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Cognitive slowing in cognitive-motor disorder associated to type 1 human immunodeficiency virus: TR and P300

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Introduction. Reaction time (RT) deficit exhibited by HIV-1 asymptomatic seropositive individuals cannot always be explained by the effect of a cognitive slowing single factor. Evidence exists that decisional and peripheral components of RT may have differential slowing.

Objectives. To assess the hypothesis of a cognitive slowing single factor as the main responsible for RT slowing in these subjects.

Methodology. Thirty two (32) HIV-1 neurologically asymptomatic seropositive individuals were compared to 29 seronegative controls in two discriminative reaction time tasks (DRT) having increased cognitive difficulty but equal motor response demands. P300 component of the event-related potential was recorded simultaneously. RT, PPI, errors, and P300 latency were assessed using ANOVA.

Results. Seropositives were slower than controls in RT, made more errors and showed delayed latencies of P300 in both tasks. However, while the increase of RT from the easier to the more difficult task was additive, the increase of P300 latencies was multiplicative.

Conclusions. These results reveal differences in patterns of slowing between central and motor information processing mechanisms. Such results suggest that a single common factor is not enough to explain cognitive slowing in HIV-1 seropositive subjects.

Key words:
Cognitive slowing. Task difficulty. HIV-1. P300. Reaction time. Cognitive-motor disorder.

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Enlentecimiento cognitivo en el trastorno cognitivo-motor asociado al virus de inmunodeficiencia humana tipo 1: TR y P300

Introducción. Los déficit de tiempo de reacción (TR) en los sujetos infectados por el virus de inmunodeficiencia humana tipo 1 (VIH-1) en las etapas iniciales de la infección no parecen siempre comprensibles por la acción de un factor general de enlentecimiento cognitivo. Existen evidencias que indican que los componentes de la decisión y periféricos del TR pueden lentificarse diferencialmente.

Objetivos. Evaluar la acción de un factor general de enlentecimiento cognitivo como causa principal de incremento del TR en estos sujetos.

Métodos. Treinta y dos sujetos seropositivos al VIH-1 neurológicamente asintomáticos fueron comparados con 29 controles seronegativos en dos tareas de tiempo de reacción discriminativo (TRD) de dificultad creciente, pero con iguales demandas de respuesta. Simultáneamente se registró el componente P300 del potencial evocado por las tareas. El TR, el IPP, los errores y la latencia del componente P300 fueron comparados mediante ANOVA.

Resultados. Los seropositivos fueron más lentos, cometieron más errores y exhibieron latencias más prolongadas que los controles, pero mientras que el incremento del TR entre tareas fue aditivo, el de latencia de P300 fue multiplicativo.

Conclusiones. Los resultados revelan una disociación en el patrón de enlentecimiento de los mecanismos centrales y los de producción de respuesta. Tales resultados sugieren que un factor general no es suficiente para explicar el enlentecimiento cognitivo de estos sujetos.

Palabras clave:
Enlentecimiento cognitivo. Dificultad de la tarea. VIH-1. P300. Tiempo de reacción. Trastorno cognitivo-motor.

INTRODUCTION

Within the context of the controversy regarding in which stage of type 1 human immunodeficiency virus (HIV-1) the

Motor-Cognitive Disorder (MCD)[1-6] may appear, one aspect of the debate is that of the significance and sensitivity of the reaction time (RT) measurements to detect the signs. While some studies recommend the use of RT in the routine assessment of seropositive subjects to HIV-1 from the initial stages of the infection[2,7-11] on the basis that the psychomotor slowing may be the earliest sign of «dementia complex» associated to HIV-1[12,13] others maintain that such indicators are not more sensitive in asymptomatic subjects than in conventional neuropsychological tests[14-20].

Although in many studies RT is used as a measure of processing speed of complex functions or specific mechanisms in many studies[6,21-29] based on the supposition that HIV-1 causes selective deterioration during the first stages, in most of the studies, RT is used to assess the most general and elemental information processing mechanisms with relatively simple tasks that involving signals detection and discrimination response and selection and execution[10]. This approach is based on the hypothesis, already formulated in the area of aging psychology[30-35], that the cognitive deterioration which these subjects will finally have is caused by the action of a general «slowing» factor that basically affects the information processing central mechanisms[36,37]. This claim is supported by RT studies were if specific task demands are not considered and response requirements remain the same, the greater the cognitive demand of the task the slower the reaction time of HIV-seropositive individuals will be[10].

However, the literature on RT in HIV-1 seropositives reveals the presence of slowing patterns that questions the action of a general factor as the only one responsible for the processing deficit. Thus, while Dunlop et al.[12], Worth et al.[11] and Perdices and Cooper[16] found that the RT deficit was only found with the increase of detection and discrimination demands, Wilkie et al.[3] and Chang et al.[38] confirmed that seropositive subjects can perform tasks with the same level of accuracy as the controls and show an increase of RT[39] or, even, that the RT differences are reduced with the increase of the cognitive demands of the tasks[14,40].

