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Subjective Perception of Cognition is Related to Mood and Not Performance

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Abstract

Background—Clinicians monitor cognitive effects of drugs primarily by asking patients to describe their side effects. We examined the relationship of subjective perception of cognition to mood and objective cognitive performance in healthy volunteers and neurological patients.

Methods—Three separate experiments using healthy adults treated with lamotrigine (LTG) and topiramate (TPM), adults with epilepsy on LTG or TPM, and patients with idiopathic Parkinson's disease. Correlations were calculated for change scores on and off drugs in the first two experiments and for the single assessment in experiment three.

Results—Across all three experiments, significant correlations were more frequent (Chi square = 259; $p \leq .000$) for mood vs. subjective cognitive perception (59%) compared to subjective vs. objective cognition (2%) and mood vs. objective cognitive performance (2%).

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Conclusions—Subjective perception of cognitive effects is related more to mood than objective performance. Clinicians should be aware of this relation when assessing patients' cognitive complaints.

Keywords

Antiepileptic drugs; quality of life; Parkinson's disease; neuropsychological assessment; depression

Introduction

Practitioners commonly rely on patient self-report of perceived difficulties with memory, attention, concentration, and language when assessing how much a disease state or its treatment might be affecting day-to-day cognitive functioning. Similarly, self-accounts of cognitive performance are often sought from participants in clinical research trials in order to monitor the safety, efficacy and side effects of the therapy or drug being studied. Therefore, the extent to which subjective perceptions of cognitive functioning correspond to objective measures of cognitive performance is crucial in determining whether or not self-reports should be considered valid appraisals of neuropsychological status upon which diagnostic, treatment, research, or regulatory decisions should be based.

Since subjective memory complaints may serve as an indicator of more general cognitive decline [1], the relationship between the subjective perception of memory impairment and objective measures of memory function has been studied extensively, especially in the elderly. In a number of cross-sectional studies of patients without dementia, subjective memory complaints were more highly correlated with measures of mood, especially depression and anxiety, than with objective measures of cognitive performance [2–7].

Memory is also negatively impacted by epilepsy [8], and patients with epilepsy are apt to report more significant memory disturbances than individuals without epilepsy [9]. Not only are self-reported memory problems by patients with epilepsy weakly correlated with standard memory and neuropsychological measures [10,11], but patients with subjective memory complaints are more likely to be depressed or anxious than those who report no memory difficulties [10,12–14].

Using the Quality of Life in Epilepsy Inventory (QOLIE-89) to measure subjective perceptions of domains known to affect daily living as well as the Profile of Mood States (POMS), Perrine et al [15] found that mood significantly correlated with QOLIE-89 subscales for both memory and attention/concentration as well as with the overall QOLIE-89 score. They also reported smaller, but significant correlations between the objective memory tests and three-self reported QOLIE-89 measures (memory, attention/concentration, health discouragement), suggesting that self-reports of memory impairment by persons with epilepsy may be a function of both mood and objective memory functioning. However, the degree to which neuropsychological measures used in these studies reflect the types of memory problems experienced in day-to-day living has been called into question [12,16]. Elixhauser et al [17] sought to address this issue by using the Rivermead Behavioural Memory Test (RBMT), a measure explicitly designed to assess everyday memory function and found similar associations between everyday behavioral memory performance, subjective perception of memory difficulties (QOLIE-89), and self-reported mood (POMS) in patients with epilepsy. Similar to Perrine et al [15], Elixhauser et al [17] found a strong association between mood and perceived cognitive function, but a smaller, yet significant, correlation between objective memory performance and perceived cognitive function, regardless of whether neuropsychological tests or measures of everyday performance were used.

Investigations into the validity of self-reports of cognitive function in patients with epilepsy have employed subjects whose seizures were controlled by antiepileptic drugs (AEDs). A cross-sectional study by Uijl et al [18] attempted to tease out the contribution of AEDs in the number of subjective complaints that patients with epilepsy conveyed to their physician. Sixty-seven percent of the 173 patients with well-controlled epilepsy reported moderate to severe complaints, most often regarding cognitive dysfunction. The two factors most closely associated with the number and severity of these complaints were high scores on psycho-neuroticism (Symptom Check List-90) and AED polytherapy. These results support the influence of mood on the subjective perception of cognitive impairment, but Uijl et al [18] did not validate those complaints by objective neuropsychological testing. In fact, there are no studies in the literature that have examined the direct effect of drug treatment on subjective perception of cognitive function and its relationship to both mood and objective performance despite the fact that this is the primary method of assessing cognitive side effects of drugs in clinical settings and in clinical trials for regulatory approval of drugs.

