Self-reported neurocognitive impairment in people living with HIV: Characterizing clusters of patients with similar changes in self-reported neurocognitive impairment 2013-2017 in the Swiss HIV Cohort Study

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Summary: Although overall self-reported neurocognitive impairment (srni) is decreasing in the Swiss HIV Cohort Study, there is a group of patients with persisting srni over time, characterized by more past opportunistic infections of the CNS, imperfect adherence to ART and depression.

Abstract

Introduction

Self-reported neurocognitive impairment (srni) in people living with human immunodeficiency virus-1 (HIV-1) infection are frequent. We use longitudinal information on srni in the Swiss HIV Cohort Study (SHCS) to identify and characterize groups of patients with persisting srni over time.

Methods

We included all SHCS patients who were assessed for srni during at least 5 visits spanning at least 2.5 years in 2013-2017. We first compared patients with srni to those without srni over the whole study period. Second, we used a hierarchical cluster algorithm to identify groups of patients with similar changes of srni over time. In both analyses, we studied clinical and demographic factors potentially influencing srni.

Results

In total, 79'683 questionnaires of 11'029 patients contained information about srni, and 8'545/11'029 (77.5%) patients had longitudinal information. The overall percentage of patients with srni decreased from 19.6% in 2013 to 10.7% in 2017. Compared to patients in the cluster with low-level srni over time, patients in the cluster with high-level persisting srni had more often a prior opportunistic infection of the central nervous system (CNS) (OR=3.7, p<0.001), imperfect adherence to antiretroviral treatment (ART) (OR=2.8, p<0.001) and a depression (OR=1.9, p<0.001).

Conclusions

Although overall srni is decreasing in the SHCS, there is a group of patients with persisting srni over time. Past opportunistic infections of the CNS, imperfect adherence to ART as well as depression were associated most with persisting srni. Patients with these characteristics should be preferentially tested for neurocognitive impairment.

Keywords: HIV, self-reported neurocognitive impairment

Introduction

Neurocognitive diseases are well-recognized comorbidities in people living with human immunodeficiency virus-1 (HIV-1) (PLWH) (1). In 1983, the first case of acquired immune deficiency syndrome (AIDS)-related encephalitis was documented and soon after, the AIDS dementia complex was defined (2,3). In 1990, a trial started studying AIDS dementia, the first of a multitude of trials studying neuro-AIDS (4,5). Until today, HIV-associated neurocognitive disorders (HAND), the collective term for neurocognitive diseases in PLWH, is the most common form of neurocognitive impairment before the age of 50 worldwide (1). HAND is divided into three subgroups: asymptomatic neurocognitive impairment (ANI), mild neurocognitive impairment (MND) and HIV-associated dementia (HAD), the most severe form. The prevalence of HAND in PLWH in the era of combination antiretroviral therapy (ART) is estimated to be up to 50%, similar to the prevalence in the pre-ART era, however with a shift from HAD to ANI and MND (6,7). Although people suffering from ANI do not show symptoms (measured on a daily life activity scale), there are higher chances of developing symptomatic forms of HAND as compared to people without ANI (8). In addition, HAND is associated with a decrease in HIV treatment adherence (9).

Our study aims to analyze self-reported neurocognitive impairment (srni) in the Swiss HIV Cohort Study (SHCS), which has been shown to correlate with symptomatic forms of HAND in a sub study (10). The SHCS with its longitudinal data collection and routine questionnaire about srni for all participants provides an ideal framework to study srni on a broad patient population. Using longitudinal information about srni, we apply an unsupervised machine learning technique tailored to the data at hand with the aim at identifying subgroups of patients with similar changes of srni over time. We study potential factors known to influence neurocognitive performance such as age, depression, alcohol consumption, recreational drug use and ART adherence.

Methods

Swiss HIV Cohort Study

The SHCS, launched in 1988, is a prospective multi-center cohort study enrolling adult PLWH in Switzerland (www.shcs.ch) (11). It represents at least 50% of all HIV-1 infected patients ever diagnosed in Switzerland, 72% of all AIDS cases and 75% of all patients receiving ART in Switzerland. For all participants, demographical information is collected at baseline. In semiannual follow-up visits, the SHCS collects laboratory and clinical data, including since 2013 three questions about srni.

