Background

The reported prevalence of cognitive impairment remains similar to that from the pre-antiretroviral therapy era ~50%. This may be partially artefactual due to the diagnostic methods commonly used, as studies with HIV-negative control groups also reportedly have high rates of cognitive impairment (29-36%).

Commonly used methods of identifying impairment rely on defining impaired test performance as an abnormal threshold of deviation from a normative score. These normative scores are defined for each neurocognitive domain in healthy participants and accounting for demographics such as age and level of education, so that normative scores for all tests are normally distributed with a consistent mean and standard deviation (SD) – for T-scores 50 (10).

Aims

In this study, we evaluated the diagnostic performance of the HIV-associated neurocognitive disorder (‘Frascati’ criteria) and the global deficit score (GDS) methods in comparison to a novel, multivariate method of diagnosis which we outline here.

Methods

Normative dataset

• A simulated ‘normative’ dataset (n=10,000) was created with mean (SD) T-scores of 50 (10) across six simulated cognitive domains following a multivariate normal distribution.

• To make the model more accurate and to account for the covariance between cognitive domains, the inter-domain correlation coefficients were set to match those of the HIV-positive group from the Pharmacokinetic and Clinical Observations in PeoPe Over fifty (’POPPY’) study, where participants underwent cognitive function testing using a computerised battery (CogState) covering six cognitive domains.

Multivariate assessment of cognitive impairment

• The Mahalanobis distance (analogous to a multivariate standard deviation) was calculated for each participant from the centre of the simulated normative dataset.

• Each Mahalanobis distance was a threshold value that was compared to the distribution of participants (2) and matched to the normative population with (0.65

• This value was then compared to a critical value to determine if impairment was present using the β distribution.

Next, the apparent prevalence of cognitive impairment was determined by applying the Frascati and GDS methods of impairment as well as the novel multivariate method (table 1).

Results

HIV-positive and HIV-negative groups from POPPY had comparable inter-domain correlation coefficients, justifying the use of the patient group’s data to model the normative population (r(2)=19.5, p<0.01, figure 1).

The proportion of the normative population labelled as having cognitive impairment was significantly lower for the Mahalanobis distance method vs. Frascati or GDS (table 2).

Discussion

The Frascati and GDS methods classify over 20% of a normative control population as cognitively impaired. This may be partly responsible for the reportedly high prevalence of cognitive impairment observed in clinical studies.

Over diagnosis of cognitive impairment is potentially problematic as it may:

• Overstate the burden of disease.

• Lead to unnecessary investigations.

• Cause psychological distress.

• Make further investigation of the underlying pathophysiology more difficult.

The novel multivariate method outlined here was more accurate with a greater positive predictive value than Frascati and GDS.

Further research testing this method needs to be performed, specifically to determine if it identifies people with greater neuropathology.

For an interactive model of these data, please see: https://jonathan-underwood.shinyapps.io/cognitive_impairment_comparision/.

Conclusion

The commonly used diagnostic criteria of HIV-associated cognitive impairment label a significant proportion of any population as cognitively impaired, with a substantial over-estimate of the true proportion. These findings have important implications for clinical research regarding cognitive health. More accurate methods of diagnosis should be implemented, with multivariate techniques offering a promising solution.

Lay summary

People living with HIV are more likely to be diagnosed with cognitive impairment than HIV-negative people. However, the amount of genuine cognitive impairment may be overestimated because the way ‘impaired’ is defined. Over diagnosis may be reduced with a new method – presented here.