.4, p= 0.0001) but not for age (F: 2.106, p= 0.10). The mean N140 latency of the patients was increased 15.5 % compared to normal controls. Both groups have a different distribution of the N140 latencies. Most controls were clustered around the mean value of 140 ms while the patients presented an asymmetric and dispersed distribution with most individuals showing latencies between 150 and 190 ms. Considering an upper limit of normality for controls (mean + 2 SD) of 166 ms, 58.33% of the patients and 5% of the controls had abnormal N140 latencies (Fig. 2B).

The difference between short and long latency components latencies (N140– N20) was significantly higher in the patients compared to controls (141.1 ± 22.9 ms vs. 112.9 ± 10.5 ms; p= 0.001) which represents that the N20-140 interval is increased 24% in the patients compared to controls.

In relation to SEPs amplitudes, the pattern of abnormalities found in the patients was different for short and long latency components: patients with SCA2 showed significantly reduced N20 mean amplitudes (Fig. 3A) as compared to normal controls (1.5± 1.0 uV vs. 3.08±1.8 uV.; p= 0.01) with a significant but modest effect of F:5.74 (p= 0.02) whereas the amplitudes of N140 (Fig. 3B) were similar for both groups (21.5±12.8 μv. vs. 21.6± 15.07; p= 0.8) with a non-significant effect of F: 0.07 (p= 0.78).

-insert Fig. 3 about here-

In order to increase the power of statistical tests to identify differences between patients and controls in N20 and N140 amplitudes, a logarithmic transformation was applied to SEPs amplitudes. After this normalization, the N20 amplitude remained significantly reduced in the group of patients (0.98±0.5 μv. vs. 0.3±0.5; p= 0.009) while the N140 amplitudes persisted not significantly different between groups (2.90±0.6 μv. vs. 2.8±0.5; p= 0.9).

Table 3 shows the correlations between the clinical variables related to SCA2 and the electrophysiological variables. The SARA scores showed a positive correlation with the N140 latency and a negative correlation

with the N20 amplitude. The CAG length had a trend to a positive correlation with the N20 latency and a negative correlation with the N20 amplitude. Similarly, there was also a trend towards a positive correlation between the duration of SCA2 disease and the N20 latency. In addition, a significant positive correlation was found between age and N140 latency in normal controls (r= 0,65; p= 0,030) but not for SCA2 patients (r= -0,03; p= 0,9) (fig. 4)

Discussion

The present study demonstrates that somatosensory evoked potentials (SEPs) are severely affected in patients with SCA2, revealing a distinctive pattern of abnormalities between early and late components. While latencies were increased for both components, amplitudes were markedly reduced for N20 but strikingly preserved for N140. This dissociation provides novel insights into the pathophysiology of sensory dysfunction in SCA2.

Short-Latency SEPs: Confirmation of Previous Findings

Our results regarding SL-SEPs are consistent with the existing literature on hereditary ataxias. Previous studies have documented increased central conduction times and prolonged N20 latencies in patients with various spinocerebellar ataxia subtypes (2,18,45–47). Pedersen and Trojaborg reported increased central conduction time (N14-N20) in half of patients with hereditary cerebellar ataxias, with relative preservation of peripheral conduction (45). Subsequent studies have corroborated these findings: Nuwer et al. observed symmetric N20 latency abnormalities in three of five patients with dominant olivopontocerebellar ataxia (18), while Nousiainen et al. described increased N19 latencies in nine of ten patients with late-onset ataxia (46). Abele et al. found delayed or absent SEPs in the majority of spinocerebellar ataxia patients, with no significant differences across types 1, 2, and 3 (2). Perreti et al. further demonstrated abnormal responses in 20% of median nerve and 87.5% of tibial nerve SEPs (47).

In a large cohort study including 82 patients with SCA2 and 62 pre-symptomatics, Velazquez-Perez et al. evidenced either increased P40 latencies (60.98%) or absent P40 waves in the patients with SCA2 (19). A progressive course of SEPs abnormalities, from subclinical to advanced clinical stages of SCA2 disease have been documented in several studies (19,48,49). Visual (50), auditory (51) and motor (52) evoked potentials are also affected in patients with SCA2.

