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ORIGINAL ARTICLE

Significance and clinical suggestions for the somatosensory evoked potentials increased in amplitude revealed by a large sample of neurological patients

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Abstract

Objectives To investigate the relationship between N20-P25 peak-to-peak amplitude (N20p-P25p) of somatosensory evoked potentials (SEPs) and the occurrence of abnormalities of the peripheral and/or central sensory pathways and of myoclonus/epilepsy, in 308 patients with increased SEPs amplitude from upper limb stimulation.

Methods We compared cortical response (N20p-P25p) in different groups of patients identified by demographic, clinical, and neurophysiological factors and performed a cluster analysis for classifying the natural occurrence of subgroups of patients.

Results No significant differences of N20p-P25p were found among different age-dependent groups, and in patients with or without PNS/CNS abnormalities of sensory pathways, while myoclonic/epileptic patients showed higher N20p-P25p than other groups. Cluster analysis identified four clusters of patients including myoclonus/epilepsy, central sensory abnormalities, peripheral sensory abnormalities, and absence of myoclonus and sensory abnormalities.

Conclusions Increased N20p-P25p prompts different possible pathophysiological substrates: larger N20p-P25p in patients with cortical myoclonus and/or epilepsy is likely sustained by strong cortical hyperexcitability, while milder increase of N20p-P25p could be underpinned by plastic cortical changes following abnormalities of sensory pathways, or degenerative process involving the cortex. SEPs increased in amplitude cannot be considered an exclusive hallmark of myoclonus/epilepsy. Indeed, in several neurological disorders, it may represent a sign of adaptive, plastic, and/or degenerative cortical changes.

Keywords Somatosensory evoked potentials · Somatosensory cortex · Cortical hyperexcitability · Neurodegenerative diseases

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Introduction

The somatosensory evoked potentials (SEPs) are a well-established neurophysiological technique for the evaluation of the somatosensory pathways from the peripheral nerves to cortex [1]. Beside their role in the intensive care unit [2], SEPs are largely used in the diagnostic workup of the neurological diseases affecting the central nervous system (CNS)[1] and, albeit with some cautions, even in those affecting the peripheral nervous system (PNS), as a complementary tool to nerve conduction study (NCS), for assessing proximal tracts of PNS [3].

First described by Dowson [4], SEPs increased in amplitude, the so-called giant SEPs, have been usually related to cortical myoclonus and especially to progressive myoclonic epilepsies (PMEs) [5–7]. Among others, giant SEPs were reported in anoxic brain injury [8], epilepsy [9], Creutzfeldt-Jakob Disease (CJD)[10], and neuronal ceroid lipofuscinosis [11]; in this framework, our group contributed to clarify the relationship between cortical hyperexcitability, reflex myoclonus, and SEPS increased in amplitude [12, 13].

However, the finding of SEPS increased in amplitude without any evidence of myoclonus or epilepsy is not uncommon in the clinical practice, albeit "sporadic" in the literature, as reported by few studies focusing on multiple system atrophy (MSA) [14], progressive supranuclear palsy (PSP) [15], autosomal recessive cerebellar ataxia type 3 [16], amyotrophic lateral sclerosis (ALS), and motor neuron diseases (MND) [17]. In particular, two recent works [18, 19] reopened the debate on the SEPs increased in amplitude and their clinical significance: the vast majority [19] or all of the patients [18] included in these cohorts suffered from various non-epileptic and non-myoclonic disorders, therefore suggesting the absence of an exclusive association with a specific pathological condition.

However, the significance of high amplitude cortical SEPs and their relation with the presence of epileptic disorders or abnormalities of somatosensory pathways are not yet fully understood.

Hence, we retrospectively evaluated all the SEPs performed in a large cohort of adult patients in our laboratory in the last 2.5 years. Other variables included the diagnosis, the presence/absence of somatosensory abnormalities, and the presence/absence of myoclonus/epilepsy. Finally, we performed a cluster analysis to obtain a grouping of individuals based on their features.

Methods

Patients and data collection

We retrospectively evaluated all consecutive SEPs (2365) performed for diagnostic purposes in our laboratory at the Neurological Institute "Carlo Besta" of Milan, from 2019, January 1st, to 2021, June 30th.

We included all tests performed on subjects with age > 14 years who completed SEPs examination in standard laboratory setting. We excluded patients with impaired consciousness and/or in intensive care unit. We identified patients with early cortical response (N20p-P25p) exceeding 7.44 μV in at least one side for upper limb stimulation, i.e., the mean value + 3 standard deviations (SD) of our internal normative data for SEPs evoked from contralateral median nerve stimulation (normative value of N20p-P25p 4.26 ± 1.06 μV) [1, 25]. For patients who had multiple assessments, only the first was considered.

For all the patients included, we collected the following data: age, diagnosis and diagnostic group (see below), presence/absence of cortical myoclonus and/or epilepsy and of abnormalities of CNS/PNS sensory conduction, and N20p-P25p for both side of stimulation.