We previously published two double-blind studies that compared the effects of two AEDs on neuropsychological function in healthy volunteers [19] and in patients with epilepsy [20]. In this paper, we re-analyzed those data to investigate the relationship of subjective perception, mood and objective cognitive performance as a function of AED treatment effects, i.e., lamotrigine (LTG) and topiramate (TPM). We hypothesized that changes in perception of cognition across drug/non-drug conditions would be more related to changes in mood than to changes in objective cognitive performance.

Since the number of studies that have examined the validity of subjective perception of cognitive performance in patients with neurological diseases remains limited, we also examined the robustness of the relationship between subjective perception of cognition and mood in a new cross-sectional study, that is the first to examine this association in patients with Parkinson's disease.

Materials and Methods

All studies were conducted under the principles of the Helsinki Accords and were approved by the local ethics committees.

Experiment 1: Healthy volunteer AED cognition study

Methodology and prior results have been described in detail elsewhere [19] and are outlined below.

Study Design and Prior Results—Randomized, double-blind, repeated measures, crossover investigation. As previously reported, subjects had significantly better performance on 80% of the neuropsychological variables for lamotrigine compared to topiramate; there were no variables that exhibited superior performance for topiramate [19].

Subjects—Forty-seven (47) healthy paid volunteers (19 men; 28 women; mean age = 37 years) without history of neurologic or psychiatric diseases including drug abuse completed this study.

Procedure—Subjects were treated with each AED in monotherapy for a 12-week period (7 weeks of dose escalation followed by 4 weeks of maintenance, and then a 1 week taper off of AED) followed by a 4-week washout period off AED. Target dose was 300mg/day for both drugs. Subjects underwent neuropsychological testing on four occasions: two AED conditions and two non-drug conditions. The mean (range) blood levels for LTG on the day of

neuropsychological testing was 4.7 mcg/mL (1.6–7.0) and for TPM was 9.3 mcg/mL (2.8–15.8). The mean LTG dose was 298 mg/day and mean TPM dose was 300 mg/day.

Neuropsychological tests—The test battery to assess AED neuropsychological effects consisted of 17 tests: Cognitive performance measures: 1) attention/vigilance—Continuous Performance Task, Digit Cancellation Test, Visual Serial Addition Test; 2) memory—MCG Paragraph Memory, Selective Reminding Test; 3) language—Controlled Oral Word Association Test (COWA), Boston Naming Test, Semantic Fluency Test; 4) cognitive and motor speed—Lafayette Grooved Pegboard, Choice Reaction Time; 5) other cognitive tests—Stroop Color-Word Test^l, Symbol Digit Modalities Test (SDMT); Behavioral measures: Profile of Mood States (POMS-adjective checklist to assess mood; subscales include Tension/Anxiety, Depression, Anger/Hostility, Vigor, Fatigue, and Confusion/Bewilderment), and subjective cognitive function rating scales (i.e., attention, language, and memory) from the Quality of Life in Epilepsy-89 (QOLIE-89). A–B Neurotoxicity Scale, Adverse Events Profile, Side Effects and Life Satisfaction (SEALS) and SF-12 (generic 12-item quality of life scale) were also administered but were not included in the present analysis. Thus, a total of 14 tests with 33 variables were used in the present analysis including three subjective perception of cognition, seven mood, and 23 objective cognitive performance measures for each of the two AED conditions.

Experiment 2. Patients with epilepsy AED cognition study

Study methodology and prior results have been described in detail elsewhere [20] and are outlined below.

Study Design and Prior Results—Randomized, double-blind, repeated measures, parallel group investigation. As previously reported, cognitive performance at the end of the maintenance phase was better for lamotrigine than topiramate when using a combined summary score reflecting performance on all neuropsychological measures (415 vs. 315, $p < .001$) [20].

Subjects—192 patients (116 men, 76 women) aged 18 years or older (mean age = 40 ± 13) with a diagnosis of partial epilepsy who were currently receiving carbamazepine or phenytoin as monotherapy or combined with one additional antiepileptic drug that did not change the enzyme-inducing status of carbamazepine or phenytoin completed the study. The mean ($\pm$ SD) baseline depression score (CES-D) was 17 (12).