These results indicate that it would be necessary to establish the respective contribution of the central and motor components to RT latency in order to elucidate the nature and evolutive course of cognitive slowing associated to MCD and especially the significance of RT in this slowing. An appropriate technique to differentiate it is by recording simultaneously RT and event-related brain electrical activity, particularly the latency of the P300 component of the event-related potential.

Although there are studies that have evaluated the P300 component in HIV-1 infected subjects[41-44] and have found sensitive changes in this component in both symptomatic and asymptomatic seropositive subjects, few of them have used it in combination with RT measurements[45,46] and with a chronometric approach[47].

The present study aims to assess the relative contribution of the RT cognitive and motor components to the cognitive slowing that seems to distinguish seropositive subjects to HIV-1 in the early stages of the infection using the combined recording of RT and P300 component. In this way, it aims to examine the role of the general slowing factor in the cognitive deficits of the subjects.

METHODS

Cognitive assessment

Two visual oddball discriminative reaction time (DRT) tasks with growing difficulty and with the same response demands were designed. A white square with five horizontal parallel black lines inserted was used as frequent stimulus in both tasks. In the first task (DRT1), the infrequent stimulus consisted in a square with three parallel vertical lines inserted in the first task (DRT1) and in the second one (DRT2), it was a square with four parallel black horizontal vertical lines inserted. The difference in orientation and amount of lines between the stimuli of each task showed two progressive levels of the discrimination difficulty between stimuli having the same perceptual nature.

The stimuli were exposed at the center of a video screen (placed at 1.25 m from the subjects), subtending a visual angle of 5 degrees for 1 sec. and against a black background. Stimuli probability was 80 % and 20 % and they were delivered at random, with the restriction that not more than two infrequent stimuli would appear successively (a program controlled the series). The interstimulus interval was 1.5 seconds. Presentation order of the tasks was balanced through the subjects. The subject's response consisted in pressing a key for each infrequent stimulus and another one for a frequent one. Two series of 100 stimuli were administered. The RT of each response and its accuracy were recorded. In addition, with the frequent stimulus as target, the subjects performed a SRT with the same presentation conditions as in the DRT tasks. The subjects were instructed to respond as quickly and accurately as possible.

Psychophysiological evaluation

An EEG recording was made during the tasks performance using a Medicid 3E (Neuronic S.A). Amplifier bandpass was settled at 05-30 Hz and data were gathered at a sampling rate of 200 Hz. Nineteen surfaces silver electrodes were placed according to the 10-20 International System[48]. Linked earlobes were used as reference and a forehead electrode as ground. The electrooculogram was recorded bipolarly at the outer canthi of the left eye. Impedance was maintained below 5 KOhm.

Artefact free EEG epochs of 1124 ms (100 ms pre-stimulus) time locked to the onset of stimuli were stored for off-line averaging. Epochs associated to incorrect responses or to RT out of a time window from 200 to 1000 ms were excluded from analysis. The P300 component was visually identified as the most prominent positive peak within a time window from 300 to 800 ms. The latency was measured as the intersection point of the ascending and descending slopes of the component.

Sample

32 neurologically asymptomatic seropositive to the HIV-1 infection males and 29 seronegative controls comparable for age ($t[59] = 1.58$; $p < 0.12$) and educational level ($X^2 = 1.2$; $p < 0.26$) participated in the study. The seropositive subjects were randomly obtained from a sample of 50 asymptomatic seropositives subjects previously studied[39]. All of them were residents in the «Los Cocos» community belonging to the AIDS sanitarium of Santiago de Las Vegas in La Havana where they receive systematic care. An evaluation of the Clinical Record (that includes a periodic psychological evaluation) and an interview prior to the study reported made it possible to exclude those subjects having a background or current manifestations of psychiatric disorders (depression, anxiety) or neurological ones (and cephalic brain trauma, epilepsy), background or current consumption of alcohol, drugs or psychodrugs. Furthermore, those subjects who had received treatment with antiretroviral drugs were excluded. The immune system status of each subject was determined in the week prior to the onset of the study through a CD4 T cell count. In addition, information was obtained on the time of probable infection of each seropositive subject. The control group was obtained from the whole group of administrative, maintenance and service workers of the sanitarium as it was a population with a detailed knowledge on the infection and the risks and who were carefully evaluated for possible background of behavior that would involve risk of catching the disease in order to be hired. All the subjects participated voluntarily and gave their written informed consent. Table 1 provides the description of the sample.

Statistics

RT and errors from the two series of the each task were averaged and compared using ANOVAs (group: seropositives and controls; Task: SRT, DRT1 and DRT2). Mean latency of the individual average evoked potentials for each task was analyzed with a repeated measures ANOVA where the group and task were used as factors between subjects and site (Fz, Cz and Pz) as repeated measures factor. The post-P300 interval (PPI) or interval included between the peak latency of the P300 component and RT latency of each task was compared between the groups using an ANOVA (group and task).