Diagnosis and diagnostic groups

All the patients were organized in 16 groups according to their neurological diagnosis (Table 1), i.e., autoimmune disorders affecting CNS as multiple sclerosis (MS); leukodystrophies; CNS tumors; vascular encephalopathies and strokes; cognitive disorders; epileptic and/or myoclonic syndromes; hereditary spastic paraplegias (HSP); motor neurone diseases (MND); myopathies and disorders of the neuromuscular junction; neuropathies; Parkinson disease (PD), parkinsonisms and related disorders; spino-cerebellar ataxias (SCA); and non-immunological and non-neoplastic myelopathies. Patients affected by a neurological disease not included in the previous lists were included in "other neurological diseases," patients with functional disorders. Patients without a definite diagnosis or with two or more neurological diseases/syndromes were included in "unknown/undetermined" diagnosis group.

Somatosensory evoked potentials

SEPs examination was performed according to the recommendations for the clinical use [1]. SEPs were elicited by stimulating the right and left median nerve at the wrist just above the motor threshold and recorded at the peripheral and cortical level using Ag–AgCl skin electrodes. Skin–electrode impedance was kept less than 5 KΩ. For the upper limbs, SEPs early cortical responses (N20 and P25) were recorded contralaterally to the side of median nerve stimulation on C3'/C4'-Fz, according to the positions of the standard 10–20 system. The value of the N20p-P25p for upper limbs SEPs was collected for the subsequent analysis. Data were collected with Nicolet EDX system, Natus Neurology, Middleton, WI, USA, at sampling frequency of 2 kHz and filtered in 5–2000 Hz band. See also Table 1SS in the supplementary files for the detailed SEPs recording parameters.

Table 1 Overview of the diagnosis for all patients and their inclusion into groups

Etiological group (*N* patients)	
Multiple sclerosis and other CNS autoimmune diseases (30)	Autoimmune encephalitis (2), autoimmune limbic encephalitis (1), Devic syndrome (2), RR-multiple sclerosis (16), PP-multiple sclerosis (1), SP- multiple sclerosis (1), myelitis (5), isolated optic neuritis (2)
Leucodistrophies (12)	Adrenomyeloneuropathy (2), Alexander disease (1), adrenoleucodystrophy (7), undertemined leucoencephalopaty (2)
CNS tumors (13)	Ependymoma (3), meningioma (3), metastasis (3), ependimoma (3), neurinoma (1)
CNS vascular diseases (7)	Vascular encephalopathy (ischemic) (3), lacunar stroke (ischemic) (2), hemorragic stroke (2)
Cognitive disorders (23)	Alzheimer disease and mixed dementia (3), Fahr syndrome (1), fronto-temporal dementia (5), idiopathic normal-pressure hydrocephalus (3), Lewy-body dementia (1), prion disease-CJD (8), prion disease-FFI (1), prion disease-GSS (1)
Epileptic and myoclonic syndromes (20)	15q11.2 duplication (1), Aicardi syndrome (1), neuronal ceroid lipofuscinosis-3 (1), progressive myoclonic epilepsy type 1 (2), Jeavons syndrome (1), juvenile myoclonic epilepsy (1), KCNA1 mutation (1), KCNA2 mutation (1), SCNA1 mutation (1), sialidosis (1), undetermined epileptic/ myoclonic syndrome (9)
Hereditary spastic paraplegia (10)	KIF1A-mutation (1), spastic paraplegia type-4 (2), spastic paraplegia type-5 (1), undetermined hereditary progressive paraparesis (6)
Motor neurone diseases (50)	Genetic forms of MND – ARGHX (1), genetic forms of MND – C9ORF72 (2), genetic forms of MND – OPTN (1), genetic forms of MND – RUNX2 (1), genetic forms of MND – SOD1 (2), genetic forms of MND – TARDBP (1), genetic forms of MND – UBQLN2 (1), sporadic-bulbar onset ALS (8), sporadic-limb onset ALS (24), post-polio syndrome (1), primary lateral sclerosis (7)
Myopathies (13)	Myotonic dystrophy type 1 (1), inclusion body myositis (1), myasthenia gravis (3), stiff-person syndrome (3), undetermined myopathy (5)
Neuropathies (18)	Brachial plexus neuritis (2), alcoholic neuropathy (1), anti-MAG peripheral neuropathy (1), diabetic neuropathy (2), hereditary sensory-motor neuropathy (2), MGUS-related neuropathy (1), amyloidosis (1), vincristine-induced peripheral neuropathy (1), small fiber neuropathy (1), postherpetic neuralgia (1), undetermined neuropathy (5)
Parkinson disease and parkinsonism (28)	Corticobasal degeneration (4), multiple system atrophy (14), Parkinson disease (3), progressive supranuclear palsy (4), vascular parkinsonism (2), undetermined parkinsonism (1)
Spinocerebellar ataxias (8)	Autosomal recessive cerebellar ataxia 2 (1), CANVAS (1), undetermined spino-cerebellar ataxia (6)
Myelopathies (32)	Chiari malformation type 1 (2), spinal arteriovenous fistula (2), discal herniation (cervical) (1), discal herniation (lumbar) (2), Hirayama disease (3), traumatic injury (2), spinal stenosis (20)
Other neurological diseases(20)	AMPPE (1), Bechet disease (1), dystonia (2), fibromyalgia (2), headache (4), neurosyphilis (1), combined sclerosis (carential) (3), paraneoplastic neurological syndromes (3), essential tremor (3)
Functional disorders (9)	
Unknown or undetermined etiology (15)	