Procedures—In this randomized, double-blind, parallel-group design, randomization was stratified by age (<50 years, >50 years) so that comparable numbers of patients in different age groups received each treatment, thereby minimizing the influence of age-related changes in cognition. A screening phase of up to 2 weeks was followed by an 8-week dose-escalation phase during which LTG and TPM were introduced and titrated to target doses of 500 mg/day for LTG and 300 mg/day for TPM on which patients were maintained for 8 weeks. Mean ($\pm$ SDs) daily doses were 493.6 mg (33.9 mg) for LTG and 299.3 mg (4.7 mg) for TPM. Mean (SD) trough serum concentrations were 4.8 (3.9) ug/mL for LTG and 4.9 (2.5) ug/mL for TPM at end of maintenance.

Neuropsychological tests—The following neuropsychological measures were administered at screening, end of dose-escalation phase, and end of maintenance phase: COWA, Stroop Color Word Test, Digit Cancellation, Lafayette Grooved Pegboard, Rey Auditory Verbal Learning Test (RAVLT), and SDMT, Center for Epidemiological Studies Depression Scale (CES-D), POMS, and the cognitive scale from the Quality of Life in Epilepsy-31 (QOLIE-31; single subjective cognitive measure). The Adverse Events Profile was also given but was not included in the present analyses. A total of 15 variables were

analyzed: one subjective perception of cognition, eight mood, and six objective cognitive performance measures for each of the two AED groups.

Experiment 3: Parkinson's disease cognition study

Study Design—This was a cross-sectional analysis with assessment of neuropsychological function.

Subjects—Fifty-eight (58) patients (19 female and 39 male) with idiopathic Parkinson's disease with a mean age 68.3 ± 8.5 years and disease duration of 6.88 ± 5.04 years served as subjects. None of the subjects had clinical depression; all subjects were on stable dopaminergic therapy.

Neuropsychological tests—The battery of tests included: 1) General Cognitive function: Mini Mental State Examination (MMSE) [21] and the Mattis Dementia Rating Scale Total Scaled Score (DRS Total Score) [22]; 2) Frontal Function: COWA, Semantic Animal Naming Fluency, Stroop Task interference, Trail Making Test-Part B [23]; 3) Memory: Hopkins Verbal Learning Test-delayed recall [24]; 4) Depression: Geriatric Depression Scale (GDS) [25]; and 5) Perceived Cognition/Memory Dysfunction: subscale items of the PDQ-39 [26]. There were 11 total variables: three subjective perception, one mood, and seven objective cognitive performance.

Data Analyses

For Experiments 1 and 2, change scores between the non-drug condition to each drug state were calculated for each participant across the objective cognitive measures, subjective perception of cognitive function, and mood measures. Pearson correlations for the change scores between the objective cognitive, subjective cognitive, and mood measures were calculated, resulting in 502 correlations for Experiment 1 and 124 correlations for Experiment 2.

For Experiment 3, a total of 31 Pearson correlations were used to assess the relationship of perceived cognitive functioning to objective cognitive performance and mood. We chose a p value $< .01$ for all studies as a compromise between Type I and II errors in order to provide some control for the multiple comparisons, but also to permit examination of the pattern of correlations across the three sets of experiments. As a further control for Type I error, the pattern of correlations across all studies combined were compared using Chi square analysis.

Results

A summary of the correlations results for the combined experiments and for each individual experiment are depicted in Table 1. The occurrence of significant correlations across all three experiments differed for the comparisons of subjective cognitive perception, mood, and objective cognitive performance (Chi square = 259; $p \leq .000$). Comparisons of mood vs. subjective cognitive perception were much more likely to exhibit significant correlations. The pattern of correlations was similar for each of the three experimental groups.

Experiment 1: Healthy volunteer AED cognition study

Relationship between perception of cognition and mood

LTG treatment: The subjective measure of memory (QOLIE-memory; [non-drug average minus drug]) showed a significant ($p < .01$) negative correlation with the total score on the POMS ($r = -.424$), as well as with 4 of 6 subscales of the POMS: Depression ($r = -.424$); Anger ($r = -.367$); Fatigue ($r = -.411$); Confusion ($r = -.524$). QOLIE-Attention was negatively

correlated ($p < .01$) with the total POMS score ($r = -.691$), as well as with 5 of 6 subscales: Tension ($r = -.425$); Depression ($r = -.663$); Anger ($r = -.470$); Fatigue ($r = -.548$); Confusion ($r = -.733$).

QOLIE-Language was negatively correlated ($p < .01$) with the total POMS score ($r = -.416$), as well as with 3 of 6 subscales: Anger ($r = -.417$), Fatigue ($r = -.488$), and Confusion ($r = -.633$).