The increased SL-SEPs latencies observed in SCA2 may result from demyelination, dispersion or reduced efficiency of impulse conduction along the somatosensory pathway. Although SL-SEPs data alone are insufficient to identify the exact anatomical site of conduction disturbance (53), converging evidence from nerve conduction studies (8,9,49) and postmortem examinations indicates that these abnormalities arise from a combination of peripheral and central lesions, including involvement of sensory nerves, dorsal roots, posterior columns, brainstem, and thalamic nuclei (11,54–57).

Long-Latency SEPs: Novel Findings and Pathophysiological Implications

SL-SEPs are exquisitely sensitive to the integrity of the lemniscal pathway up to primary somatosensory cortex (S1), but are largely insensitive to the subsequent, complex cortical processing that is profoundly disrupted in cerebellar ataxias (18,32,58). On the other hand, the N140 is considered a marker of sensory integration, attention, and cognitive processing of the stimulus which is generated in a distributed network involving the secondary somatosensory cortex (S2), posterior parietal cortex, and possibly the cingulate cortex, and is heavily modulated by thalamocortical circuits, cortico-cortical connections and cerebellar influences (31,59–63).

This study provides the first evidence of a distinctive pattern of N140 abnormalities in SCA2, characterized by significantly increased latencies in the majority of patients alongside a surprising preservation of amplitudes. This finding aligns with previous reports of impaired cognitive evoked potentials, such as the P300, in SCA2, which have been shown to correlate with disease severity and duration (7,9,64,65). The N140 can be conceptualized as a somatosensory analogue to the P300, reflecting higher-order cognitive processing of sensory input.

Critically, the preservation of N140 amplitudes distinguishes our findings from those reported for the P300 potential, which typically shows amplitude reduction in SCA2. This discrepancy may be attributable to methodological differences, particularly the absence of a classical oddball paradigm for N140 elicitation in the present study (34).

The N140 is generated within a distributed cortical network encompassing the secondary somatosensory cortex (SII), posterior parietal cortex, insula, cingulate, and frontal regions (15,20,27–30). Its modulation depends critically on intact cerebello-thalamo-cortical circuits (31,66,67). The thalamus, a major hub affected in SCA2 (11,54), represents a key node where cerebellar output influences cortical processing. Thus, thalamocortical pathology in SCA2 is expected to directly disrupt N140 generation, providing a physiological correlate of higher-order sensory and cognitive dysfunction.

Possible Influence of the SCA2 Cerebellar Dysfunction on N140 Abnormalities

The cerebellum's role in N140 modulation has been elegantly demonstrated through experimental paradigms. Transient inhibition of cerebellar activity using transcranial theta burst stimulation reduces N140 amplitude in healthy subjects (33). Furthermore, patients with cerebellar lesions exhibit abnormal middle-latency SEP components in the N140 range, specifically showing a lack of normal inhibitory modulation—indicating disrupted cerebellar filtering of sensory inflow to higher-order cortices (68). Molinari et al. proposed that the cerebellum acts as a "predictive state estimator," with its output being necessary for the efficient operation of cortical networks responsible for higher-order sensory potentials like the N140 (67). Consequently, delayed N140 responses in SCA2 may indicate not only thalamocortical dysfunction but also a direct electrophysiological signature of failed cerebellar modulatory influence on the cerebral cortex.

Cerebellar dysfunction is one of the hallmarks of SCA2. The N140 abnormalities observed in this study could be partially attributed to disrupted cerebellar modulation of attention to somatosensory signals. Patients with cerebellar lesions frequently present also with affective disturbances—including apathy, depression, disinhibition, and impaired emotional recognition (65, 69)—collectively referred to as the cerebellar cognitive affective syndrome (CCAS) (69, 70). These deficits have been linked to degeneration within specific cerebro-

cerebellar circuits, particularly those involving the posterior cerebellar vermis and fastigial nucleus. These structures are key nodes of the "limbic cerebellum" and connect to paralimbic and association cortices (70, 71).