Legend: *RR*, relapsing–remitting; *PP*, primary progressive; *SP*, secondary progressive; *CJD*, Creutzfeldt-Jakob disease; *FFI*, fatal familial insomnia; *GSS*, Gerstmann-Sträussler-Scheinker disease; *MND*, motor neuron disease; *ALS*, amyotrophic lateral sclerosis; *MGUS*, monoclonal gammopathy of undetermined significance; *CANVAS*, cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome; *AMPPE*, acute multifocal placoid pigment epitheliopathy

Two clinical neurophysiologists (DRS and DC) revised 308 SEPs and 201 NCS tests from as many patients in order to assess abnormalities of central and/or peripheral somatosensory system The raters independently evaluated SEPs and ENG, classifying them in a dichotomic way, i.e., presence or absence of CNS and/or PNS sensory abnormalities, respectively. In case of disagreement, they reviewed the examinations together, until a shared decision was reached.

Statistical analysis

We analyze difference of N20p-P25p amplitude with respect to age, gender and groups of patients with or without epilepsy/myoclonus, and CNS/PNS sensory pathway abnormalities using Kruskall-Wallis and Mann–Whitney *U* tests. To analyze difference of N20p-P25p related to age, we divided the sample in age-related quartiles. Patients without NCS data were excluded. However, we included all patients for the cluster analysis, assuming as normal those patients having normal peripheral response at the SEPs examination and no sensory symptoms or reduced sensation at neurological examination.

To obtain the natural occurrence of subgroups of patients, a two-step cluster analysis with Schwarz's Bayesian Criterion was conducted considering age, presence of epilepsy/myoclonus, presence of abnormalities in CNS and/or PNS pathways, and left and right SEP amplitudes. This is a hybrid approach to determine the

number of clusters based on a statistical measure of fit and to use both categorical and continuous variables at the same time. To verify whether the clusters were different from one another, we performed statistical analysis using Kruskall-Wallis and chi-square tests with the cluster group as between-subjects factor. All of the statistical analyses were carried out using Statistical Package for the Social Sciences software, version 27 (SPSS Inc., Chicago, IL, U.S.A); *p*-values of <0.05 were considered statistically significant.

Results

Characteristics of the sample and descriptive statistics

All the data are summarized in Table 2 and Figs. 1 and 2.

We identified 308 patients (123 males, mean age 55.2 years, range 14–91 years) with SEPs increased in amplitude. Mean N20p-P25p was 9.4 ± 3.3 and 9.5 ± 3.3 μV for left and right median nerve stimulation, respectively. A minority of them showed abnormalities of the CNS or PNS sensory pathways (39.6% and 16.6%, respectively). Epilepsy and/or myoclonus occurred only in the 13.0% of the patients.

MND represented the largest group of patients (15.9% of the total), followed by CNS autoimmune diseases (MS for the most) and patients with diseases affecting spinal cord (for both, 10.3% of the total), PD and parkinsonisms (9.1% of the total), cognitive disorders (7.5% of the total), epileptic and/or myoclonic patients (6.2% of the total), and patients affected by neuropathies (5.8% of the total). No other group reached 5% of the total. Patients with unknown/undetermined diagnosis were 4.9% of the total.

Statistical analysis

N20p-P25p was neither significantly different in presence of CNS alterations (left: $U = 6411$, $p = 0.779$; right: $U = 6492$,

Table 2 Data summary grouped by age-related quartiles and by etiological groups

	Number of patients	Age (years)	Sex (M/F)	N20p-P25p amplitude (μV)		Sensory CNS abnormalities (Y/N)	Sensory PNS abnormalities (Y/N/undetermined)	Presence of epilepsy and/or myoclonus (Y/N)
				Left	Right			
Age quartiles								
First	79	14–46	33/46	9.9 ± 4.3	9.8 ± 3.7	21/58	6/38/35	19/60
Second	72	47–59	29/43	8.6 ± 2.5	9.0 ± 2.6	23/49	10/33/29	8/64
Third	77	60–68	30/47	9.6 ± 3.0	9.3 ± 3.2	35/42	17/41/19	7/70
Fourth	80	69–91	31/49	9.4 ± 3.0	9.9 ± 3.6	42/38	19/37/24	6/74
	308	**14–91**	**123/185**	**9.4 ± 3.3**	**9.5 ± 3.3**	**122/186**	**52/151/105**	**40/268**
Etiological groups								
MS and autoimmune diseases	32	45.6 ± 17.9	6/26	9.1 ± 1.7	9.0 ± 3.2	18/14	1/4/27	2/30
Leucodistrophies	12	27.5 ± 18.8	9/3	9.8 ± 3.9	9.5 ± 2.5	8/4	2/10/0	4/8
CNS-tumors	10	57.4 ± 16.0	5/5	8.0 ± 2.5	8.3 ± 3.2	7/3	1/2/7	1/9
CNS-vascular	7	63.1 ± 16.6	2/5	9.7 ± 4.6	9.8 ± 1.2	4/3	0/1/6	0/7
Cognitive disorders	23	66.9 ± 9.0	10/13	9.1 ± 1.6	9.2 ± 2.3	6/17	1/8/14	10/13
Epilepsy/myoclonus	20	28.4 ± 19.4	8/12	13.9 ± 6.7	12.1 ± 5.6	4/16	3/6/11	20/0
HSP	10	43.7 ± 21.6	6/4	10.7 ± 4.1	8.9 ± 3.3	1/9	0/7/3	0/10
MND	49	62.4 ± 13.2	16/33	8.5 ± 2.0	8.7 ± 2.2	16/32	4/45/0	0/49
Myelopathies	13	56.2 ± 19.9	6/7	8.5 ± 1.4	9.1 ± 1.9	3/10	1/12/0	0/13
Neuropathies	18	62.3 ± 20.2	11/7	9.1 ± 2.2	9.5 ± 2.5	5/13	18/0/0	0/18
PD and parkinsonism	28	69.4 ± 8.1	11/17	9.8 ± 4.3	10.1 ± 3.3	11/17	4/15/9	2/26
SCA	8	60.0 ± 5.9	3/5	9.3 ± 1.6	7.9 ± 3.0	7/1	1/4/3	2/6
Spinal cord diseases	32	56.4 ± 18.9	13/19	9.4 ± 2.6	9.8 ± 4.1	17/15	10/14/8	1/31
Other neurological	22	53.0 ± 18.8	9/13	9.2 ± 2.5	9.3 ± 3.0	9/13	2/11/9	0/22
Functional disorders	9	54.3 ± 16.7	1/8	9.0 ± 3.7	11.6 ± 4.8	0/9	0/4/5	0/9
Unknown/undetermined	15	58.7 ± 17.6	7/8	9.2 ± 3.1	10.2 ± 3.6	5/10	3/3/9	0/15
	308	**55.3 ± 19.7**	**123/185**	**9.4 ± 3.3**	**9.5 ± 3.3**	**122/186**	**52/151/105**	**40/268**