Definitions

The three questions on srni are: "Is the patient aware of frequent memory loss in normal daily life?" (short: frequent memory loss), "Does the patient experience difficulties in paying attention in normal daily life?" (short: concentration difficulties) and "Is the patient aware of slowing down in reasoning or solving problems?" (short: slowing down in reasoning). Each question can be answered with "never", "hardly ever" and "yes, definitely". We considered "yes, definitely" in at least one of these questions as srni. Opportunistic infections included all stage B and C diseases as classified by the Center for Disease Control. Opportunistic infections of the CNS included HIV-related encephalopathy, toxoplasmosis of the brain, progressive multifocal leukoencephalopathy, cryptococcal meningitis, primary lymphoma of the brain and other forms of encephalitis (**Section S1.6, Figure S5**). The body mass index (BMI) was defined as the weight (in kg) divided by the height (in m) squared. Hepatitis C virus (HCV) infection was defined as the presence of HCV specific antibodies or a positive HCV RNA test. Syphilis infection was defined as a positive venereal disease research laboratory or rapid plasma reagin test confirmed by a treponema specific test, where we differentiated whether the patient ever had a positive syphilis test result, or whether the first test reported in the SHCS was positive (short: past syphilis). Depression was defined as being diagnosed by a psychiatrist or other physician in at least one follow-up visit during the study period (12). Imperfect adherence to ART was based on self-reporting of the patients and defined as missing at least one dose of ART at least once a week. Self-reported adherence was validated in Glass et al (13) and shown to be significantly correlated with treatment failure and mortality. High alcohol consumption was defined as moderate or severe alcohol use, as defined by the WHO guidelines. Intake of recreational drug use was based on patients' self-reporting.

Study Population

We included patients who completed at least 5 questionnaires on srni spanning at least 2.5 years in 2013-2017, i.e., information for at least half of the possible observation period 2013-

2017 with completed questionnaires every six months (**Figure 1**). First, we compared patients with srni in at least one follow-up visit with those patients who did not have srni in all follow-up visits. Second, we used a hierarchical cluster approach restricted to patients with srni in at least one follow-up visit to identify groups of patients with similar changes of srni over time.

Comparison of patients with and without srni

We compared patients with srni in at least one follow-up visit to patients having no srni in any follow-up visit using Wilcoxon-rank and Fisher exact tests. All analyses were performed with R (version 3.4.4).

Definition of clusters

For each completed questionnaire on srni, the patient could either get a score of '0' if there was no srni, '1' for srni in one question, '2' for srni in two questions or '3' for srni in all three questions. **Figure 2** shows a schematic summary of the algorithm used to find clusters of patients with similar scores over time: First, the scores of each patient were linearly interpolated over time (**Figure 2A**). The area under the curve (AUC) was then calculated for each patient in each of the years 2013-2017 separately (**Figure 2B**). The pairwise distances between the AUCs of the patients were calculated using the Manhattan-metric (**Figure 2C**). Based on the pairwise distances, we continued with the complete-linkage clustering algorithm, a hierarchical algorithm that sequentially combines initially single elements to clusters. The algorithm groups patients with similar trends of srni, measured by the before calculated AUCs (**Figure 2D**). We concentrated on the top three cluster groups of the resulting dendrogram.

Comparison of the clusters

We compared patients in the largest cluster group with patients in the two other cluster groups, respectively. Potential factors associated with srni were compared between the cluster groups using univariable and multivariable logistic regression. Continuous covariables were included in the form of restricted cubic splines (14), using the R package *rms* (15) (**Section S1.1-S1.5, Figures S1-S4**).

Results

Srni in the SHCS

In 2013-2017, a total of 83'144 follow-up visits of 11'068 patients were recorded in the SHCS. Of those, 79'683 (95.8%) questionnaires of 11'029 (99.6%) patients contained completed information about the three questions on srni. The percentage of patients with srni decreased over time from 19.6% (1'730/8'812) in 2013 to 10.7% (1'006/9'377) in 2017. The domain with most srni was frequent memory loss, followed by concentration problems and slowing down in reasoning (**Figure 3**). A total of 8'545/11'029 (77.5%) patients completed at least 5 questionnaires spanning at least 2.5 years in 2013-2017, with 2'754/8'545 (32.2%) patients having srni in at least one domain (see **Section S4, Figures S21, S22** for a comparison of patients with longitudinal information about srni and those without).