Table 1 Characteristics of participants (mean values are offered)

Variable	Seropositives (32)	Controls (29)
Age	34.23 (9.58)	30.65 (9.49)
Years of schooling	11.78 (2.92)	12.86 (3.38)
Time of probable infection (years)	9.25 (2.61)	
T4 cell count (U/mm^3)	511 (132.6)	

RESULTS

Reaction time

Table 2 shows the mean values of RT per group and task. A group ($F[1.177] = 41.90$; $p < 0.00001$) and task ($F[1.177] =$

Table 2 Mean and Standard deviation of RT, errors, P300 latency for each site and PPI obtained from Cz

	Seropositives		Controls	
	Mean*	SD	Mean	SD
Reaction time				
SRT	403.59	113.45	333.64	102.06
DT1	538.17	59.53	465.68	51.33
DT2	642.59	69.42	555.14	62.29
Errors				
E_TD1	1.97	1.33	1.83	1.71
E_TD2	3.41	3.00	1.97	1.52
P300 lat.				
DT1				
Fz	447.63	52.14	416.44	54.95
Cz	448.06	50.33	415.71	48.27
Pz	446.49	49.10	420.86	55.69
DT2				
Fz	561.83	76.89	477.00	73.48
Cz	567.86	70.93	480.83	65.38
Pz	572.25	66.50	491.86	67.62
PPI				
PPI_DT1	90.77	75.01	48.01	45.98
PPI_DT2	75.28	79.93	71.90	59.87

*ms. TRS: simple reaction time; DT1: discriminative reaction time 1; DT2: discriminative reaction time 2; SD: standard deviations; ms: millisecons; E_DT1: amount of errors in DT1 task; E_DT2: amount of errors in DT2 task; Fz, Cz, Pz: registry sites; PPI_DT1: post-P300 interval in DT1 task; PPI_DT2: post-P300 interval in DT2 task.

127.11; p<0.0001) effect was observed. No interaction of group by task was observed (p<0.81). The seropositive subjects were slower than the controls regardless of the task. The magnitude of the differences between the groups reached 70 ms in SRT, 73 ms in DRT1 and 87 ms in DRT2, which means that the increase was comparable in the three tasks. Figure 1 shows the RT distribution of each group in each task.

The RT differences observed indicate a decrease in the speed of the information processing in seropositive subjects. Such an outcome is in agreement with a number of reports in which both more complex SRT as well as DRT tasks were used[3,4,21]. However, it differs from that obtained in other studies[16-20,40] and from that observed for this same group of subjects in the two DRT tasks used by Amador and Mayor[39].

Even so, the most relevant aspect of this study is the constant or additive character of the RT increase between growing cognitive difficulty tasks in the seropositive subjects. This pattern of additive slowing is similar to that reported by Hardy & Hinkin[10,49] for asymptomatic seropositive subjects and suggests that the locus of the cognitive slowing in these subjects would be more in the peripheral or sensoriomotor processing than in the central thought ones.

Errors

Comparison of errors was made between DRT tasks. Table 2 shows the mean errors per group and task. The seropositive subjects committed more errors than the controls (F[1.118]=4.66; p<0.03) but only in DRT2 (p<0.001). The DRT2 task caused more errors than the DRT1 one (F[1.116]=4.62; p<0.03). No interaction of the group per task was observed (p<0.08). Figure 2 shows the performance of the groups in each task.

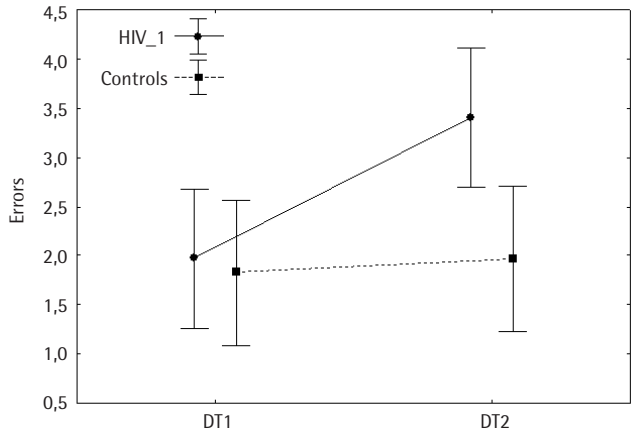

Figure 2 *Distribution of errors of each group in the two DRT tasks. DTR: discriminative reaction time; DT1: discriminative reaction time 1; TD2: discriminative reaction time 2.*

P300. Comparison of latencies

Table 2 shows the mean latency of the P300 component per group and task. Figure 3 describes the behavior of the groups in the two tasks. A group effect (F[1.118]=27.47; p<0.0001), task effect (F[1.118]=72. 98; p<0.0001) as well as an interaction of group per task (F[1.118]=6.27; p<0.01) are observed. Furthermore, there was a Site effect (F[2.236] = 4.74; p<0.01; ε=0.62). The seropositive subjects have more prolonged latencies than the controls in DRT2 (p<0.0001) but not in DRT1 (p<0.06). The Pz site showed more prolonged latencies than the Fz and Cz sites that were equivalent.