Legend: *MS*, multiple sclerosis; *HSP*, hereditary spastic paraplegia; *MND*, motor neuron disease; *PD*, Parkinson disease; *SCA*, spino-cerebellar ataxias

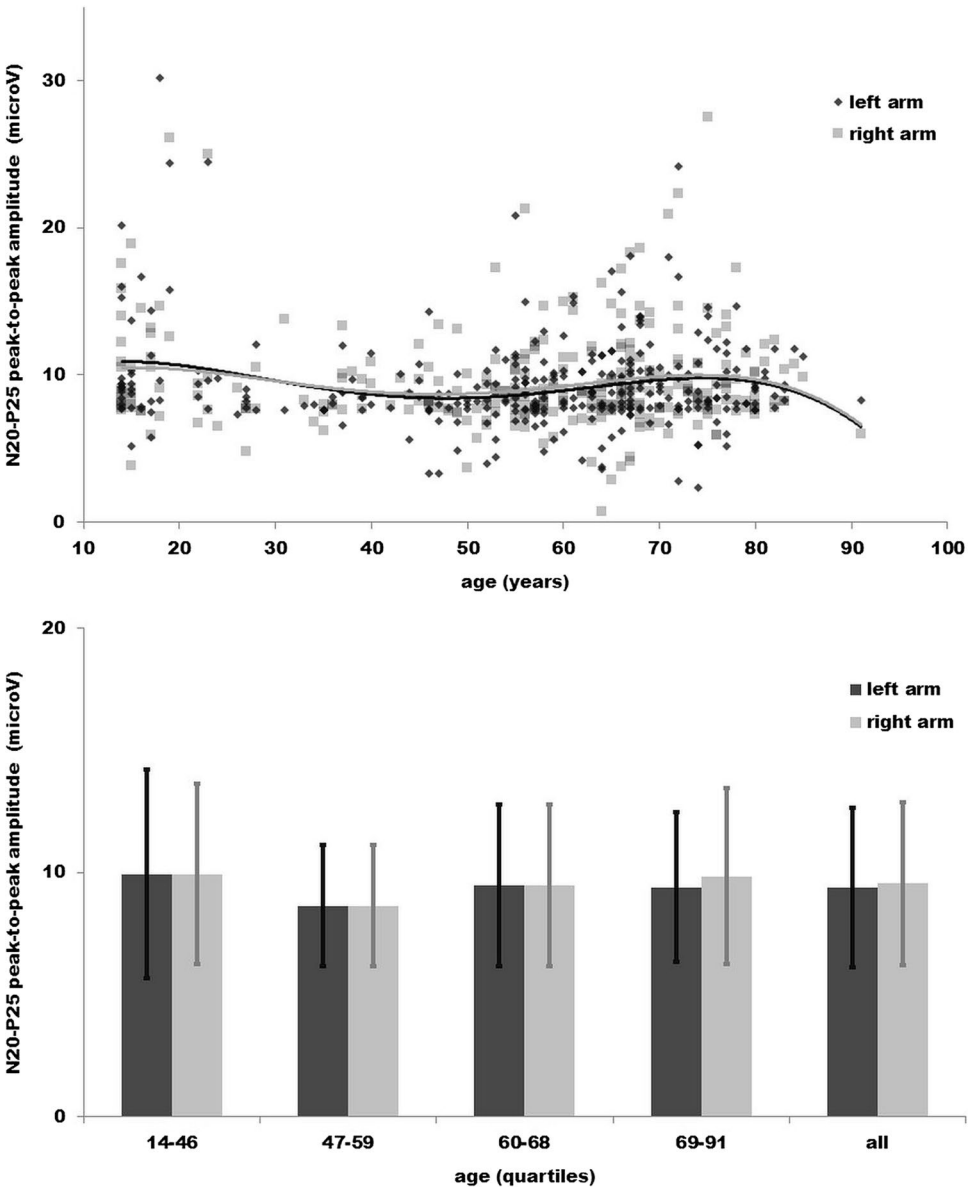

Fig. 1 In the upper part of the figure, single data of the N20p-P25p amplitude for the left and right median nerve stimulation related to the age of patients are represented as dark gray diamonds and light gray squares, respectively; in the same colors, in the lower part of the figure, the means and the standard deviations of the N20p-P25p amplitude for the left and right median nerve are grouped in four quartiles of age