Comparison of patients with and without srni

We compared the key available demographic and clinical characteristics between 2'754 patients with srni and 5'791 patients without srni (**Table 1**). Patients with srni were on average one year older ($p < 0.001$), less likely to be male (69.4% vs. 72.6%), $p = 0.002$) and more likely to belong to the transmission group of intravenous drug users (IDU) (17.5% vs. 8.8%, $p < 0.001$). Patients with srni had more often viral blips (35.5% vs. 31.7%, $p < 0.001$), more often prior opportunistic infections (50.3% vs. 43.1%, $p <0.001$) as well as CNS opportunistic infections (6.1% vs. 3.3%, $p < 0.001$). In addition, patients with srni were more likely to have a current or past HCV coinfection (24.1% vs. 15.2%, $p < 0.001$), a depression (45.8% vs. 22.7%, $p < 0.001$) and imperfect adherence to ART (15.6% vs. 9.5%, $p < 0.001$). The average time on ART was 2 years longer for patients with srni ($p < 0.001$) compared to patients without srni and there were differences in ART drug classes: In particular, 78.2% of the patients with srni and 68.7% of the patients without srni used protease inhibitors (PI) ($p < 0.001$) and similarly for integrase strand inhibitor (INSTI) use (20.7% vs 15.7%, $p < 0.001$). In addition, there was a difference in the use of Efavirenz (51.3% vs 54.8%, $p = 0.003$) and Dolutegravir (43.1% vs 40.8%, $p = 0.048$). See **S3.1** for a more detailed analysis of ART treatment over time. Patients with srni reported more often high alcohol consumption (12.2% vs. 6.9%, $p < 0.001$) and intake of recreational drugs (42.6% vs 31.0%, $p < 0.001$).

Patients with similar trends of srni over time

The top three cluster groups contain 2'224 (80.8%), 343 (12.5%) and 187 (6.8%) patients, respectively (**Figure 4A**). The three cluster groups are characterized by a different mean score of srni over time. The largest cluster group, "Cluster 1", is characterized by a

constant low mean score over time, ranging from a score of 0.29 to 0.45, which is lower compared to the overall score, which ranges between 0.49 and 0.73. The second largest cluster group, "Cluster 2", is characterized by a decreasing mean score over time. The mean score was 1.99 in 2013, which is the highest mean score among the three clusters groups, but was decreasing to 0.37 in 2017, i.e., lower compared to "Cluster 1". The smallest cluster group, "Cluster 3", is characterized by a constant high mean score ranging from 1.72 to 2.4. (**Figure 4B**). See **Section S2.2** for more information on srni in the cluster groups and Section **S2.3, Figures S9-S11,** for a subanalysis of "Cluster 1".

Comparison of the three cluster groups

There was no significant difference in the age, gender, ethnicity and BMI of patients when comparing patients in "Cluster 1" with patients in the other two cluster groups, respectively. The transmission group IDU was significantly associated with being in "Cluster 3" compared to "Cluster 1" (OR =1.5, p = 0.029), but the effect disappeared in the adjusted model (OR = 1.2, p = 0.5). Patients in "Cluster 1" had a significantly higher CD4 nadir as compared to patients in "Cluster 2" (p < 0.001, adjusted: p = 0.002), but no significant difference in the CD4 nadir was observed between patients in "Cluster 1" and patients in "Cluster 3". There was no significant difference in the CD4/CD8 ratio and occurrence of viral blips when comparing the three clusters (**Section S3.3-S3.4, Figures S18, S19**). However, there were significant differences in the prevalence of previous opportunistic infections as well as opportunistic infections of the CNS, with an odds ratio of 1.8 (p = 0.004; adjusted OR = 1.5, p = 0.06) for "Cluster 2" and an odds ratio of 3.4 (p < 0.001; adjusted OR = 3.9, p < 0.001) for "Cluster 3". No significant differences between the prevalence of HCV and syphilis could be seen in both comparisons. The difference in the prevalence of depression was significant in the comparison of "Cluster 1" with "Cluster 3" with an odds ratio of 3.2 (p < 0.001; adjusted OR = 1.9, p < 0.001), but the effect disappeared in the adjusted model for the comparison of "Cluster 1" with "Cluster 2" (OR = 1.8, p < 0.001; adjusted OR = 1, p =0.9). There was a significant difference between the proportion of patients who reported imperfect adherence to ART when comparing "Cluster 1" with "Cluster 3" (OR = 2.2, p < 0.001; adjusted OR = 3.1, p < 0.001). No significant difference between drug classes were seen, except for the prescription of dolutegravir (**Section S3.1-S3.2, Figures S12-S17**). Patients in "Cluster 3" reported more often high alcohol consumption compared to "Cluster 1" (OR = 2.0, p < 0.001; adjusted OR = 1.7, p = 0.009). There was no significant difference in recreational drug use when comparing the cluster groups, neither for all the single substances analyzed (**Section S3.5, Figure S20**).