Under normal conditions, these circuits coordinate the integration of sensory stimuli with emotional salience, attentional resources, and social-emotional context (63, 72) which are crucial to N140 integration. In patients with SCA2, degeneration of these cerebellar nodes may desynchronize the same networks responsible for both generating a coherent N140 response and producing appropriate affective responses.

The delayed N140 latency is also congruent with the severe slowing of cognitive processing observed in patients with SCA2 (65). This cognitive slowing, one of the earliest and most disabling non-motor symptoms detectable even in patients with mild ataxia (64), likely results from disruption of the cerebellum's role in coordinating the temporal dynamics of cognition. Further investigations are necessary to evaluate the exact relationship between N140, cognition and cerebellar dysfunction.

Is N140 Delay Merely a Reflection of N20 Delay?

Given that the N140 component appears after the N20 potential, it is essential to determine whether the increased N140 latency merely reflects the primary delay at the N20 level. Our finding that patients showed similar percentages of latency increment for the N20 (22.5%), the N140 (15.5%), and the N20-N140 interval (24.5%) suggests a dual mechanism: a primary delay in conduction from peripheral receptors to the primary somatosensory cortex, and an additional secondary delay in the activation of neuronal networks subserving cognitive processing. with both contributions being of similar magnitude. Therefore, it is not likely that increased N140 latency merely reflects the primary delay at the N20 level but a combination of peripheral and central disorders of somatosensory function.

The Preservation of LL-SEPs Amplitudes: A Key Observation

The pattern of delayed N140 latencies with concomitant preservation of N40 amplitudes, in patients with SCA2 represents one of the most intriguing findings of this investigation. This pattern suggests a predominance of "dyssynchrony" over "degeneration" in the underlying pathology—at least in early to mid-stage disease. This interpretation suggests that the motor symptom of dysmetria and its cognitive counterpart, dyschronometria, may share a common electrophysiological mechanism in patients with SCA2.

Additionally, the preservation of LL-SEPs amplitudes may be attributable to intrinsic features of the distributed network underlying N140 responses. This network involves a large neuronal population with polysynaptic circuits, substantial divergence, and signal amplification, such that even a reduced input can activate the entire network (20,26,27,37). In contrast, the neuronal circuits mediating SL-SEPs generation are finely tuned for spatial localization, with minimal divergence to preserve transmission fidelity, resulting in activation of a relatively small neuronal population (24,25,30). These fundamental differences explain why N140 can be recorded even in patients with very abnormal N20. Future studies using longitudinal imaging or neuropathological data should be needed to confirm this electrophysiological hypothesis.

N140 as a Complement to N20: Advantages and Limitations

This investigation demonstrates that N140 serve as an excellent complement to N20 in evaluating somatosensory pathway function in SCA2. N140 offer substantially higher amplitudes, require fewer stimuli, show reduced vulnerability to interference, and can be elicited with a wide variety of stimulus modalities (light touch, vibration, heat, cold). Furthermore, N140 assess higher-order processing of somatosensory information—a dimension not captured by SL-SEPs (22,23).

However, N140 also have important limitations. While highly sensitive, they are relatively nonspecific regarding the anatomical level of dysfunction. Abnormal N140 latencies may result from peripheral lesions, central lesions at various levels, or—most likely—a combination of both.

Correlations with Clinical and Molecular Parameters

The positive correlation between SARA scores and N140 latency—but not N140 amplitude—is consistent with the group comparisons showing preserved amplitudes but delayed latencies in patients. This finding suggests that N140 latency could represent a sensitive and objective marker for monitoring clinical progression of ataxia, the hallmark of cerebellar degeneration in SCA2 (3,6). The documented recovery of N140 responses after stroke rehabilitation further suggests that this potential could also serve as an electrophysiological marker of functional improvement in interventional trials (73).

The lack of correlation between N140 amplitude and SARA scores, disease duration, or CAG repeat length confirms the robustness of this potential, which remains relatively preserved—albeit delayed—from early to advanced disease stages. This should be interpreted as an advantage, as the N140 can often be identified, albeit delayed, when other SEP components are absent.

