

COMMENTARY

Neurocognitive dysfunction in mood disorders

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There has been considerable interest in the neurocognitive functioning of subjects with mood disorders (Bearden et al., 2001). From a theoretical viewpoint, the dysfunction provides insight (especially when monitored with fMRI) into the biological underpinnings, for example, structure and pathway integrity, of mood disorders. From a practical viewpoint, neurocognitive dysfunction underpins many of the activities of daily life and contributes significantly to social, and especially occupational, performance.

Neurocognitive dysfunction can, in broad terms, be regarded as "trait or state". When a person is euthymic and between episodes, trait dysfunction may be seen and there is a growing literature of neurocognitive performance in euthymic mood disorder subjects (Ferrier & Thompson, 2002). When the subjects are unwell - depressed or manic - neurocognitive deficits will result from state and trait contributions and will be influenced by the medication used to treat the person.

The boundaries of specific neurocognitive functions are often blurred, and this is particularly true of executive functions (Funahashi, 2001). Many simple tests are a combination of many functions, for example Reverse Digit Span (RDS) clearly involves immediate memory but, unlike Forward Digit Span (FDS), requires an ability to manipulate information and self-monitor performance (executive functions) to represent digits in reverse order. Many tests of executive function: the Wisconsin Card Sorting Test (WCST), Tower of Hanoi, FAS verbal fluency and so on, are complex and the functions examined by the test may be affected differentially by mood disorder. We can only recommend the use of several, well established, well-defined tests when examining executive function and also recommend looking carefully at results for

differential effects.

The methodology of neurocognitive investigation appears straightforward superficially, but there are both overt and hidden pitfalls. Unipolar disorder or depressive episodes (in DSM-IV or ICD-10) are broad clinical categories. They can embrace symptoms including psychosis, agitation, retardation or contrasting biological symptoms (for example insomnia or hypersomnia). Even bipolar disorder - within its narrower definition - is becoming less clearly bounded with the classification of subtypes of bipolar disorder and a broadening spectrum. Careful specification and quantification of symptomatology in the experimental design will be of help in understanding and comparing results of different studies.

Controlling for potentially confounding variables may be problematic. It is reasonable to wish to compare subjects of broadly similar pre-morbid "abilities". Many proxies have been used, for example, years of education or social class, and each has its different problems. However, illness variables, such as hospitalisations, age, severity or recurrence of illness are also strong predictors of neurocognitive performance (Elliott, 1998). Controlling IQ is particularly problematic. Executive function, however defined, is an important contributor to IQ. If IQ is controlled, then experimentally we should look for differences in the contributions of IQ from several neurocognitive functions. Measurement of IQ itself is time-consuming and brief tests which correlate with IQ are often used. The Digit Symbol Substitution Test is a correlate of "fluid intelligence". The National Adult Reading Test (NART) often finds favour as a proxy of "crystallised intelligence" (Lezak, 1995). The NART however, appears to be culturally dependent. Some items are

even geographically or occupationally specific. Separate versions of the NART are available for use in the UK and the US. To have face validity, a test used in India should therefore be in the person's first language and culturally sensitive.

Computer tests greatly assist data-processing, being both sensitive and precise, but they can be strongly affected by a subject's familiarity with a computer. This may be dependent upon education, culture and many other influences. Thus they should be used with care in populations unfamiliar with computers.

Care is needed in the timing of neuropsychological testing. Circadian (and other) rhythms control endocrine function, especially cortisol levels, which in turn influence cognitive performance (Moffitt et al., 1994; Porterfield et al., 1997). Testing should be carried out at the same time of day. Timing in relation to the menstrual cycle also needs consideration (Rosenberg et al., 2002).

When examining patients who are unwell, either clinically or sub-clinically, residual mood symptomatology can have an important influence on neurocognitive performance. Recent bipolar literature has shown that, even in prospectively verified euthymic bipolar patients, residual symptomatology influences measured performance (Ferrier et al., 2002; Cavanagh et al., 2002). Different ways of controlling for residual symptomatology have been proposed and involve either ANCOVA (Ferrier et al., 1999) or partial correlation analysis (Clark et al. 2002). Our recent work suggests that these methods are equally effective if not equivalent. In studies of unwell patients, a longitudinal design with 6 to 12 months follow-up would be most welcome, to see fully the extent of deficits during illness and the extent and rate of recovery after illness.