Discussion

The overall proportion of patients with srni in the SHCS was decreasing over the last 5 years in all three domains, namely memory loss, slowing down in reasoning and concentration problems. This is surprising when comparing our results to other longitudinal studies about neurocognitive impairment in resource-rich countries: Sacktor et al (16) found an increase of HAND in the years 2009-2012, emphasized however that HAND was not a progressive condition for the majority of virally suppressed participants. Similarly, Heaton et al (17) followed patients in the CNS HIV Antiretroviral Therapy Effects Research Cohort and found slightly more patients with worsening compared to improving neurocognitive impairment. However, our study analyzes for the first time longitudinal srni for a very large cohort, including a broad patient population not restricted to any patient characteristics such as age or prior knowledge on neurocognitive or psychiatric problems.

Despite the overall decline of srni, there are still patients with persisting srni. It is well-known that effective ART alone cannot eliminate neurocognitive problems, e.g., Simioni et al showed that also patients with long-standing suppression of viremia show cognitive dysfunction (10). It is therefore crucial to understand different factors associated with srni and to identify groups of patients without improvement over time.

By using machine learning techniques, we identified groups of patients with similar changes of srni over time. We employed a clustering algorithm with parameters tailored to this research question to identify patterns in the data set. Using hierarchical clustering algorithms to detect patterns in large longitudinal data sets is informative and has been used before for epidemiological research in HIV cohorts (18).

Most patients belonged to “Cluster 1”, characterized by a low mean score of srni. We could identify two more cluster groups of patients: “Cluster 2”, characterized by a decreasing mean score of srni, has a higher proportion of patients with previous CNS opportunistic infections and depression as compared to “Cluster 1”. Patients in “Cluster 3”, characterized by a high mean score of srni not improving over time, had as well more often a previous CNS opportunistic infections, depression and imperfect adherence to ART as compared to “Cluster 1”. It is interesting that although most CNS opportunistic infections happened long ago (**Section S1.6**), this was factor had the largest impact on srni. Noteworthy, imperfect adherence to ART was significantly higher in “Cluster 3” compared to “Cluster 1”, but not for “Cluster 2”. In a smaller pilot study from the SHCS, Kamal et al (9) showed a correlation between adherence and HAND (and other non-psychiatric cognitive impairment), where adherence was measured with a

medication electronic monitoring system and all patients had neuropsychological evaluations. Moreover, it was shown that self-reported adherence to ART as measured in the SHCS correlates well with virologic failure and mortality (13), suggesting that self-reported adherence correlates well with actual adherence. Due to small effects, many different drug regimens and changes in ART prescriptions, as well as considerable potential for confounding and selection bias, we refrained from interpreting weak differences seen in different drugs or drug classes. One factor which was significant in both comparisons was depression, which shows the importance of taking into consideration psychiatric comorbidities when assessing srni.