TPM treatment: There was no demonstrable relationship between QOLIE-memory and any mood measures. The QOLIE-Attention was negatively correlated ($p < .01$) with POMS-Fatigue ($r = -.519$) and positively correlated with POMS-Vigor ($r = .416$). QOLIE-Language showed a negative correlation with total POMS average score ($r = -.444$), as well as with Fatigue ($r = -.408$), and Confusion ($r = -.482$).

Relationship between cognitive performance and mood

LTG treatment: There were significant positive correlations ($p < .01$) between CRT – Initiation and total POMS average score ($r = .391$) as well as with Anger ($r = 0.434$), Confusion ($r = .500$), and Fatigue ($r = .440$).

TPM treatment: The Animal Naming Fluency Test was negatively associated ($p < .01$) with the total POMS score ($r = -.417$) and Confusion ($r = -.461$). Boston Naming Test was significantly associated with POMS Vigor ($r = -.373$). Grooved Pegboard was positively associated with POMS Anger ($r = .385$).

Relationship between cognitive performance and perception of cognition

LTG treatment: Both QOLIE-Language ($r = -.456$, $p = .002$) and QOLIE-Attention ($r = -.384$, $p = .009$) were associated with only a single measure of cognitive functioning, Choice Reaction Time – Initiation. QOLIE-Memory showed no association with cognitive performance.

TPM treatment: There were no significant correlations reported between any of the three measures of perception of cognition and those of cognitive performance.

Experiment 2: Patients with epilepsy AED cognition study

Relationship between perception of cognition and mood

LTG treatment: Bivariate correlations on change scores across all points revealed significant correlations ($p < .01$ with r values ranging from -0.316 to 0.626) for the QOLIE-31 cognitive subscale to all eight measures from the CES-D and POMS.

TPM treatment: Five out of eight measures (i.e., CES-D and POMS – confusion, fatigue, tension, and total) were significantly correlated with the QOLIE-31 cognitive subscale.

Relationship between cognitive performance and mood

LTG treatment: There were no significant correlations between any of the objective measures and those of mood.

TPM treatment: Only Digit Cancellation showed a significant association with a mood measure (POMS Depression: $r = .349$, $p < .005$).

Relationship between perception of cognition and cognitive performance

LTG treatment: No objective measures were correlated to the QOLIE-31 cognitive subscale.

TPM treatment: COWA was the only objective measure of cognitive performance that was significantly associated with the QOLIE-31 cognitive subscales ($r = .304$, $p < .007$).

Experiment 3: Parkinson's disease cognition study

Relationship between perception of cognition and mood—All three measures of perceived cognition had moderate positive association with the Geriatric Depression Scale (GDS) ($p < .001$).

Relationship between cognitive performance and mood—There were no significant correlations between any of the objective measures of cognition and the GDS.

Relationship of perception of cognition and cognitive performance—There was no significant association between any of the measures of perceived cognition and measures thought to assess frontal lobe functioning (i.e., COWA, Stroop, and Trail Making Test- Part B). None of the measures of perception of cognition were negatively correlated with the memory measure (i.e., Hopkins Verbal Learning Test – delayed). Using the MMSE and the Mattis Dementia Rating Scale (DRS) as measures of general cognitive function, the perceived cognition item of the PDQ-39 was significantly associated with MMSE ($r = -0.364$, $p = 0.005$), but none of the items of perceived cognition/memory dysfunction were significantly correlated with the DRS.

Discussion

We have demonstrated in two double-blind, randomized, repeated measures design studies of healthy volunteers (crossover) and epilepsy patients (parallel-group) that the subjective perception of AED cognitive effects is more related to mood than objective neuropsychological performance. Similar to prior cross sectional studies in epilepsy patients [15,17], we have also demonstrated the same phenomenon in patients with Parkinson's disease. Self-report of cognitive impairment can be affected by some diseases (e.g., anosognosia). However, the pattern of a strong relationship of mood to subjective perception of cognition in contrast to our other comparisons was also seen in healthy volunteers and in a variety of disease states including those without a primary effect on the brain.

The pattern of significant correlations is unlikely due to chance given that the large majority of significant correlations occurred for mood versus subjective cognitive perception, which was statistically greater than other contrasts. Further, the findings in our present studies are consistent with a number of prior studies from disparate patient populations including epilepsy [15,17], psychogenic nonepileptic seizures [27], coronary artery bypass surgery [28], Cushing's Disease [29], cancer [30], multiple sclerosis [31,32], and psychiatric disorders [33,34]. The observation of a similar pattern across independent samples, different clinical conditions, different neuropsychological measures, and different experimental designs in our studies as well as in others replicates the finding that mood is a primary contributor to subjective cognitive complaints, and illustrates the robustness of this effect. Researchers and clinicians must consider with skepticism the subjective cognitive ratings of healthy subjects or patients with a wide range of medical conditions, since there is now sufficient evidence for the position that these reports are frequently a function of mood rather than actual cognitive functioning.