The comparison of latencies also revealed a slowing in the speed of information of seropositives as well as an increase in slowing as a function of the increase of the cogni-

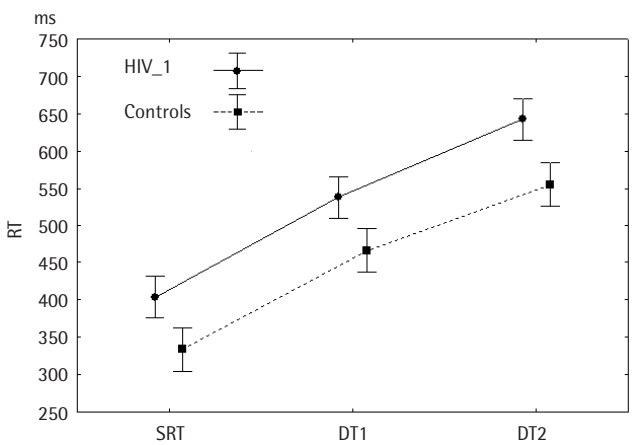

Figure 1 *RT distribution of each group in each one of the three tasks. SRT: simple reaction time; DT1: discriminative reaction time 1; TD2: discriminative reaction time 2; RT: reaction time; ms: milliseconds.*

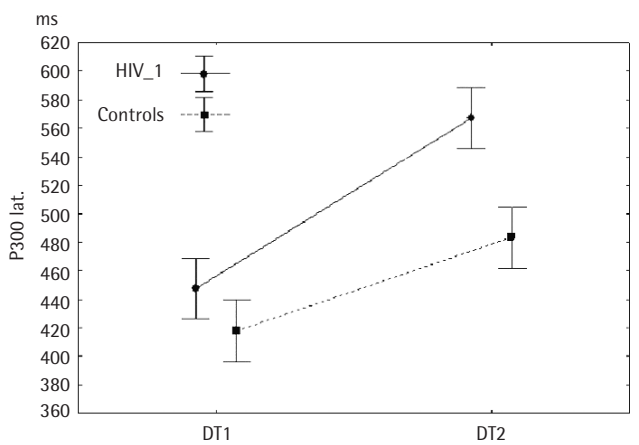

Figure 3 *Distribution of P300 latencies of each group in each one of the two DRT tasks. DT1: discriminative reaction time 1; TD2: discriminative reaction time 2; P300_lat: P300 component latency; ms: milliseconds.*

tive demands of the task for this group. Increased errors committed in DRT2 are consistent with this result. Such a finding, on its part, gives support to the hypothesis of the action of a general factor of cognitive slowing similar to that proposed by Becker and Salthouse[36] and Becker et al.[37], in HIV-1 infected subjects, based on RT regression studies and with conventional neuropsychological tests.

Post-P300 interval

Table 2 presents the mean value of PPI per group and task. No group effect ($p < 0.06$), Task effect ($p < 0.73$) or Group Interaction per task ($p < 0.11$) were observed. The PPI of the seropositive subjects was more prolonged than that of the controls in DRT1 ($p < 0.01$). It was equivalent in the DRT2 task ($p < 0.85$). There, while the PPI increased in the controls in 24 ms from DRT1 to DRT2 (from 48 to 72 ms), it decreased in 16 ms (from 91 to 75 ms) in the seropositive subjects. These variations of the PPI, however, did not reach significant differences within any of the groups. Figure 4 shows the reduction of PPI in the seropositive subjects.

Reaction Times, latency of the P300 components and PPI

The analyses of the RT and of the P300 component latency suggest the probable simultaneous presence of two slowing patterns of the speed of information processing: one acting on the central processes in a multiplicative fashion and the other acting on the peripheral ones in an additive fashion. A slowing pattern of this appearance has been suggested by Cerella[33,34] in aged subjects using theoretical models of regression of RT in tasks of increasing cognitive demands.