$p = 0.676$) nor PNS alterations (left: $U = 11{,}083$, $p = 0.763$; right: $U = 10{,}338$, $p = 0.201$), while it was significantly higher in patients with epilepsy and/or myoclonus (left: 9.06 ± 2.73 µV vs. 11.81 ± 5.24 µV, $U = 3125$, $p < 0.001$; right: 9.28 ± 3.08 µV vs. 11.07 ± 4.29 µV, $U = 3731.5$, $p = 0.002$). See Table 2 for details.

The asymmetric distribution of the sample across ages caused different interval of ages for the quartiles: 14–46 ($N = 79$, 26.3 ± 11.7 years), 47–59 ($N = 72$, 54.2 ± 3.4 years), 60–68 ($N = 77$, 64.7 ± 2.5 years), and 69–91 ($N = 80$, 75.6 ± 4.6 years). No differences in N20p-P25p were found among quartiles (left: $H(3) = 5.92$, $p = 0.115$; right: $H(3) = 3.06$, $p = 0.383$, Table 2).

Excluding groups consisting of less than 10 subjects or with unknown etiology, a statistically significant difference in SEP amplitudes between the different etiology was found only for left side ($H(9) = 18.89$, $p = 0.026$). Post-hoc test revealed that patients with myoclonus or epilepsy had larger left N20p-P25p amplitudes with respect to all the other groups.

Clusters analysis

Data of cluster analysis are summarized in Table 3 and Fig. 3.

The two-step cluster analysis identified four clusters, with the ratio largest/smallest clusters 2.70 (124:46 patients). Patients included in the cluster #1 showed no abnormalities of CNS or PNS sensory pathways and absence of epilepsy and myoclonus. In cluster #2, most of the patients had epilepsy and/or myoclonus. All the patients included in cluster #3 showed PNS abnormalities of the sensory pathways; in cluster #4, all the patients showed abnormalities of CNS sensory pathways.

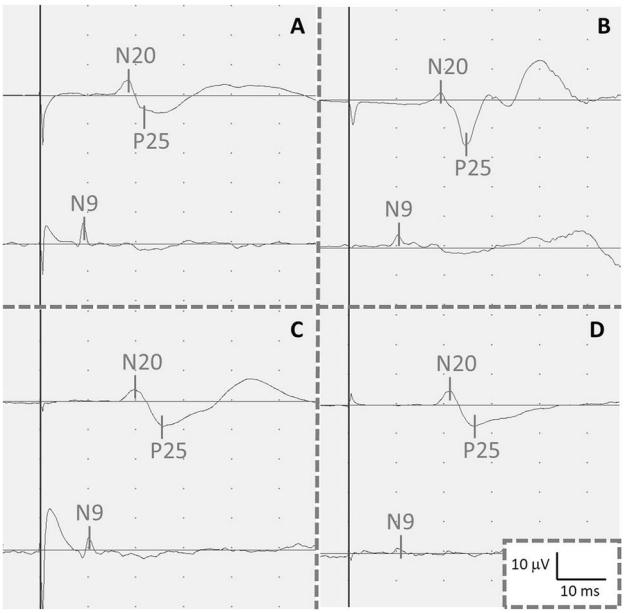

Fig. 2 Four examples of N20p-P25p increased in amplitude in four different patients with a **A** functional tremor (female, 55 years), **B** lumbar stenosis (female, 65 years), **C** remitting-relapsing MS (female, 22 years), **D** and diabetic neuropathy (male, 60 years). Data are related to the right nerve stimulation for all the patients; upper traces are related to cortical responses (recorded at C3'-Fz), and lower traces to peripheral responses (recorded at the right Erb's point)

Post-hoc tests revealed that the differences were significant for the following parameters: both clusters #1 and #2 had patients younger than #3 and #4; patients of cluster #2 had N20p-P25p higher than #1, #3, and #4, while there were no significant differences in the male/female ratio between the clusters. Moreover, clusters differed from each other for the presence/absence of CNS and PNS abnormalities, epilepsy and/or myoclonus, and for the composition of patients.

Discussion

Characteristics of the whole sample and statistical analysis

Demographic characteristics of our sample were comparable to similar studies [18, 19]; no significant differences of N20p-P25p related to age or sex and between patients with or without CNS or PNS sensory abnormalities were found.

In the literature, the term "SEPs increased in amplitude" and "giant SEPs" are indifferently used. Despite in former works reporting myoclonic patients, the term giant SEPs was restricted to a N20p-P25p reaching very high values (> 15 µV); [12, 13] in more recent ones [18, 19], the same nomenclature has also been adopted for much smaller SEP amplitude; in our study, we preferred to use the term "SEPs increased in amplitude," because we cannot propose a limit value to differentiate between the"increased" and the "giant" SEPs (even considering confounding factors which we could not disentangle retrospectively, such as the intake of antiepileptic drugs).