In contrast to the N140, the correlations for N20 revealed a different pattern, with N20 amplitude—rather than latency—showing a positive association with SARA scores. The positive correlation between SARA scores and N20 amplitude—but not N20 latency—suggests that amplitude may be a better marker of disease progression than latency for this particular SEP component. This finding likely reflects the high percentage of absent N20 responses, even at early disease stages; once the response is absent, latency can no longer be quantified. Previous studies have extensively documented correlations between N20 parameters and SARA scores, proposing central conduction time as a sensitive, quantitative biomarker for tracking clinical progression in SCA2 (74–77).

The correlation between SL-SEPs and SARA scores in patients with SCA2 has been extensively studied substantiating that as clinical ataxia worsens SEPs abnormalities such as prolonged latencies, reduced amplitudes of cortical potentials (N20, P40) and increased percentage of absent cortical responses become more pronounced. Therefore, SEPs parameters, especially central conduction time, are proposed as sensitive, quantitative, and objective electrophysiological biomarkers that track clinical progression in SCA2 (74–77).

Previous studies have reported a positive correlation between SL-SEPs central conduction times and disease duration, which is usually of lower magnitude than the very strong SEPs-SARA correlations (12,75,78–83). However, in the present investigation, we found no significant correlation between SL-SEPs data and disease duration.

The absence of significant correlations between electrophysiological parameters and disease duration or CAG repeat length in our study contrasts with some previous reports (12,75,79,84) but aligns with others (19,46,60). Several studies have documented important disagreements regarding these correlations, which may be attributable to heterogeneity in biological and technical factors influencing data collection, processing, and interpretation. Our specific findings may also reflect the narrow distribution of CAG repeat length (SD: 2.6) and disease duration (SD: 4.8 years) in our sample, which may have reduced statistical power to detect correlations between these variables.

Study Limitations

This study has several limitations. First, it was not possible to evaluate SL-SEPs and determine CAG repeat length in all patients with SCA2. Nonetheless, despite the reduced sample size for these specific analyses, significant differences between patients and controls were still detectable. Second, complete age-matching between patients and controls was not achieved. However, two observations suggest that this age mismatch had minimal influence on our results: 1) the lack of significant age effects in intergroup statistical tests, and 2) the divergent pattern of age-N140 latency correlations between patients and controls (Fig. 4), suggesting that patient abnormalities are independent of age.

Conclusion or summary

Our study demonstrates that N140 is an excellent complement to N20 in the evaluation of somatosensory function. N140 have two main advantages over N20: 1- Allows the evaluation of the attentional processing of somatosensory inputs which is not possible with N20. 2- Are technically easier to record than N20 which facilitates the recording of somatosensory cortical responses in adverse conditions such as advanced disease or several technical challenges. These advantages would be particularly important in the context of clinical trials.

Declarations

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Authors' contributions:

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Data collection: R.P.L., R.T.V., Y.V.M., N.S.V., Z.L., M.F, B.A.H., Y.N.

Data analysis: J.G., R.P.L., R.T.V., B.A.H., R.R.L, and L.V.P.

Data interpretation: J.G., R.P.L., R.T.V., B.A.H., R.R.L, and L.V.P.

Writing-original draft: J.G., R.P.L., R.T.V, R.R.L. and L.V.P.

Writing-review & editing: All authors reviewed the manuscript

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Data sharing statement: All data supporting the findings of this study are available within the paper and its Supplementary Information

