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Neurological soft signs (NSS) and cognitive deficits in HIV associated neurocognitive disorder

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ABSTRACT

Neurological soft signs (NSS) are frequently found in severe mental disorders, such as Alzheimer's disease, schizophrenia or HIV associated neurocognitive disorder (HAND) which includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia. To characterize NSS in patients with HIV we examined them with respect to neuropsychological deficits typically found in the disorder.

67 HIV + patients without a history of head trauma, opportunistic infections, severe psychiatric disorders or acute confounding comorbidities of the Central nervous system (CNS) were recruited. NSS and neuropsychological deficits were examined on the Heidelberg scale and the Cambridge Neuropsychological Test Automated Battery (CANTAB), respectively. Semantic and phonemic verbal fluency were additionally established.

According to NIMH and NINDS criteria, 18 patients were diagnosed with ANI and 21 with MND, 28 showed no cognitive deficits. NSS total scores were significantly correlated with several cognitive domains and NSS subscales. These correlations were confirmed when motor performance was entered as a covariate.

According to our findings, NSS in HIV positive patients are significantly correlated with deficits in a broad range of neuropsychological domains. Similar findings were reported in schizophrenia, emphasizing the transdiagnostic character of NSS and supporting NSS examination in screening HIV patients for HAND.

1. Introduction

Neurological soft signs (NSS) or subtle motor and sensory deficits are frequently found in a wide range of psychiatric conditions, in particular schizophrenia, and organic brain disorders such as Alzheimer's disease (Schroder et al., 1991; Toro and Schroder, 2019). Hence, NSS can be considered as a transdiagnostic phenomenon. As demonstrated in a wealth of studies in patients with schizophrenia, NSS vary in the clinical course with severity of the condition as demonstrated by decreasing scores when psychopathological symptoms are in remission; for review see: (Bachmann et al., 2014; Bachmann and Schroder, 2017). They are significantly associated with a broad range of neuropsychological deficits involving attention, psychomotor speed, autobiographical and declarative memory, executive functioning, or theory of mind (Herold et al., 2019). Along with this, changes in multiple cerebral sites including the frontal, parietal and temporal cortices, the basal ganglia, the thalamus and the cerebellum were identified as correlates of NSS (Heuser et al., 2011).

HIV associated neurocognitive disorder (HAND) is a frequent condition, present in approximately half of the persons living with HIV (Heaton et al., 2010; Simioni et al., 2010). Since the introduction of combined antiretroviral therapy (cART), the prevalence of HIV- associated dementia (HAD) became rare, however milder forms of HAND, became more frequent. Milder forms of HAND: asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) primarily characterized by impaired episodic memory and executive functions, also involves deficits in attention and visuo-constructive abilities (Cysique et al., 2004; Smail and Brew, 2018). Our group (Toro et al., 2018) recently showed increased NSS scores in patients with HAND when compared with both, cognitively unimpaired persons living

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with HIV and healthy controls. However, NSS scores were even significantly higher in the cognitively unimpaired persons living with HIV than the healthy controls. These findings indicate that NSS may facilitate early recognition and diagnosis of HAND, a crucial aspect in the comprehensive evaluation of these patients.

In the present study, we sought to investigate the associations between NSS and cognitive deficits typically obtained in persons living with HIV. As a transdiagnostic phenomenon, we expected NSS scores to be significantly correlated with a wide range of cognitive deficits.

2. Methods

2.1. Subjects and clinical assessments

Sixty-seven persons living with HIV without a history of head trauma, opportunistic infections, severe psychiatric disorders or acute confounding comorbidities of the CNS were recruited. The groups were classified as HIV cognitively healthy, ANI, and MND following NIMH and NINDS criteria (Antinori et al., 2007). NSS and neuropsychological deficits were examined with the Heidelberg scale (Schroder et al., 1991) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994), respectively. In addition, phonemic and semantic verbal fluency were examined (Olabarrieta-Landa et al., 2015). Further methodological details are given in (Toro et al., 2018).

2.2. NSS and neuropsychological testing

NSS were examined on the Heidelberg scale (Schroder et al., 1991), which comprises 16 items on five factors (motor coordination, sensory integration, complex motor tasks, right/left spatial orientation and hard signs). Ratings are protocoled on a 0-3-point scale (no/slight/moderate/marked abnormality). The psychometric properties of the Heidelberg scale – including those of the Spanish version used in the present study - are well established (Bachmann et al., 2005; Schroder et al., 1991; Valenzuela et al., 2014). For neuropsychological testing, the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994) was applied. The following outcome measures were considered:

- Psychomotor speed and attention:
  - o Motor control (MOT), with MOT mean latency as the time taken to touch the cross after it appeared (MOTL) and MOT mean error as the accuracy of the subject's pointing (MOTE).
  - o Reaction time (RTI), with RTI five choice movement time, as the time taken to touch the stimulus after the press pad button has been released (RTIM) and RTI five choice reaction time, as the speed which the subject releases the press pad button in response to a stimulus (RTIR).
- Episodic Memory:
  - o Paired Associates learning (PAL), with PAL total errors as the total number of errors across all assessed problems and all stages (PALT) and PAL total errors (6 shaped, adjusted) as the total number of errors made at the 6-pattern stage (PAL6).
- Abstract thinking and planning:
  - o Stockings of Cambridge (SOC), with SOC problems solved in minimum moves as the number of occasions upon which the subject has successfully completed a test problem in the minimum possible number of moves (SOCP).
- Executive Functions:
  - o Intra/extradimensional set shift (IED), with IED total errors as the efficiency in attempting the test (IEDT) and IED stages completed as the total number of stages the subject completed successfully (IEDS).
- Spatial Working Memory (SWM):
  - o Spatial Working Memory (SWM), with SWM between errors as the times the subject revisits a box in which a token has previously been found (SWMB) and SWM strategy as the times the subject begins a new search with a different box for 6 and 8 box problems (SWMS).

CANTAB was complemented with semantic and phonemic verbal fluency (FAS) (Olabarrieta-Landa et al., 2015) and premorbid verbal IQ assessed with the WAIS verbal scale (Schretlen et al., 2005). Z scores corrected for educational level and age were calculated using the CANTAB database. Further methodological details are given by Toro and collaborators (Toro et al., 2018).

2.3. Statistical analyses

Groups were compared by calculating analyses of variance (ANOVA) with Duncan post hoc tests or χ^2-tests when appropriate. To assess the potential associations between NSS scores and the neuropsychological deficits considered, Pearson correlation coefficients were calculated. Significant correlations between NSS and neuropsychological domains were entered in a multivariable regression analysis with age, educational level, actual CD4 count and total NSS as independent variable.

3. Results

According to NIMH and NINDS criteria, 18 persons living with HIV were classified as ANI and 21 with MND, while 28 did not show cognitive deficits (HIV- cognitively healthy). Table 1 shows demographic and clinically relevant data. There were no significant differences regarding age, years of education, NART and CD4 cell count nadir. The proportion of subjects with undetectable viral load (defined as <20 copies/mL) were higher in cognitive healthy and ANI in comparison to MND ($p = 0.015$).

Results for NSS and neuropsychological testing are summarized in Table 2. When compared with the HIV- cognitively healthy group, those with ANI and MND showed significant increased values on the NSS subscale right/left spatial orientation ($F = 5.3$, $p = 0.007$). The highest NSS total scores were obtained in the MND group followed by ANI and the HIV- cognitively healthy ($F = 2.7$, $p = 0.077$; trend level only).

On the other hand, NSS total scores were significantly correlated with MOT, PAL, SOC, SWM but not with IED, RTIR and semantic fluency. Similar results were obtained for the NSS subscales motor

Table 1
Demographic and clinical variables of study participants.

Variable	HIV-ANI	HIV-MND	HIV-cognitively healthy	ANOVA or X^2
N	18	21	28	
Age	45.1 ± 13.4	39.4 ± 8.5	37.5 ± 8.9	p = 0.06
Gender (%males)	100	100	100	
Educational level	15.1 ± 2.0	15.3 ± 3.0	16.0 ± 2.7	p = 0.46
NART	99.89 ± 9.1	97.95 ± 14	102.2 ± 12.7	p = 0.49
Lifetime depression n (%)	10 (55.6)	14 (66.7)	17 (60.7)	p = 0.78
Lifetime substance abuse n(%)	1 (5.6)	3 (14.2)	3 (10.7)	p = 0.67
% on ART	89	95	93	p = 0.75
Actual CD4 count (cels/mm3)	509 ± 240	377 ± 176	436 ± 209	*p* = 0.15
CD4 nadir(cels/mm3)	219 ± 186	377 ± 176	213 ± 143	*p* = 0.25
Undetectable Actual Viral load <20 copies/mL (%)	78	53	89	*p* = 0.015
Viral load (copies/mL) at time of diagnosis	270682 ± 288664	157639 ± 212841	209447 ± 411022	*p* = 0.62

(i) ANI: Asymptomatic neurocognitive impairment, (ii) MND: Mild neurocognitive disorder, (iii) VL: viral load, (iv) NART: National Adult Reading Test.

Table 2
NSS and Neuropsychological Scores (means and standard deviations) with the results of a Duncan test.