However, the simultaneous action of two factors of information processing slowing but acting in opposite sense

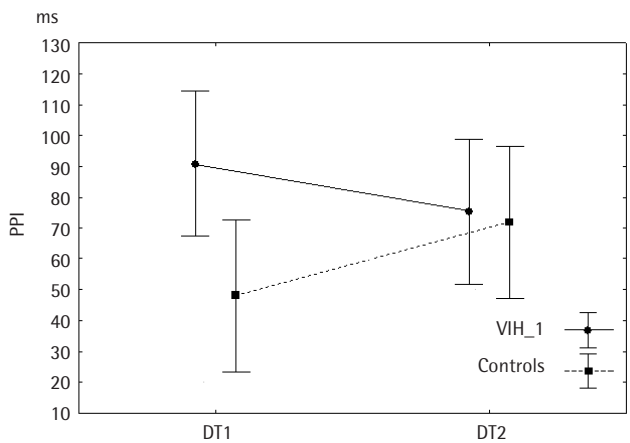

Figure 4 *Distribution of PPI of each group in each one of the two DRT tasks. DT1: discriminative reaction time 1; TD2: discriminative reaction time 2; PPI: post-P300 interval; ms: milliseconds.*

to that observed here has been reported by Bashore[35]. The interpretation (an additive effect of slowing for the P300 latency component and a multiplicative one for RT) has been supported, on the one hand, by the differential sensitivity of the P300 and RT latencies to response strategy changes[50-53] and, on the other, by the general tendency observed in elderly subjects to adopt conservative processing strategies that assure the maintenance of a steady accuracy level under condition of increasing processing requirements (speed-accuracy trade off)[54,55]. Therefore, the RT in the Bashore study would be reflecting a constant slowing effect due to the delay of the processes prior to response selection and execution (stimulus evaluation and memory set up-dating) plus the effect of adopting a conservative response strategy. The latency of the P300 component, on its part, would only reflect the duration of the previous central processes, basically represented by the Na and N200 components[56] and probably, in addition, the duration of the operations that correspond to the P300 component itself.

From this view, the results observed here would suggest considering that seropositive subjects adopt a strategy of accelerating the response as the task complexity increases (trade-off) accuracy for speed. Such a strategy takes it for granted that the response execution and selection processes partially or totally superimpose the stimulus evaluation processes.

If the seropositive subjects of this study really adopt an acceleration strategy of the response processes, the duration of the processes subsequent to the P300 component latency, included in the PPI, should be reduced contingently with the increase of the task complexity. However, this effect does not occur statistically. The absence of differences of PPI observed in the DRT2 task is not due to a significant decrease in PPI in the seropositive subjects, but rather to the combination of a mild acceleration of the response (16 ms) in this group, with a mild increase of the response duration in the controls (24 ms). All considered, the fact that the multiplicative effect of the task difficulty on the P300 component latency in the seropositive group is reduced to an additive effect in RT implies that at least a part of these subjects should have accelerated their response processes.

A pos hoc analysis of the differences of PPI in each subject made it possible to verify that, in fact, 19 (59%) of the seropositive subjects decreased PPI duration between tasks. The average reduction was 87 ms ($p < 0.0001$). However, none of them adopted a real parallel processing strategy (RT/P300 ratio quotient less than 1). In the control group, on its part, 7 (24%) of the subjects decreased the PPI between tasks in an average magnitude of 46 ms ($p < 0.10$) and two of them consistently adapted a parallel processing strategy.

A response acceleration of this magnitude in this subgroup suggests that, on the one hand, the RT differences existing between them and the controls in the DRT tasks may uniquely or predominately be originated by the slowing of the central processing mechanisms as an effect of

the task complexity and that, on the other hand, they could achieve RTs comparable to the controls in the SRT, a task that does not require central processing demands. Comparison of RT in this task showed an equivalence between controls and this seropositive subgroup ($t[46] = 1.90$; $p < 0.06$). A similar analysis between this subgroup of the remaining seropositive subjects (13 in whom there was no reduction in PPI) and the controls had had statistically significant differences between them ($t[40] = 2,13$; $p < 0.02$). In turn, an ANOVA that compared each seropositive subgroup with the control group regarding P300 component latency in each task revealed not only a group effect but also an interaction effect between group and task for the subgroup that accelerated its response ($F[1.92] = 12.00$; $p<0.001$). On the contrary, in the subgroup that did not accelerate its response, only a group effect was observed. That is, there was a much lower effect of increase of task complexity on the central processing mechanisms.

In this way, the contribution of the decisional and motor components of RT to the slowing of the information processing speed shown by the seropositive subjects of this study suggests that they do not have a homogeneous cognitive slowing pattern. Although a global deficit of central processing and response production processes has been observed in both subgroups, the deficit pattern of each component is different between them and reveals a partially dissociated mechanism of slowing: a subgroup with a mild slowing in the response production processes and a more severe deficit of the central mechanism and another one with the opposite pattern. The existence of such partially dissociated slowing patterns indicates that resorting to a general factor as responsible for the main proportion of the information processing slowing deficit shown by HIV-1 infected subjects in the initial stages of the infection is not sufficient to explain the RT deficit they show. The deficit of the response production processes may be as important as the central one. Even more, the relative preservation of the response production mechanisms may mask the status of the central processing mechanisms.