Studying neurocognitive impairments in a large patient population longitudinally is hardly feasible, due to expensive and time-consuming neuropsychological testing to diagnose HAND. In accordance with EACS guidelines, the SHCS included three questions about memory loss, slowing down in reasoning and concentration problems in the follow-up interview for all patients. This allowed us to study srni in a large and representative patient population encompassing all major transmission groups. One limitation of this study is that srni might not translate into actual neurocognitive impairments. In a large sub study of the SHCS, the NAMACO (Neurocognitive Assessment in the Metabolic and Aging Cohort) study, 981 participants underwent standardized neuropsychological assessment by neuropsychologists (19,20). The overall prevalence of neurocognitive impairment, as diagnosed using Frascati criteria, was 40% and 27% of the participants were diagnosed with HAND (19). Simioni et al (10) analyzed the correlation of HAND with the three neurocognitive questions in 50 patients with and 50 patients without srni, excluding patients with depression. They found a prevalence of HAND in 84% of patients with srni (24% asymptomatic HAND for patients with srni), and a prevalence of HAND in 64% for patients without srni (60% asymptomatic HAND for patients without srni). Hence, this sub study only found a weak association between the three questions on srni and actual neurocognitive impairment. In particular, patients with asymptomatic forms of HAND could not be detected with these subjective questions. The positive and negative predictive values of the three questions to predict cognitive impairment is unknown but will be analyzed within the NAMACO study. Our study, however, uses longitudinal information on srni. Having persistent srni over a longer period of time might hence be less susceptible to the conditions on that day and potentially yield a higher correlation with HAND. Having said that, any associations of the three questions and HAND are still uncertain and formal testing for HAND in patients with persisting srni would be the next step and planned in the NAMACO study. One limitation regarding the analysis of risk factors is that reactive syphilis tests are an imperfect marker for syphilis and we cannot distinguish between incident and prevalent syphilis.

In summary, our findings show that srni significantly decreased in 2013-2017, which most likely can be attributed to more potent and earlier initiation of therapies used in recent years (21,22) and decreasing treatment failures in the SHCS (23). Furthermore, our results

suggest that all patients with a history of CNS opportunistic infections should be screened in-depth for neurocognitive problems, even if the opportunistic infection occurred a long time ago and the patient has been on suppressive ART for many years. In addition, patients reporting imperfect adherence to ART or having a depression should be considered for further screening of neurocognitive problems. Selecting patients for in-depth neurocognitive screening based on these three criteria is in particular useful for cohorts and patients without longitudinal information about srni.

NOTES

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Competing interests

HFG has received unrestricted research grants from Gilead Sciences and Roche; University of Zurich clinical research priority program, Viral Disease, Zurich Primary HIV Infection Study grant; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from ViiV, Gilead Sciences, Sandoz and Mepha; and

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FIGURES and TABLES

Figure 1

Flow chart to illustrate the study design.

Figure 2: Schematic representation of the hierarchical cluster algorithm used to find clusters of patients with similar scores of self-reported neurocognitive impairments over time. **2A**: Trajectories of the score (0 to 3) over time. **2B**: The area under the curve (AUC) of the trajectories for each year 2013 to 2017. **2C**: The pairwise distances of the AUCs of the patients. **2D**: The resulting dendrogram of the patients.

Figure 3: The percentage of patients with self-reported neurocognitive impairment from 2013 until 2017. 'Questionnaires' denotes the number of completed questionnaires on the three questions about neurocognitive impairment and 'Patients' the respective number of patients.

Figure 4: 4A) The dendrogram resulting from the cluster algorithm. We chose to pick the top three cluster groups for further analysis. **4B)** The mean scores in the three top cluster groups, in addition to the overall mean score of all patients included in the cluster analysis. See **Section S2.1, Figures S6-S8**, for further sub cluster groups.

Table 1

Variable		Patients with self-reported neurocognitive impairment	Patients without self-reported neurocognitive impairment	p value
Self-reported neurocognitive impairment	**Any domain**	**2'754**	**5'791**	
	Concentration (n, perc)	1'724 (62.6%)		
	Slowing down in reasoning (n, perc)	1'291 (46.9%)		
	Memory loss (n, perc)	2'366 (85.9%)		
Years of follow-up	(median, IQR)	4.2 [3.9, 4.5]	4.3 [4.0, 4.5]	0.029
Completed questionnaires	(median, IQR)	9.0 [8.0, 9.0]	9.0 [8.0, 9.0]	0.108
Birth year	(median, IQR)	1965 [1959, 1971]	1966 [1960, 1974]	< 0.001
Diagnosis year	(median, IQR)	2001 [1993, 2007]	2003 [1996, 2008]	< 0.001
Sex	male (n, perc)	1'910 (69.4%)	4'206 (72.6%)	0.002
Ethnicity	white (n, perc)	2'177 (79.0%)	4'542 (78.4%)	0.535
Risk group	Intravenous drug users (n, perc)	481 (17.5%)	511 (8.8%)	< 0.001
	Men who have sex with men (n, perc)	1'102 (40.0%)	2'754 (47.6%)	< 0.001
	Heterosexual (n, perc)	1'025 (37.2%)	2'255 (38.9%)	0.128
	Other (n, perc)	146 (5.3%)	271 (4.7%)	0.217
Highest body mass index	(median, IQR)	26.1 [23.7, 29.2]	25.9 [23.5, 28.7]	0.021
CD4 nadir	(median, IQR)	190 [84, 288]	209 [101, 312]	< 0.001
Lowest CD4/CD8 ratio	(median, IQR)	0.22 [0.12, 0.36]	0.24 [0.14, 0.39]	< 0.001
Viral load	AUC: 2013-2017, copies/mL (median, IQR)	910.0 [0.0, 14511.0]	0.0 [0.0, 12816.7]	0.083
	Viral blips (n, perc)	979 (35.5%)	1'837 (31.7%)	< 0.001
Opportunistic infections	Any (n, perc)	1'385 (50.3%)	2'496 (43.1%)	< 0.001
	Central nervous system (n, perc)	168 (6.1%)	190 (3.3%)	< 0.001