Statistical power is often lacking in recently published studies. Sites to perform power calculations are readily accessible and free on the Internet (for example G-power: www.psych.uni-duesseldorf.de/aap/projects/gpower) and for use in simple designs nomograms are available (Altman, 1982). Although avoidance of type I errors is important, type II errors are a significant

problem in low-powered studies. We can only reiterate Videbech's caution not to over-interpret the results of negative studies (Videbech, 1997). Thus, there is a major need in the literature for well-designed studies of high statistical power, which focus on a limited number of hypotheses to resolve the uncertainties current in the literature.

Most neurocognitive studies are carried out on patients and, as clinicians, our primary duty is to the recovery and health of our patients. Treating disorders may be expected to improve neurocognitive performance but the net effect is a balance of this improvement and side-effects of the treatment itself. This balance was recently demonstrated in our study of euthymic bipolar patients, some of whom were medicated with lithium or valproate and others were drug-free. No significant difference was found between the groups although the drug-free subjects performed non-significantly less well on tests of executive function (Goswami et al., 2003 - personal communication). Drug effects (Stein et al., 1998) are often a major uncertainty in studies. Benzodiazepines in particular have significant, deleterious effects on neurocognitive performance (Hartman, 1995). Antipsychotic drugs, despite producing improvement in positive symptoms of schizophrenia, have unwanted cognitive side-effects (King, 1994). The mood stabilisers, sodium valproate and lithium, appear to have relatively small effects upon neurocognitive performance (Devinsky, 1995; Honig et al., 1999; Stip et al., 2000). Nevertheless, uncertainty about drug effects frequently compromise the results of many studies.

A recent study in this journal (Tandon et al., 2002) illustrates the difficulties faced by investigators. Their study, interestingly, showed that in unipolar patients there were deficits on the WCST, which were linked to the severity and duration of illness. Wisely, they did not attempt to control for perceived "abilities", but used the NART only to exclude those with marked learning disabilities. Higher ability subjects (with greater years education) as expected, performed the WCST better than those with less education.

The study was commendably large with 50 patients and 30 controls giving the possibility of useful statistical power. The sex ratio (approximately 5:1) is somewhat unusual. Given of small number of females and the study, it might have been better to restrict the study to males only, and thereby eliminate the confounding influence of menstrual cycle phase or other performance-related gender differences upon the results.

By studying patients who were unwell with differing severity of symptomatology, the "state-trait" distinction could not be explored satisfactorily. Control and correlation of illness severity and performance on the WCST could have proved helpful. A longitudinal follow-up for 6 to 12 months would have established deficits clearly and their eventual recovery. A single aspect of executive function was examined and the inclusion of tests examining other aspects of executive functioning would enhance the scope of the work. Localisation of the structures subserving the WCST has proved problematic. It may not be a "pure" frontal lobe task, but involve neural circuits linking frontal lobe to other cortical structures (Anderson et al., 1991; Grafman et al., 1990). On this single test, Tandon (2002) reported that controls performed less well than Western counterparts, emphasising the value of performing studies in India but also emphasising the need for culturally sensitive tests.

Considerable uncertainties arose from the treatments the patients received. Priority has to be given to patient care, of course; however, uncertainties can be reduced by excluding from the study subjects taking drugs with considerable neurocognitive consequences, especially neuroleptics and benzodiazepines. Patients who had received ECT in the past, correctly, were excluded from the study, as were those with a history of abusing drugs or alcohol. Unfortunately it is difficult to see how to adequately account for differences in treatment received by subjects in the study.

In summary, the study illustrates well the conflict between the need for simple, well-designed well-powered studies asking unambiguous question and the limits placed on research by the priority of patient care.

The study has produced interesting findings, underlined the value of culturally sensitive research in the Indian population and has provided helpful pointers for experimental design in the future.

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We are grateful to Drs. Moore and Gallagher, for their interest in our paper and a lucid, detailed commentary. As pointed out rightly by them, the neuro-cognitive performance is influenced by several confounding factors. Also important to note is the contribution of educational, social, occupational and environmental factors upon the performance of an individual on the assessment tests for one or several cognitive domains.

Our study was planned mostly on depressed patients reporting at the out patient clinic with variable severity, duration and medication status. The setting of the study thus was influenced more by the patient care priorities, rather than stringent research practices.

Singular assessment on WSCT (computer version) was used to facilitate the rapidity of assessments. The findings though interesting could neither differentiate the state-trait dichotomy nor

could take several confounding factors into account due to the methodological constraints and statistical tests utilised.

Suggestions like, considering the influence of gender and socio-educational-cultural factors on assessment and longitudinal follow-up are valid and may be taken into account while planning any study intended to investigate the neuro-cognitive performance in patients and controls in Indian population.