Doubts about the single action of a general factor in the production of the information processing speed deficits have already been stated in psychology of aging. Both in this area and in that of HIV-1 infection, most of the evidence that supports the hypothesis of the general factor of slowing comes from RT studies. The RT offers a global measure of processing speed that, due to the differential sensitivity of its components to different factors[57], does not make it possible to distinguish the contribution of the processes that participate in the task execution. More recently, it has been suggested[49,58] that elderly subjects may apply a different balance for the same task than the younger subjects between the control processes and subordinate ones and that this could be due both to compensation mechanisms due to the decrease in activity in processing functions and/or in the control functions such as strategy changes. In the case of HIV-1 infected subjects, the so-called brain reserve[9] along with similar factors of compensation and strategy change, may be playing a modulator role of slowing. The specific way that each one of the factors contributes to the slowing of the processing speed in these subjects cannot be directly inferred through measurements of RT latency. Use of complementary measures such as the P300 component may contribute to clarify this question. However, in the case of the P300 component, the fact that the occurrence of the peak latency is a marker of the duration of the stimulus evaluation processes and not of the total duration of the activity of the central processes implies that there may be processing stages remaining within the post-P300 intervals that are not strictly related with the motor execution (response selection and organization) in which an important component of the reduction of processing speed may be arising.

Recording of other components of brain electrical activity evoked as the Premotor Potential[60], recording electromyographic activity, as well as other variables of RT[61,62] or its fragmentation in the central and motor components seem to be necessary to determine how many factors and which factors modulate the cognitive slowing in this seropositive HIV-1 subjects at initial stages of the infection.

CONCLUSIONS

Evaluation of the central and motor components of RT in the DRT tasks of increasing difficulty revealed that the cognitive slowing in subjects seropositive to the human immunodeficiency virus type 1 may be modulated differentially by the deficit in these components: the deficit in the response production processes may be as important as the central deficit. This suggests, on the one hand, that resorting to a general factor as single or predominant responsible one of the cognitive slowing observed in the CMD is not sufficient to explain it. And, on the other hand, that the specific way in which each one of the factors contributes to the information slowing speed in these subjects cannot be directly inferred through the measurements of the total RT latency. The use of information slowing speed event-related potentials of other RT indicators or the instrumental fragmentation of RT in its component processes are necessary to determine the nature and dynamics of this deficit. This has potential implications for the assessment of treatments, prognosis of the evolution of the deficits in these subjects and their possible rehabilitation.

REFERENCES

1. Dunlop O, Bjorklund R, Abdelnoor M, Myrvang B. Total reaction time: a new approach in early HIV encephalopathy? Acta Neurol Scand 1993;88:344-8.
2. Clemente-Millana L, Portellano, JA. Evaluación neuropsicológica de los déficit cognitivos en la infección por el virus de la inmu-