According to our interpretation of the cluster analysis, an enlarged N20p-P25p could be related to different pathophysiological conditions: a "strong" cortical hyperexcitability reflected in the very large amplitude of the cortical response in cortical myoclonus and epilepsy, as in patients of #2; a "mild" cortical hyperexcitability possibly resulting from degenerative processes involving cortex, as in patients of #1; or from plastic (maladaptive) cortical changes following PNS or CNS abnormalities of sensory pathways, as in patients of #3 or #4, respectively.

Patients included in #2 mainly had myoclonus and epilepsy and they had a significantly higher N20p-P25p with respect to patients included in other clusters, confirming that markedly large cortical response to somatosensory input is usually related to the presence of myoclonus/epilepsy. These patients have long been considered to have cortical hyperexcitability, as for PMEs and other myoclonic [6, 7, 15] or epileptic syndromes [12], prion diseases, [10] and some forms of parkinsonism with myoclonus [20]. In these patients, increased N20p-P25p is probably related to an abnormal response to the input occurring in the somatosensory and motor primary cortex due to their "intrinsic" hyperexcitability [21], further enhanced by a cortical-subcortical (thalamic) loop [22]. This pathophysiological aberrant circuitry is also involved in the genesis of the reflex cortical myoclonus [6, 7, 12, 22].

In patients included in #3 and #4, the increased N20p-P25p might be probably related to plastic changes in somatosensory cortex following modifications in the body representation, due to peripheral and/or central body-brain pathways abnormalities. As demonstrated in studies based on functional neuroimaging, a remapping of the cortical somatotopy is present in patients following limb amputation[23] or brachial plexus avulsion [24], in spinal cord injury [25], in MS [26], in stroke [27], and even in neuropathic painful syndromes [28]. The plastic changes to sensory deprivation, with deafferented areas replaced by neighboring representations, may result in a remodeling of the boundaries of the body map of the somatosensory cortex [25]. Some authors even stated that these plastic changes could be maladaptive [25, 29], thus contributing to secondary pathological conditions, such as hyperalgesia, allodynia, neuropathic pain, and phantom sensations [23]. To date, little is known about the link between enlarged N20p-P25p, (maladaptive) plastic changes after damage of the sensory pathways, and the occurrence of sensory symptoms. Interestingly, temporary deafferentiation determines increase of earlier components of SEPs, including N20 and P25 [30,

Table 3 Cluster analysis

		Cluster #1	Cluster #2	Cluster #3	Cluster #4	*p*	Post-hoc test
Number of patients		124	52	46	86		
Age (years)		52.3 ± 18.5	45.4 ± 24.4	64.6 ± 18.5	60.4 ± 17.0	$H(3) = 31.3$, $p < 0.001$	$p < 0.001$ between #1 and #3, #4; $p \leq 0.001$ between #2 and #3, #4
Gender (M/F)		40/84	20/32	25/21	38/48		
N20p-P25p amplitude (μV)	Left	8.5 ± 1.8	13.0 ± 5.3	9.1 ± 2.5	8.8 ± 2.2	$H(3) = 47.8$, $p < 0.001$	$p < 0.001$ between #2 and #1, #3, #4
	Right	9.2 ± 2.2	12.5 ± 5.2	9.3 ± 2.7	8.4 ± 2.4	$H(3) = 31.0$, $p < 0.001$	$p < 0.001$ between #2 and #1, #3, #4
PNS abnormalities (Y/N)		0/124	6/46	46/0	0/86	$\chi^2(3308) = 270.2$, $p < 0.001$	
CNS abnormalities (Y/N)		0/124	14/38	21/25	86/0	$\chi^2(3308) = 217.3$, $p < 0.001$	
Presence of seizures/myoclonus (Y/N)		0/124	40/12	0/46	0/86	$\chi^2(3308) = 226.3$, $p < 0.001$	
Number of patients per etiological group							
MS and autoimmune diseases		12	3	1	16	$\chi^2(45,308) = 293.9$, $p < 0.001$	
Leucodistrophies		2	5	1	4		
CNS-tumors		2	0	1	7		
CNS-vascular		2	1	0	4		
Cognitive disorders		8	10	0	5		
Epilepsy/myoclonus		0	20	0	0		
HSP		6	3	0	1		
MND		30	0	4	15		
Myopathies		10	0	1	2		
Neuropathies		0	0	18	0		
PD and parkinsonism		13	4	4	7		
SCA		1	1	2	4		
Myelopathies		11	3	10	8		
Other neurological		11	0	2	9		
Functional disorders		8	1	0	0		
Unknown/undetermined		8	1	2	4		

Legend: *MS*, multiple sclerosis; *HSP*, hereditary spastic paraplegia; *MND*, motor neuron disease; *PD*, Parkinson disease; *SCA*, spino-cerebellar ataxias

31]. Hence, we could speculate that the partial deafferentation of somatosensory cortex may result in a similar increase in the patients of clusters #3 and #4. Indeed, clusters #3 and #4 were populated by patients with neuropathies and with abnormalities of the ascending sensory pathways as myelopathies, MS, and SCA, respectively.