Hepatitis C	(n, perc)	664/2'742 (24.2%)	880/5'751 (15.3%)	< 0.001
Syphilis	any positive test (n, perc)	686 (24.9%)	1'557/5'787 (26.9%)	0.052
	first test positive (n, perc)	324 (11.8%)	663/5'787 (11.5%)	0.690
Depression	(n, perc)	1'261 (45.8%)	1'312 (22.7%)	< 0.001
Antiretroviral therapy	On ART (n, perc)	2'738 (99.4%)	5'750 (99.3%)	0.571
	Years on ART (median, IQR)	14.1 [8.4, 20.4]	12.0 [7.1, 19.2]	< 0.001
	Imperfect adherence (n, perc)	431/2'739 (15.7%)	548/5'746 (9.5%)	< 0.001
	NNRTI (n, perc)	1'778 (64.6%)	3'868 (66.8%)	0.042
	PI (n, perc)	2'153 (78.2%)	3'978 (68.7%)	< 0.001
	INSTI (n, perc)	570 (20.7%)	909 (15.7%)	< 0.001
	Efavirenz (n, perc)	1'413 (51.3%)	3'173 (54.8%)	0.003
	Dolutegravir (n, perc)	1'186 (43.1%)	2'362 (40.8%)	0.048
High alcohol consumption	(n, perc)	337 (12.2%)	400 (6.9%)	< 0.001
Recreational drugs	Any drug (n, perc)	1'166/2'736 (42.6%)	1'779/5'739 (31.0%)	< 0.001
	Cannabis (n, perc)	1'000/2'736 (36.5%)	1'504/5'739 (26.2%)	< 0.001
	Cocaine (n, perc)	513/2'736 (18.8%)	778/5'739 (13.6%)	< 0.001
	MDMA/XTC (n, perc)	222/2'736 (8.1%)	397/5'739 (6.9%)	0.050
	Heroin (n, perc)	224/2'736 (8.2%)	169/5'739 (2.9%)	< 0.001
	Chemsex drugs (n, perc)	160/2'736 (5.8%)	262/5'739 (4.6%)	0.012
	LSD (n, perc)	33/2'736 (1.2%)	31/5'739 (0.5%)	0.002

Table 1: *Basic characteristics of the study population. In case not all patients had information about the corresponding variable, we reported the number at risk in addition (e.g. for Hepatitis C). IQR = interquartile range, Syphilis 'ever' refers to least one positive syphilis test recorded in the SHCS, Syphilis 'previous' refers to patients whose first syphilis test was positive, ART = antiretroviral therapy, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, INSTI = integrase inhibitor, MDMA/XCT = 3,4-Methylendioxy-N-methylamphetamin, Chemsex drugs = Methamphetamine, GHB (4-hydroxybutyric acid), Mephedrone or Ketamine, LSD (Lysergic acid diethylamide*