nodeficiencia humana tipo 1 (VIH-1). Rev Neurol 2000;31: 1192-201.
3. Wilkie FL, Eisdorfer C, Morgan R, Loewenstein DA, Szapocznik J. Cognition in early human immunodeficiency virus infection. Arch Neurol 1990;47:433-40.
4. Martin A, Heyes MP, Salizar AM, Kampem DL, William J, Law WA, et al. Progressive slowing of reaction time and increasing cerebrospinal fluid concentrations of quinolic acid in HIV-infected individuals. J Neuropsych Clin Neurosci 1992;4:270-9.
5. Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, et al, the HNRC group. The HNRC 500- Neuropsychology of HIV infection at different disease stage. J Int Neuropsychol Soc 1995; I:231-51.
6. McArthur JC, Grant I. HIV Neurocogntive disorders. In: Gendelman HE, SA Lipton SA, Epstein L, editors. The Neurology of AIDS. New York: Chapman and Hall, 1998; p. 449-523.
7. Hinkin Ch, Castellón SA, Seteven A, Hardy DJ. Dual task performance in HIV-1 infection. J Clin Exper Neuropsychol 2000;22: 16-24.
8. Martin EM, Pitrak DL, Novak RM, Pursell KJ, Mullane KM. Reaction times are faster in HIV-seropositive patients on antiretroviral therapy: a preliminary report. J Clin Exp Neuropsychol 1999; 21:730-5.
9. Ayuso-Mateos JL, Pereda M, Gómez del Barrio A, Echevarría S, Farinas MC, García-Palomo D. Slowed reaction time in HIV-1-seropositive intravenous drug users without AIDS. Eur Neurol 2000;44:72-8.
10. Hardy DJ, Hinkin CH. Reaction time performance in adults with HIV/AIDS. J Clin Exper Neuropsychol 2002;7:912-29.
11. Worth JL, Savage CR Baer L. Esty EK. Navia BA. Computer-based neuropsychological screening for AIDS dementia complex. AIDS 1993;7:677-81.
12. Dunlop O, Bjorklund RA, Abdelnoor M, Myrvang B. Five different tests of reaction time evaluated in HIV seropositive men. Acta Neurol Scand 1992;86:260-6.
13. Hinkin CH, van Gorp WC, Satz P. Neuropsychological and neuropsychiatric aspects of HIV infection in adults. In: Kaplan HI, Saddock BJ, editors. Comprehensive textbook of psychiatry. Baltimore: Williams and Wilkins, 1995; p. 1669-80.
14. Nance M, Pirozzolo F, Levy J, Fernández F. Simple and choice reaction time in HIV–, HIV+ and AIDS patients. Int Conf AIDS 1990; 6:173 (abstract no. F.B.383).
15. Martin A, Kampen D, Salazar AM, Williams J, Law W, Roller T. Slowed cognitive processing in HIV+ patients in comparison to psychiatric controls. Int Conf AIDS 1989;5:210 (abstract no. W.B.O.43).
16. Perdices M, Cooper DA. Simple and choice reaction time in patients with human immunodeficiency virus infection. Ann Neurol 1989;25:460-7.
17. Damos DL, John RS, Parker ES, Levine AM. Anti-retroviral therapy and cognitive function. Aviation Space Environm Med 1997;68:900-6.
18. González R, Heaton RK, Moore DJ, Letendre S, Ellis RJ, Wolfson T, et al. HIV Neurobehavioral Research Center Group. Computerized reaction time battery versus a traditional neuropsychological battery: detecting HIV-related impairments. J Int Neuropsychol Soc 2003;9:64-71.
19. Karlsen NR, Reinvang I, Froland SS. A follow-up study of neuropsychological function in asymptomatic HIV-infected patients. Acta Neurol Scand 1993;87:83-7.
20. Sarazin FF, Morrison L, Hawley-Foss N, Cameron DW. Efficiency of decision making and mental processing in asymptomatic HIV seropositive cases: a prospective investigation. Int Conf AIDS 1992;8:133 (abstract no. PuB 7504).
21. Rourke SB, Bassel C, Halman MH. Contribution of attention, psychomotor speed and executive processing skills to verbal memory in HIV-1 disease. Neuroscience of HIV Infection. J Neurovirol 1998;4(Suppl.):364.
22. Hinkin CH, Castellon SA, Hardy DJ, Granholm E, Siegle G. Computerized and traditional stroop task dysfunction in HIV-1 infection. Neuropsychol 1999;13:306-16.
23. Castellon SA, Hinkin CH, Myers HF. Neuropsychiatric disturbance is associated with executive dysfunction in HIV-1 infection. J Int Neuropsychol Soc 2000;6:336-47.
24. Sorensen DJ, Martin EM, Robertson LC. Visual attention in HIV-1 infection. Neuropsychol 1994;8:424-32.
25. Maruff P, Malone V, McArthur-Jackson C, Edelstein HE, Chirurgi VA. Abnormalities of visual spatial attention in HIV infection and the HIV-associated dementia complex. J Neuropsychiat Clin Neurosci 1995;7:325-33.
26. Nielsen-Bohlman L, Boyle D, Biggins C, Ezekiel F, Fein G. Semantic priming impairment in HIV. J Int Neuropsychol Soc 1997; 3:348-58.
27. Stout JC, Salmon DP, Butters N, Taylor M, Peavy G, Heindel WC, et al., the HNRC group. Decline in working memory associated with HIV infection. Psychol Med 1995;25:1221-32.
28. Becker JT, Caldararo R, Baddeley AD, Dew MA, Heindel WC, Banks G, et al. Methodological considerations in estimating speed of cognitive operations. J Int Neuropsychol Soc 1995;1: 3-9.
29. Martin EM, Robertson LC, Sorensen DJ, Jagust WJ, Mallon KF, Chirurgi VA. Speed of memory scanning is not affected in early HIV-1 infection. J Clin Exper Neuropsychol 1993;15:311-20.
30. Birren JE, Woods AM, William MV. Behavioural slowing with age: causes, organization, and consequences. In: Poon L, editor. Aging in the 1980's. Washington: Psychological Issues. Amer Psychol Assoc. 1980; p. 293-308.
31. Salthouse TA. Speed of behavior and its implications for cognition. En: Birren JE, Schaie KW, editores. Handbook of the psychology of aging. New York: Van Nostrand Reinhold, 1985; p. 400-26.
32. Salthouse TA. A theory of cognitive aging. Amsterdam: North-Holland, 1985.
33. Cerella J, Poon LW, Williams DM. Age and complexity hypothesis. In: Poon L, editor. Aging in the 1980's. Washington: Psychological Issues. Amer Psychol Assoc. 1980; p. 332-40.
34. Cerella J. Information processing rates in the elderly. Psychol Bull 1985;98:67-83.
35. Bashore T. Age-related changes in mental processing revealed by analyses of event-related brain potential. In: Rohrbaug JW, Parasuranam R, Johnson R, editors. Event-related potentials: basic issues and applications. New York: Oxford University Press, 1990; p. 242-75.
36. Becker JT, Salthouse TA. Neuropsychological tests performance in the acquired immunodeficiency syndrome: independent effects of diagnostic group on functioning. J Int Neuropsychol Soc 1999;5:41-7.

