Published in final edited form as:

Neuropsychology. 2011 January ; 25(1): 125–130. doi:10.1037/a0020859.

Subjective Cognitive Complaints and Longitudinal Changes in Memory and Brain Function

Timothy J. Hohman, BA^{1,2}, Lori L. Beason-Held, PhD¹, Melissa Lamar, PhD³, and Susan M. Resnick, PhD¹

¹Laboratory of Personality and Cognition, National Institute on Aging, NIH

²Department of Psychology, The American University, Washington, DC

³Department of Psychiatry, University of Illinois, Chicago, IL

Abstract

Objective—Subjective cognitive complaints are often used in the diagnosis of memory and other cognitive impairment. This study examined whether cognitive complaints are associated with longitudinal changes in cognition and cross-sectional differences in regional brain function during memory performance in 98 participants with a mean age of 75.

Method—The Cognitive Failures Questionnaire (CFQ) assessed cognitive complaints and mixed effects regression models were used to determine whether mean CFQ scores predicted rates of change in cognitive function over a period of 11.5 years.

Results—Higher CFQ scores, reflecting increased subjective complaints, were associated with steeper rates of decline in immediate and delayed recall on the California Verbal Learning Test. Voxel-based regression analysis was used to determine the cross-sectional relationship between CFQ scores and regional cerebral blood flow measured by PET during a resting condition and during verbal and figural memory tasks. Higher levels of cognitive complaints were associated with increased activity in insular, lingual and cerebellar areas during memory tasks.

Conclusions—These findings offer some support for the validity of subjective cognitive complaints as markers of age related changes in memory and brain activity.

Keywords

Aging; Cerebral Blood Flow; Memory; Cognitive Failures

Introduction

Subjective memory complaints are typically an implicit component of the diagnosis of early stages of clinical dementia and Mild Cognitive Impairment (MCI) (Clement, Belleville, & Gauthier, 2008). Memory complaints may be based on self-report from a patient, or a report from an informant, a relative or friend, who may observe changes in the patient's cognitive functioning. These subjective reports are critical in identifying subtle changes in everyday functioning that cannot be captured in other ways. As it is apparent that memory decline begins many years before clinical symptoms result in a diagnosis of dementia (Driscoll et al., 2006; Kawas et al., 2003), subjective cognitive complaints may detect changes before

they are observed on objective neuropsychological tests and may assume increasing importance in identifying cognitive decline and impairment at the earliest possible stage.

Attempts to use subjective cognitive complaints to predict objective cognitive performance have yielded mixed results. Some studies have shown a relationship between subjective complaints and future dementia (Jungwirth et al., 2008), some have shown a relationship between complaints and delay recall tasks (Manes, Serrano, Calcagno, Cardozo, & Hodges, 2008), while other studies have shown no relationship between subjective memory complaints and memory performance regardless of age (Mendes et al., 2008). Furthermore, judgments of cognitive ability are often deemed overconfident, unreliable, and influenced by the context in which they are made (Simon & Bjork, 2001). When a relationship between subjective complaints and objective performance is observed in older adults, it can often be attributed to personality factors or emotional disposition (Hanninen et al., 1994; Minett, Da Silva, Ortiz, & Bertolucci, 2008). Nevertheless, some reports indicate that memory complaints are an early indication of memory impairment, even when adjusting for affect (Jorm, Christensen, Korten, Jacomb, & Henderson, 2001; Schaafsma, Homewood, & Taylor, 2009). These inconsistencies have raised questions about the utility of subjective memory complaints in clinical diagnoses (Reid & MacLulich, 2006).

If subjective memory complaints are a valid indicator of cerebral dysfunction, then a subjective measure of cognitive complaints should predict concurrent physiologic differences and longitudinal cognitive decline (Manes et al., 2008). However, only a limited number of studies have examined the longitudinal relationships between subjective memory complaints and objective performance (Ahmed et al., 2008; Dufouil, Fuhrer, & Alperovitch, 2005; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). The results of these longitudinal studies were mixed as well, with some indicating that subjective memory complaints were useful for identifying individuals who are at risk for future dementia, others finding that subjective memory complaints were useful for predicting changes in objective performance over time, and other results indicating the lack of a relationship between memory complaints and objective performance.

In this study, we test the hypothesis that elevated scores on a measure of cognitive complaints, the Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982), predict longitudinal declines on objective memory tests over an average period of 11.5 years. Further, we investigate whether levels of cognitive complaints are related to regional brain activity during memory performance at the time of CFQ assessment.

Methods

Subjects

All participants in the neuroimaging study of the Baltimore Longitudinal Study of Aging (BLSA) completed the CFQ. We used cognitive data from 101 participants (58 male, 43 female). The mean baseline age was 66.82 (6.9 SD; Range = 53.0 – 83.3) with a mean education level of 16.6 years (2.4 SD; Range = 8 – 20). Mean age and education were not significantly different for men and women.

All participants were in generally good health at baseline imaging evaluation without evidence of CNS disease, severe cardiovascular or pulmonary disease, major psychiatric disorders including depression, or metastatic cancer. Approximately half of the sample was hypertensive, the majority of which was controlled with medication. Participants with a consensus diagnosis of mild cognitive impairment (MCI) and dementia at any point during

the follow-up period were excluded from the analyses, along with participants with stroke, cancer, and brain damage.