Figure 1

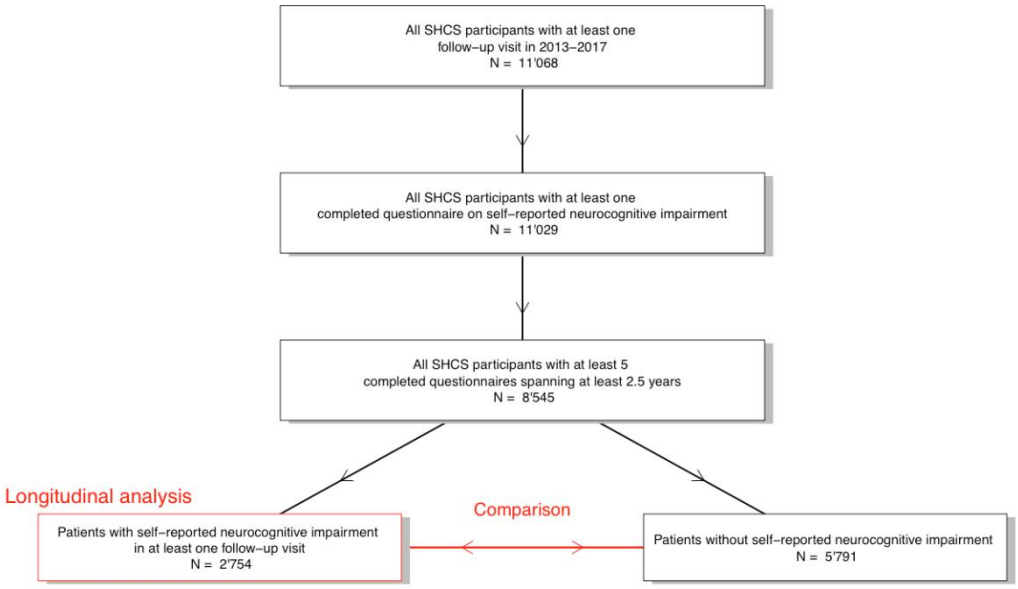
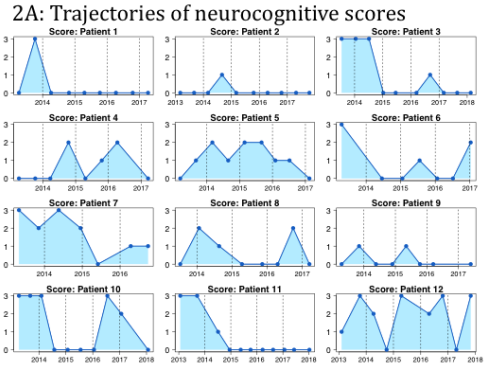


Figure 2

2A: Trajectories of neurocognitive scores



2B: AUCs of the trajectories by year

	2013	2014	2015	2016	2017
Patient 1	1.754	0.208	0.000	0.000	0.000
Patient 2	0.000	0.474	0.030	0.000	0.000
Patient 3	3.000	2.296	0.001	0.455	0.029
Patient 4	0.000	0.902	0.665	1.361	0.227
Patient 5	0.836	1.503	1.845	0.815	0.100
Patient 6	2.088	0.269	0.501	0.469	1.952
Patient 7	2.419	2.528	0.572	0.938	
Patient 8	0.887	1.236	0.061	0.815	0.432
Patient 9	0.577	0.147	0.428	0.000	0.000
Patient 10	3.000	0.990	0.000	1.913	1.118
Patient 11	2.887	1.060	0.000	0.000	0.000
Patient 12	2.195	1.269	2.520	2.375	1.284

2C: Distances of the AUCs

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Patient 1	0.00	2.05	3.82	4.70	4.97	3.32	5.62	3.20	1.67	5.06	1.98	7.68
Patient 2	2.05	0.00	5.33	2.65	4.60	5.18	7.44	2.93	1.30	6.58	3.50	9.14
Patient 3	3.82	5.33	0.00	6.16	5.23	5.38	2.33	4.00	5.48	3.85	1.83	7.53
Patient 4	4.70	2.65	6.16	0.00	3.29	5.50	5.70	2.57	3.16	5.20	5.30	6.49
Patient 5	4.97	4.60	5.23	3.29	0.00	6.03	5.01	2.44	3.95	6.64	5.25	5.01
Patient 6	3.32	5.18	5.38	5.50	6.03	0.00	3.91	4.47	4.13	4.41	4.51	5.70
Patient 7	5.62	7.44	2.33	5.70	5.01	3.91	0.00	4.32	6.63	4.58	4.31	6.08
Patient 8	3.20	2.93	4.00	2.57	2.44	4.47	4.32	0.00	3.01	4.20	3.48	6.21
Patient 9	1.67	1.30	5.48	3.16	3.95	4.13	6.63	3.01	0.00	6.72	3.65	8.49
Patient 10	5.06	6.58	3.85	5.20	6.64	4.41	4.58	4.20	6.72	0.00	3.21	4.23
Patient 11	1.98	3.50	1.83	5.30	5.25	4.51	4.31	3.48	3.65	3.21	0.00	7.08
Patient 12	7.68	9.14	7.53	6.49	5.01	5.70	6.08	6.21	8.49	4.23	7.08	0.00