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Tables

Table 1: Clinical and electrophysiological results of each patient

Patient	Age	Gender	Time of evolution	# CAG repeats	SARA scores	N20 response	N20 results	N140 response	N140 results
1	51	M	-	-	-	R	N	R	N
2	45	M	19	43.0	16	R	A	NR	NR
3	64	F	7	35.0	9	R	A	R	A
4	52	M	-	-	-	R	A	R	N
5	31	M	-	-	-	NR	NR	NR	NR
6	60	M	18	38.0	10	NR	NR	NR	NR
7	51	M	18		11	NR	NR	NR	NR
8	51	F	12	39.0	14	R	A	R	A
9	51	F	13	35.0	12	R	A	R	A
10	53	F	18	39.0	12	R	N	R	N
11	43	M	20	39.0	14	R	A	R	A
12	38	M	16	45.0	14	R	A	R	A
13	58	F	-	-	-	NR	NR	R	N
14	60	M	-	-	-	R	N	R	N
15	46	F	16	41.0	9	NR	NR	R	A
16	43	F	11	-	-	R	N	R	N
17	61	F	-	38	13	NP	NP	R	A
18	76	F	-	-	-	NP	NP	R	A
19	55	M	19	39	15	NP	NP	R	N
20	74	M	-	-	10	NP	NP	R	N
21	63	M	12	41	12	NP	NP	R	A
22	72	M	-	-	11	NP	NP	R	A
23	36	M	-	-	7	NP	NP	R	N
24	49	F	-	-	14	NP	NP	R	A
25	44	F	15	37	16	NP	NP	R	A
26	27	M	-	-	8	NP	NP	R	N
27	62	F	16	37	12	NP	NP	R	A
28	46	M	12	39	13	NP	NP	R	A

R: Response, NR: No response, N: Normal, A: Abnormal, NP: Not performed, - Not available

Table 2: Summary of the main demographic, clinical, and molecular features of normal controls and patients with SCA2

	Controls	Patients
# of subjects	**34**	**28**
Age (years, mean±SD)	**39±12.05**	**52,2±12.1**
Female (N; %)	**14; 41.17**	**6; 40,0**
Evolution (years)		**14,4± 4,8**
SARA scores		**12,10± 2,4**
# CAG repeats		**39,3± 2,6**

Table 3: Correlations between the clinical and the electrophysiological variables related to N140 and N20 potentials. Each cell contains: Pearson coefficient; P values.

	N140 Latency	N140 Amplitude	N20 Latency	N20 Amplitude
SARA scores	0,5; p= 0,02	0,03; p= 0,8	0,43; p= 0,3	- 0,74; p= 0,05
CAG length	- 0,30; p= 0,3	- 0,33; p= 0,2	0,74; p = 0,08	- 0,70; p = 0,07
Disease duration	- 0,39; p= 0,2	- 0,02; p= 0,9	0,37; p= 0,3	- 0,62; p= 0,09

Figures

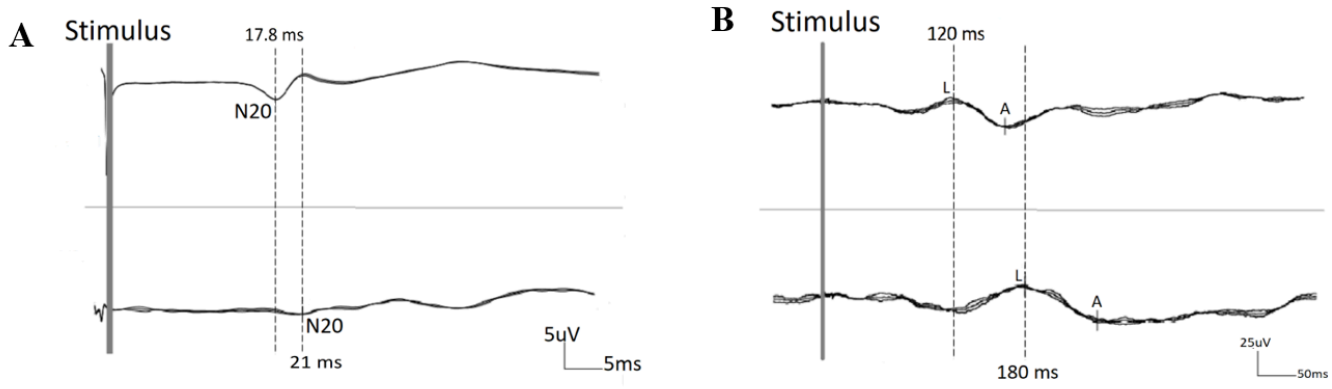


Figure 1

Recordings of SL-SEPs (N20) (**A**) and lL-SEPs (N140) (**B**) in normal controls (upper traces) vs. patients with SCA2 (lower traces). N140 and N20 latencies are both increased in the patients. N20 amplitude is reduced and dispersed, however N140 amplitude is preserved.