In cluster #1, no patients showed abnormalities of sensory pathways, myoclonus, or epilepsy. Hence, we may assume that in cluster #1, SEPs increased in amplitude were related to pathophysiological (degenerative?) changes occurring at the cortical or cortico-subcortical level, as for the patients with MND and parkinsonisms (including MSA, PSP) and with primary dementia. Few studies evaluated the presence of enlarged cortical response in the neurodegenerative diseases: in a study focused on SEPs in ALS, patients showed a larger N20p-P25p, with respect to the healthy subjects; moreover, median survival time after examination was shorter in the group of ALS with N20p-P25p greater than 8 μV [17]. This large N20p-P25p was interpreted as a sign of cortical hyperexcitability in the sensorimotor cortical areas in the first stages of ALS, due to the early loss of cortical interneurons, preceding the loss of the upper motor neuron. Again, early components of SEPs were found in PSP [15] and in MSA [14], probably reflecting a mild form of cortical hyperexcitability. To our knowledge, no other studies focused on SEPs increased in amplitude, even if it is well-known that unbalancing of the cortical excitability is present in dementia Alzheimer type, sporadic ALS, fronto-temporal dementia, PD and parkinsonisms [32], in MS [33], and in genetic form of ALS/FTD patients, [34] as demonstrated by means of transcranial magnetic stimulation. All together, these data support the hypothesis that an unbalance of cortical excitability is present in the early stages of some neurodegenerative diseases involving the sensorimotor areas of the cortex.

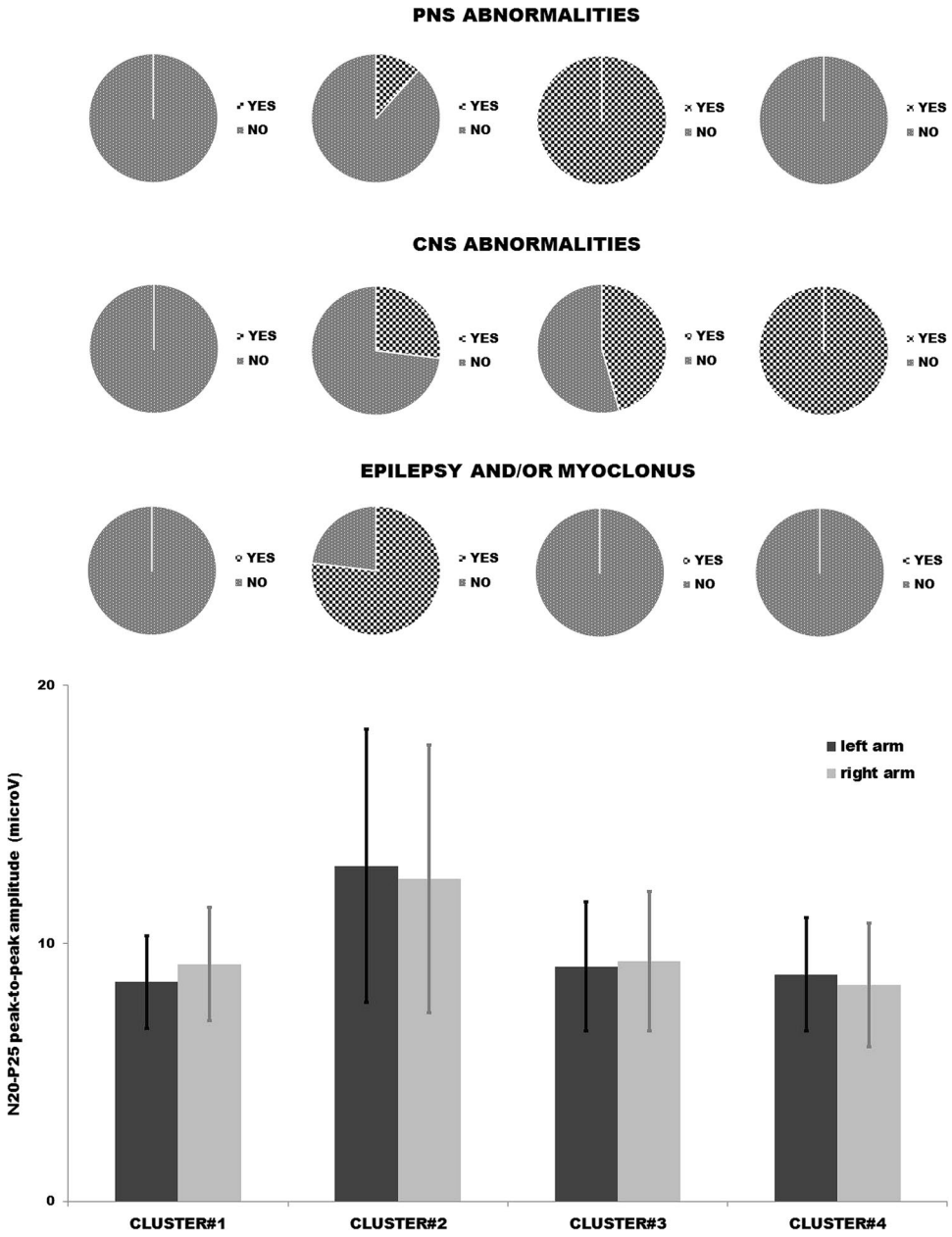

Fig. 3 The different features of the four groups identified by the cluster analysis are shown: for each cluster, the percentage of patients with PNS and CNS abnormalities of the sensory system and of patients with epilepsy/myoclonus is represented in the upper part of the figure, together with the means and the standard deviations of the N20p-P25p amplitude for the left and right median nerve stimulations in the lower one. Cluster #2 showed significantly higher N20p-P25p values with respect to other groups