2D: Resulting hierarchical clustering of the patients

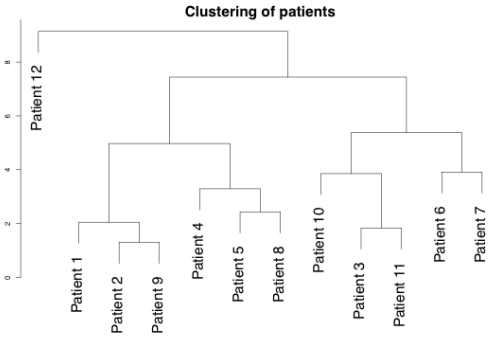


Figure 3

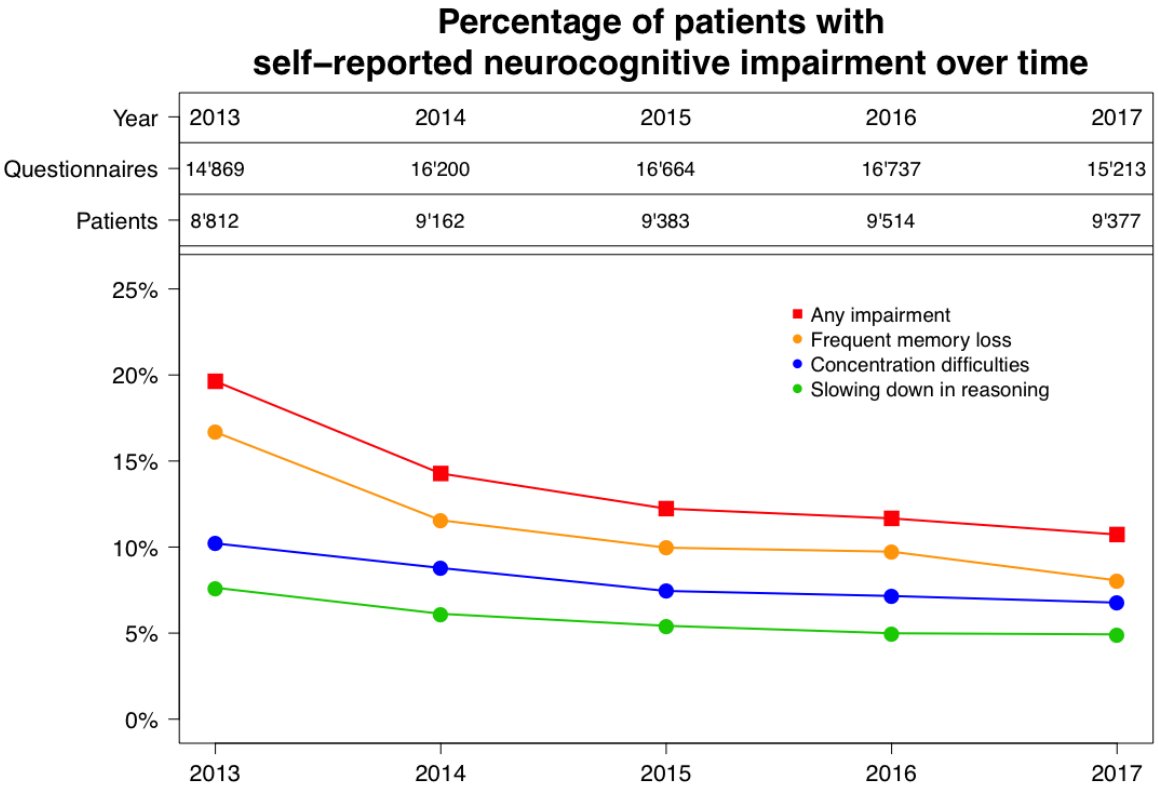


Figure 4