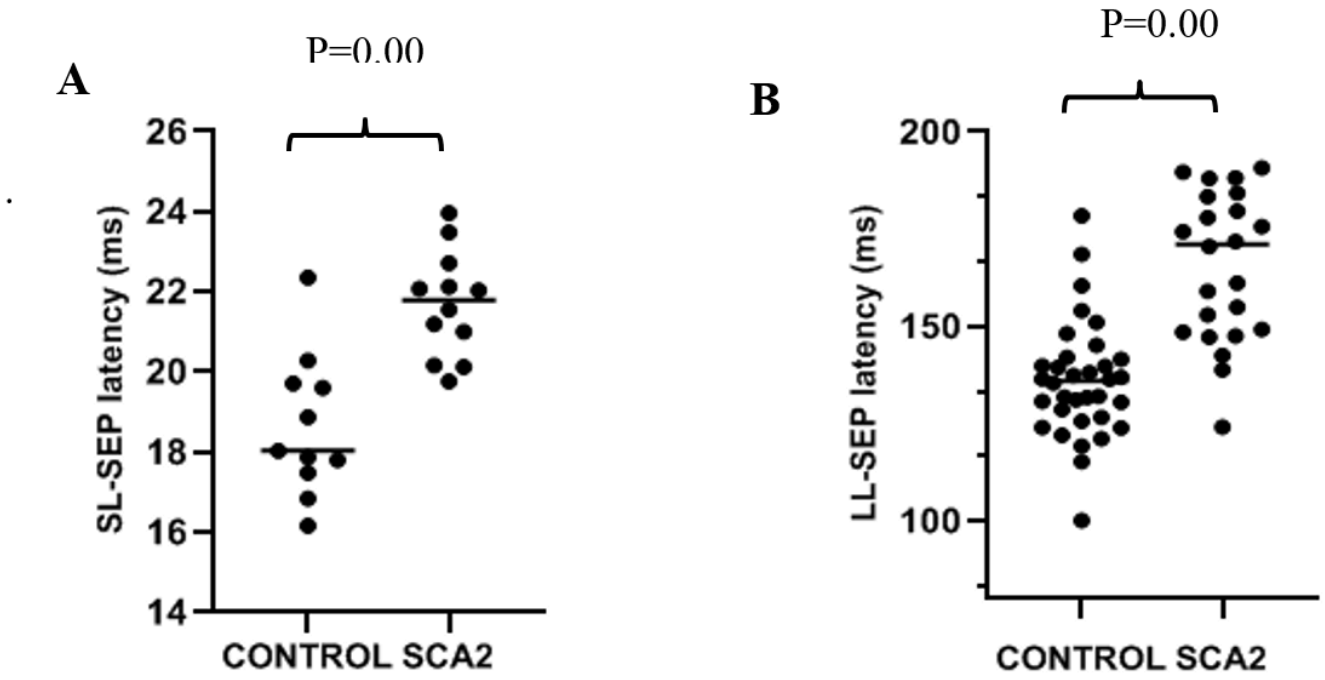


Figure 2

Comparison of latencies of SL-SEPs (N20) (**A**) and LL-SEPs (N140) (**B**) responses in controls vs. SCA2 patients. N140 and N20 latencies are both significantly increased in SCA2