One limitation of this study is the relatively large number of correlations performed. Because no consensus exists regarding Type I error control, the choice between minimizing Type I errors vs. Type II errors should be based upon context-dependent pragmatic considerations where informed personal judgement plays a vital role [35]. We consider our approach using a conservative value of .01 to indicate statistical significance to represent an appropriate balance. Although it is possible that some of the significant correlations result from chance associations,

the overall pattern of findings cannot be easily attributed to chance or spurious correlations alone, as evidenced by our chi square analysis. Thus, the pattern more likely reflects a dissociation between objective and subjective measures of cognition in their relationship to mood.

We do not assert that there is no relationship between subjective and objective measures of cognitive abilities. Several studies including our own have shown a significant correlation between objective cognitive test performance and perceived cognitive function, though the correlations are not nearly as frequent or strong as those between mood and subjective reports [15,17,36]. For example, Elixhauser et al. found that both mood and objective memory performance were independent predictors of perceived memory functioning, but the explained variance for mood and memory performance combined ($R^2 = 0.58$) is only slightly higher than the predictive value for the mood scales alone ($R^2 = 0.56$) [17].

We report few significant correlations between mood and cognitive performance in the present study. Depression can produce a reversible cognitive impairment called “pseudodementia” [37]. The cognitive performance of both adult and elderly patients with unipolar depression has also been reported to improve after treatment with antidepressants [38], but the improvement can be modest or absent [39]. Moreover, non-elderly patients with unipolar or bipolar depression have been shown to have impaired cognition even in an euthymic state [40]. Therefore, the degree to which depression affects cognitive performance is not consistent across all groups studied. We found few significant correlations between mood and cognitive performance in the present study.

In subjects who manifested a negative mood, the extent of their depressed state may not have been sufficient to affect their objective cognitive performance but was sufficient to affect their perception of everyday functioning; none of the present studies was designed to test this hypothesis. Nevertheless, our results clearly underscore the necessity for clinicians and researchers to take into account mood, medical condition, and drug treatment when assessing the validity of subjective cognitive ratings.

In the clinical setting, physicians monitor adverse cognitive side effects of medications by spontaneous patient reports or by asking patients. Clinical trials conducted for regulatory approval of drugs depend primarily on patient report to determine safety with regard to cognitive side effects. Thus, patient care and regulatory safety assessments rely on patients’ perception to determine adverse drug-induced cognitive side effects even though their perception is much more related to mood than actual cognitive performance. Patient perception alone may not adequately assess for important cognitive side effects in both clinical practice and research investigations including regulatory studies. This concern is especially important in groups with increased susceptibility such as children and the elderly. Even a modest untoward effect on cognitive performance might be problematic in children over the course of neurodevelopment or in the elderly due to their increased vulnerability to drug-induced cognitive side effects.

Problems with objective measurement of drug-induced decrements in cognitive performance include time, costs, sensitivity of the measurements, test-retest effects, availability of trained personnel for cognitive assessments, and confounding effects of various clinical factors. Within research trials, these effects can be addressed and should be considered a part of the regulatory process. In a clinical practice setting, there is presently no proven and pragmatic methodology to assess patients on an individual basis. Standardized, brief computerized cognitive batteries and electroencephalographic measures combined with mood and drug toxicity questionnaires offer hope [41], but additional research is needed. In the interim, clinicians need to consider the impact of mood on their patients’ complaints of cognitive problems. They should assess

mood and evaluate its contribution in comparison to the underlying disease state and the potential risk that the drug may adversely affect cognitive function. Possible therapeutic actions might include treatment of mood or other contributing diseases or alteration of the drug regimen.

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Table 1

Summary of percent significant correlations (# significant/# total correlations) for all studies combined and each individual study.

	All Studies Combined	Healthy Volunteers	Epilepsy Patients	Parkinson Patients
Perception of Cognition vs. Mood	59% (36/61)	48% (20/42)	81% (13/16)	100% (3/3)
Perception of Cognition vs. Cognitive Performance	2% (4/171)	1% (2/138)	8% (1/12)	5% (1/21)
Mood vs. Cognitive Performance	2% (9/425)	2% (8/322)	1% (1/96)	0% (0/7)