Not all patients fully fit into our interpretative model; some patients in #2 showed neither myoclonus nor epilepsy: the inclusion in this cluster is probably due to the large N20p-P25p amplitude which has influenced the composition of #2. Then, sensory abnormalities in myopathies and in neuromuscular junction diseases are largely underestimated, even in neurophysiological examinations [35]. Hence, these myopathic patients probably showed increased N20p-P25p as a result of plastic changes related to sensory abnormalities, such as altered proprioception, due to the myopathy; their inclusion in #1 was due to the fact that these abnormalities were unrevealed by conventional neurophysiological examination.

Furthermore, the existence of patients with functional disorders in our sample was certainly the most counterintuitive finding of our study, because it is challenging to speculate for them adaptive or primary degenerative cortical changes. Some authors showed that changes in bodily self-representation can modulate even "low-level" somatosensory cortical responses and processing [36–39]. Albeit contradictory, these data may support the hypothesis about the presence of abnormal self-awareness and/or self-representation in the functional patients. Because in our sample only 9 of 308 patients enrolled showed functional disorders, these data must be considered anecdotal and further studies need to confirm and clarify the relationship between the finding of enlarged N20p-P25p and the presence of a functional disorder.

The possible use of SEPs increased in amplitude in the clinical context

In our case series, different neurological disorders were represented, validating the hypothesis that SEPs increased in amplitude could not be considered per se as neither a marker of a specific disease nor of a sign (myoclonus) and nor to a definite pathophysiological process. Especially in non-myoclonic patients, the occurrence of a large N20p-P25p should induce clinicians to further investigate a possible degenerative process involving somato(motor) cortex considering the clinical, neurophysiological, and neuroradiological picture as a whole. In ALS patients, the increased N20p-P25p highlights subclinical early cortical involvement; [17] in parkinsonisms, this finding is probably more frequent in MSA and PSP than in PD; in cognitive disorders, very large N20p-P25p strongly relates to a prion disease (first of all CJD).

Finally, more than one pathophysiological process could contribute in determining the presence of enlarged N20p-P25p which, therefore, does not clarify the presence of a definite condition. Again, the occurrence of an enlarged N20p-P25p must be managed carefully, especially for diseases with poor prognosis and/or heavy personal implications, as for ALS, dementia, and parkinsonisms: in the single patients, the identification of a neurological disease still remains the result of an integrated and extended diagnostic process and the prognosis depends on many factors which cannot be considered alone.

Limitations

Some limitations must be accounted; the prevalence of the increase in amplitude of the earlier components of SEPs which we found in our study may not reflect the real one in the neurological disorders: we more frequently included diseases for which the execution of SEPs was integrated in the routinely diagnostic work-up. This sample bias depended on the retrospective nature of our study.

Finally, we took into consideration only the earliest cortical components of SEPs, while previous works stressed that also later components and the dynamics of the recovery of SEPs could be abnormal [7, 15]. However, our primary aim was to investigate about the significance of a finding (i.e., increased N20p-P25p) usually underestimated in the daily diagnostic work-up.

Conclusion

So far, SEPs increased in amplitude are usually considered a sign of cortical hyperexcitability and related to the presence of cortical reflex myoclonus and epilepsy, even if a growing number of evidence lead to rethink about their significance. In this study, we demonstrated that very large N20p-P25p correlated with cortical myoclonus and/or, with a lesser extent, epilepsy, while mild increased N20p-P25p could reflect adaptive, plastic, and/or degenerative cortical changes.

Our data open a window in considering SEPs increased in amplitude more than a "simple" neurophysiological sign of cortical myoclonus and, considering that SEPs examination is a low-cost, largely used technique, we propose it as a first-level diagnostic tool for all the conditions in which a degenerative or plastic rearrangement of somatosensory cortex can be hypothesized.

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Author contribution Davide Rossi Sebastiano: conceptualization (lead); data curation-other groups (equal); and writing-original draft (lead). Daniele Cazzato: data curation-other groups (equal) and writing-review and editing (lead); Elisa Visani: formal analysis (lead). Eleonora Dalla Bella: data curation-MND group (lead). Laura Brambilla: data curation-CNS-IMM group (lead). Grazia Devigili: data curation-PARK group (lead). Paola Caroppo: data curation-COG. DIS group (lead). Lorenzo Maggi: data curation-MYOP group (lead). Lorenzo Nanetti: data curation-SCA group (lead). Ettore Salsano: data curation-NEUROP group (lead). Laura Canafoglia: data curation-EPI-MYO group (lead). Isabella Canavero: data curation-CNS-VASC group (lead). Elena Anghileri: data curation-CNS-TUM group (lead). Deborah Bonfoco: data curation-other groups (equal). Paola Lanteri: supervision (lead) and writing-review and editing (supporting). We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship.

Declarations

Ethical approval and Informed consent None.

Consent to participate Our research involved human participants who gave informed consent for the use of data collected.

Conflict of interest The authors declare no competing interests.

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