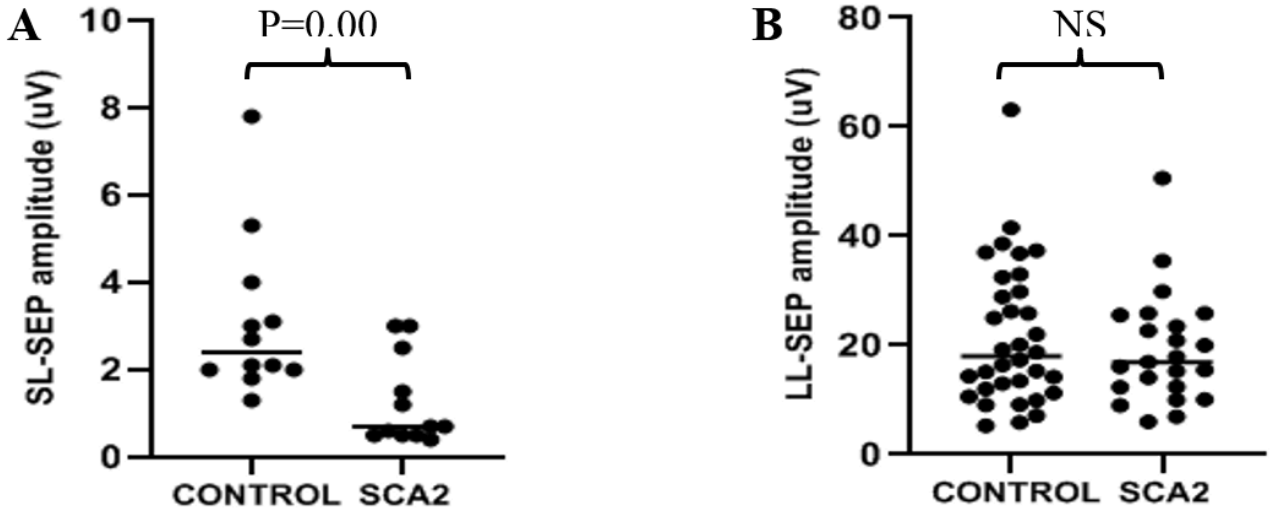


Figure 3

Comparison of amplitudes of SL-SEPs (N20) (A) and LL-SEPs (N140) (B) responses in patients with SCA2 vs. controls. Note that N20 amplitudes are significantly reduced while N140 have preserved amplitudes, with a similar distribution for patients and controls.

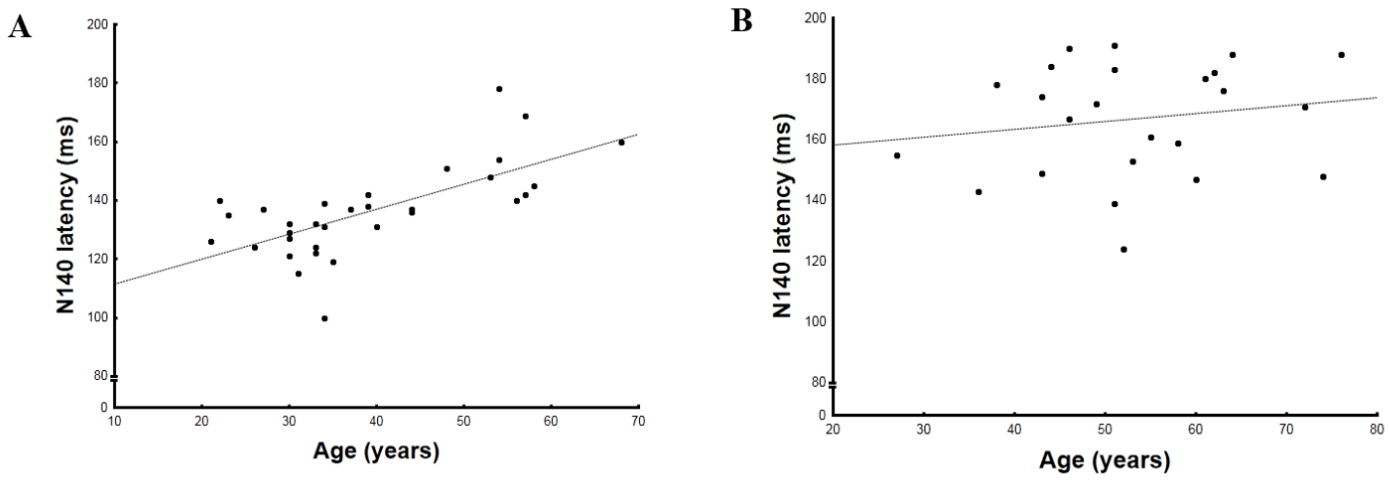


Figure 4

Correlations between age and N140 latency in both research groups. Normal controls (A) have a direct and significant correlation between both parameters which is lost in patients with SCA2 (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryDataN140SCA2JoelGutirrez.xlsx