	HIV- Cognitively Healthy (a)	ANI (b)	MND (c)	ANOVA F (2,64)	Duncan	*p*
Motor Coordination	2.3 (1.94)	4.39 (5.19)	4.52 (4.38)	2.7	–	0.07
Spatial Orientation	0.61 (0.74)	1.22 (1)	2.24 (2.84)	5.3	a <c, b	0.01
Sensory Integration	2.11 (1.31)	2.56 (2.12)	2.38 (2.84)	0.4	–	0.6
Complex Motor Task	1.07 (0.98)	1.78 (2.24)	2.1 (2.02)	2.2	–	0.1
Hard Signs	2 (1.76)	1.78 (1.59)	2.1 (2.02)	0.2	–	0.9
Total NSS	8.04 (4.09)	11.72 (10.57)	13.33 (10.01)	2.7	c > b, a	0.05
MOTL	0.8 (0.36)	0.8 (0.47)	0.83 (0.31)	0.1	–	1.0
MOTE	0.36 (0 .07)	0.33 (0.1)	0.34 (0.07)	1.2	–	0.3
IEDT	0.04 (0.9)	−0.47 (0.48)	−0.52 (0.5)	4.9	a > b, c	0.05
IEDS	0.002 (0.89)	−0.5 (0.71)	−0.58 (0.65)	4.0	a > b, c	0.05
PALT	0.63 (0.28)	−0.24 (1.13)	−0.03 (1.05)	6.8	a > b	0.01
					a > c, b	0.05
PAL6	0.44 (0.27)	−0.03 (0.76)	−0.04 (0.8)	4.8	a > b, c	0.05
RTIM	0.46 (0.73)	0.65 (0.47)	0.82 (0.7)	1.7	–	0.2
RTIR	0.40 (0.93)	0.34 (1.04)	−0.12 (1.10)	1.7	–	0.2
SOCP	0.08 (0.93)	−1.18 (0.60)	−0.9 (1.01)	13.4	a > c, b	0.001
SWMB	0.57 (0.6)	−0.29 (0.8)	−0.45 (0.89)	13.1	a > b, c	0.001
SWMS	0.44 (0.91)	−0.51 (0.83)	−0.61 (1.05)	9.4	a > c	0.001
					a > b	0.01
Semantic Fluency	0.2 (0.95)	−0.43 (0.88)	−0.47 (0.99)	3.7	a > b, c	0.05
Phonemic Fluency (F)	−0.18 (1.1)	−0.16 (0.92)	−0.88 (0.93)	3.5	b, a > c	0.05
Phonemic Fluency (A)	−0.18 (1.1)	−0.03 (0.91)	−0.52 (0.95)	1.6	–	0.2
Phonemic Fluency (S)	0.02 (0.87)	−0.02 (0.81)	−0.67 (0.9)	4.4	a, b > c	0.05

(i) NSS: Neurological Soft Signs (ii) MOTL: MOT mean latency (iii) MOTE mean error (iv)IEDT: IED total errors (v) IEDS: IED stages completed (vi) PALT: PAL total errors (adjusted) (vii) PAL6: PAL total errors (6 shapes, adjusted) (viii) RTIM: RTI five choice movement time (ix) RTIR: RTI five-choice reaction time (x) SOCP: SOC Problems solved in minimum moves (xi) SWMB: SWM between errors (xii) SWMS: SWM strategy (xiii) (F) Letter F (xiv) Letter A (xv) Letter S.

coordination. The NSS subscale right/left spatial orientation was significantly correlated with PAL, RTIR, SOC, semantic fluency and SWMB; the subscale integrative functions correlated with PAL and RTIR. The NSS subscale complex motor task was significantly associated with PAL, and RTIR. For the subscale hard signs, no significant correlations were shown. The results were confirmed when motor control was entered as a covariate. Neuropsychological test results and NSS scores are detailed on supplementary data (Supplementary Table 1).

Neuropsychological domains which correlated significantly with total NSS were selected to assess possible predictors of cognitive impairment. A regression model was performed with age, total NSS, actual CD4 count and educational level as independent variables. Our model significantly predicted PALT ($F\ (10.962) = 5.794$, $p < 0.001$, *adjusted* $R^2 = 0.380$), PAL6 ($F\ (12.377) = 3.167$, $p < 0.001$, *adjusted* $R^2 = 0.412$) and SOCP ($F\ (4.031) = 3.691$, $p = 0.006$, *adjusted* $R^2 = 0.157$) performance, but none of the other neuropsychological domains. Results are detailed in Table 3.