37. Becker JT, Sánchez J, Dew MA, López OL, Dorst SK, Banks G. Neuropsychological abnormalities among HIV-infected individuals in a community-based sample. Neuropsychol 1997;11:592-601.
38. Chang L, Speck O, Miller EN, Braun J, Jovicich J, Koch C, et al. Neural correlates of attention and working memory deficits in HIV patients. Neurology 2001;57:1001-7.
39. Amador F, Mayor J. Enlentecimiento cognitivo en sujetos seropositivos asintomáticos al virus de inmunodeficiencia humana tipo 1. Rev Neurol 2006;42:132-6.
40. Karlsen NR, Reinvang I, Froland SS. Slowed reaction time in asymptomatic HIV-positive patients. Acta Neurol Scand 1992; 86:242-6.
41. Goodin DS, Aminoff MJ, Chernoff DN, Hollander H. A long-latency event-related potential in patients infected with human immunodeficiency virus. Ann Neurol 1990;27:414-9.
42. Fein G, Biggins CA, Mackay S. Delay latency of the event-related brain potential P3A component in HIV disease. Arch Neurol 1995;6:322-35.
43. Baldeweg T, Gruzelier JH, Catalán C, Pughk K, Lovett E, Riccio M, et al. Auditory and visual event-related potential in a controlled investigation of HIV infection. EGG Clin Neurophysiol 1993;88:356-68.
44. Connolly S, Fell M, Manji H, McAllisters RH. P300 event-related potential and neuropsychological testing in HIV infection: follow-up the Middlesex MRC cohort study. In Abstracts of the seventh international conference on AIDS. Florence, 1991.
45. Linville SE, Elliot FS, Larson GE. Event-related potential as indices of subclinical neurological differences in HIV patients during rapid decision making. J Neuropsych Clin Neurosci 1996; 8:293-304.
46. Takakuwa KM, Calaway E, Naylor H, Herztig KE, Llano LM. The effect of the human immunodeficiency virus on visual information processing. Biol Psychol 1993;34:194-7.
47. Posner ML, Rueda MR. Mental Chronometry in the study of individual and group differences. J Clin Exper Neuropsychol 2002; 24:968-76.
48. Jasper HH. The ten-twenty electrode system of the international federation. EEG Clin Neurophysiol 1958;10:371-4.
49. Hardy DJ, Hinkin CH. Reaction time slowing in adults with HIV: results of a meta-analysis using brinley plots. Brain Cogn 2002; 50:25-34.
50. Pfefferbaum A, Ford J, Johnson R Jr, Wenegrad BG, Kopell BS. Manipulation of P3 latency: speed vs accuracy instructions. EEG Clin Neurophysiol 1983;64:424-37.
51. Donchin E, Coles M. Is the P300 component a manifestation of context updating? Behav Brain Sci 1980;11:355-425.
52. Coles MGH, Gratton G, Bashore TR, Eriksen CW, Donchin E. A psychophysiological investigation of the continuous flow model of human information processing. J Exper Psychol Hum Percept Perform 1985;11:529-53.
53. Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. Science 1977;197:792-5.
54. Salthouse TA, Somberg BL. Time-accuracy relationship in young and old adults. J Gerontol 1982;2:349-57.
55. Strayer DL, Wickens CD, Braune R. Adults age differences in the speed and capacity of information processing II: an electrophysiological approach. Psychol Aging 1987;2:99-110.
56. Ritter W, Simpson R, Vaughan HG. Event-related potential correlates of two stage of information processing in physical and semantic discrimination task. Psychophysiology 1983;20:168-79.
57. McCarthy G, Donchin E. A metric for though: a comparison of P300 latency and reaction time. Science 1981;211:77-80.
58. Band G, Ridderinkhof R, Segalowitz S. Explaining neurocognitive aging: a factor enough? Brain Cogn 2002;49:259-67.
59. Band G, Kok A. Age effects on response monitoring in a mental rotation task. Biol Psychol 2000;51:201-21.
60. Kutas M, Donchin E. Preparation to respond as manifested by movement-related potentials. Brain Res 1980;202:15-95.
61. Ratcliff R, Spieler D, McKoon G. Analysis of group differences in processing speed: Where are the models of processing? Psychonomic Bull Rev 2004;11:755-69.
62. Salthouse TA, Hedden T. Interpreting reaction time measures in between group comparison. J Clin Exper Neuropsychol 2002; 24:858-72.