4. Discussion

In the present study we sought to investigate NSS, i.e. minor motor and sensory deficits which typically arise in the course of severe neuropsychiatric disorders (Toro and Schroder, 2019) with respect to neuropsychological deficits in persons living with HIV. The clinical characteristics and the significantly increased NSS scores of our groups were already discussed in a previous study (Toro et al., 2018) which yielded significantly higher NSS scores even in the cognitively unimpaired group than in otherwise healthy individuals. The present study confirm and extend this finding by demonstrating significant correlations between increased NSS scores in persons living with HIV with cognitive impairment characteristic for this condition; namely impaired episodic memory and executive dysfunction. Moreover, we demonstrated that total NSS score is an important predictor of hippocampal and prefrontal function, which has been described as impaired in people living with HIV (Maki et al., 2009; Castelo et al., 2006).

Table 3
Variables predicting neuropsychological impairment in persons living with HIV.

	Total NSS			
Variable	β	Sβ	t	p
PALT	−0.048	−0.443	−3.915	0.001
PAL6	−0.038	−0.488	−4.425	0.001
SOCP	−0.037	−0.301	−2.277	0.026
SWMB	−0.026	−0.251	−1.894	0.063
SWMS	−0.013	−0.105	−0.766	0.447

(i) β = Beta weight unadjusted (ii) Sβ = Standardized Beta weight. Age, Education and Actual CD4 count were controlled in the model.

Increased NSS scores in persons living with HIV when compared to healthy controls were demonstrated in an earlier study (Toro et al., 2018). Moreover, subtle motor abnormalities similar to NSS were already found in the 1990 (Arendt et al., 1990) and conceptualized by Robinson- Papp and colleagues (2008) in the human immunodeficiency virus-dementia scale (HMDS) (Robinson-Papp et al., 2008). These findings were recently confirmed and extended by Elicer et al. (2018), who found the highest HMDS scores in persons living with HIV associated dementia followed by MND when compared with ANI. In addition to motor coordination, including gait, which are also included in the Heidelberg NSS scale, the HDMS comprises muscular strength, tone and reflexes which are not considered as motor coordination. In contrast, NSS also include sensory deficits which are not part of the HMDS (Elicer et al., 2018).

NSS were found to be closely associated with cognitive deficits, in particular episodic memory impairment and executive dysfunction including attention. Interestingly, the respective correlations were confirmed when motor control was partial out as a measure of motor retardation and/or poor test understanding. Similarly, in her study cited above, Elicer and collages reported a significant association between HMDS scores and a global T score as a combined measure of global cognitive impairment in 164 persons living with HIV (age: 52.1 ± 8.8 years). On repeated examination four years later, they found motor abnormalities to further deteriorate while cognitive impairment remained rather stable. This dissociation was assigned to the accumulation of cerebrovascular disease in the light of frequent risk factors such as hypertension, diabetes mellitus or hyperlipidemia (Elicer et al., 2018). These comorbidities were not found in our sample of young patients.

Along with the significant association of NSS and executive dysfunction reported here, Kronemer et al. (2017) demonstrated reduced working memory capacity and impaired fine motor ability to co-occur as a function of cognitive-motor dual load in 25 patients with HAND when compared to 22 healthy controls (Kronemer et al., 2017). These results confirm and extend previous studies in schizophrenia (for review (Herold et al., 2019): demonstrating significant associations between NSS and a broad range of neuropsychological deficits which included executive functions and even more complex domains such as autobiographical memory or theory of mind – i.e. domains which hardly involve motor aspects.

Since our study sample includes only young male adults, age has to be considered as a potential confounding variable. Nonetheless, NSS were shown to slightly increase with age in both MCI and AD (Urbanowitsch et al., 2015) and patients with schizophrenia (Herold et al. 2018, 2019). Further, despite all participants were on ART, differences in their specific medications should be considered as confounding variable. None of the patients included received neuroleptic medication; motor side effects of antiviral therapy are not established. In addition, two important limitations in our study need to be noted: the cross-sectional nature of the study and the lack of generalizability to woman.

The present study supports our hypothesis that NSS in persons living with HIV are associated with a broad range of cognitive deficits. From a clinical standpoint this is of considerable importance since resources for neuropsychological examinations are often scarce, as the capacity of patients for such long procedures is often limited and thus facilitates the possibility to use NSS as a screening instrument for such impairments. That similar findings were found in patients with schizophrenia, underlines the transdiagnostic character of NSS. Our findings facilitate the use of NSS as a screening tool for cognitive deficits in persons living with HIV.

Declaration of competing interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

CRediT authorship contribution statement

Gonzalo Forno: Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Fernando Henríquez:** Formal analysis, Investigation, Visualization. **María Elena Ceballos:** Investigation, Resources. **Matías Gonzalez:** Investigation, Resources. **Johannes Schröder:** Formal analysis, Writing - original draft, Writing - review & editing, Supervision. **Pablo Toro:** Conceptualization, Methodology, Validation, Resources, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary data

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