Written informed consent was obtained from each participant at each neuroimaging visit, and the study was approved by the local Institutional Review Board and the National Institute on Aging.

Cognitive Assessment

Administration of the Cognitive Failures Questionnaire began in the year 2000 for the participants in this study. The CFQ assesses subjective cognitive complaints and is composed of 25 questions relating to basic cognitive problems people may have in everyday activities, such as: Do you forget why you went to one part of the house? Do you forget whether you have turned off a light? Do you find you confuse your left and right? Questions are rated on a scale of 0 (never have this problem) to 4 (I have this problem very often), and higher scores signify greater perceived impairment. The CFQ was administered an average of 3.2 times (1.3 SD; Range = 1 – 5) across an average span of 3.5 years. Because an exploratory factor analysis of the CFQ items yielded only a single general factor, we restricted our analyses to the CFQ total score. Moreover, we used the mean CFQ score across visits to increase reliability and to provide a measure of more chronically elevated cognitive complaints.

Participants also completed a battery of twelve neuropsychological tests evaluating six cognitive domains at each visit. Memory was assessed using the California Verbal Learning Test (CVLT) and Benton Visual Retention Test (BVRT). Word knowledge and verbal ability were measured using Primary Mental Abilities Vocabulary (PMA). Attention and working memory were measured by the Digit Span Test of the Wechsler Adult Intelligence Scale-Revised, and the Trail Making Test. Digits Backward, Trails B, and Verbal Fluency (categories and letters) assessed executive function. The Card Rotations Test assessed visuospatial function. To limit the number of analyses and to focus on memory and executive function, we examined the CFQ in relation to the following measures: the CVLT (immediate free and delayed recall scores), BVRT total errors, and Trails (B-A time in seconds). Depressive symptoms were also measured by the total score on the Center for Epidemiological Studies – Depression (CES-D) scale (Radloff, 1977). Neuropsychological data from an average of 10.6 assessments (1.6 SD; Range = 5 – 14) across an average span of 11.5 years beginning in the year 1993 were used in the analyses.

Pet Scanning and Image Processing

Participants underwent PET scans beginning at baseline neuroimaging evaluation (year one) with up to eight annual follow up imaging assessments across a span of 9 years. The PET data used in the present analyses were from the first year in which the participant had a CFQ assessment and a PET evaluation during the same visit. Because the CFQ was added six years after serial PET studies began, the association between CFQ and PET imaging was analyzed cross-sectionally to assess the relationship between subjective complaints using a mean CFQ score and regional cerebral blood flow (rCBF) during memory function at the time of first CFQ administration.

PET measures of regional cerebral blood flow (rCBF) were obtained using [^{15}O]water. For each scan, 75 mCi of [^{15}O] water were injected as a bolus. Scans were performed on a GE 4096+ scanner, which provides 15 slices of 6.5 mm thickness. Images were acquired for 60 seconds from the time the total radioactivity counts in the brain reached threshold level. Attenuation correction was performed using a transmission scan acquired prior to the emission scans.

Each session included a resting scan in which participants were instructed to keep their eyes open and focused on a computer screen covered by a black cloth. Participants also underwent PET scans during verbal and figural delayed recognition memory tasks. During each recognition memory task, participants were asked to identify words or abstract designs that had been presented at the beginning of the session. Approximately thirty minutes before the first PET scan, participants were shown a list of 20 target words for the verbal task and 20 target figures for the figural task on a computer screen (see (Resnick, Maki, Golski, Kraut, & Zonderman, 1998) for detailed description). They were instructed to silently examine each item and try to remember it for later. During the verbal and figural recognition memory tasks, approximately 40 test items were shown during the PET image acquisition interval. Twenty of these were novel distracter items intermixed with the original 20 target items. Participants were asked to indicate whether or not they had seen each item before by pressing buttons in their right or left hands. Scan order was counter-balanced across subjects but remained constant over repeated assessments.

The PET scans were realigned and spatially normalized into standard stereotactic space and smoothed to full width at half maximum of 12×12×12 mm in the x, y, and z planes. To control for variability in global flow, rCBF values at each voxel were ratio adjusted to the mean global flow and scaled to 50 ml/100g/min for each image. Image processing and analysis was performed using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, London, England).

Statistical Analysis

Subjective Cognitive Complaints and Cognitive Decline—Statistical analysis was conducted using SAS 9.1 Software (SAS Institute Inc., Cary, NC). As noted above, an exploratory factor analysis of CFQ items yielded a single general factor, and thus, all analyses were based on the CFQ total score. Pearson correlations across repeated CFQ assessments (an average of 3.2 per individual) showed good stability, $r = 0.73$, $p < .0001$. The mean CFQ score was calculated as an estimate of more chronic cognitive complaints. We tested the hypothesis that higher mean CFQ scores predict longitudinal declines in cognitive function from baseline (on average, 8 years prior to initial CFQ) to last cognitive assessment. Mixed effects models were employed with mean CFQ as the independent variable and specific cognitive outcomes from objective testing as dependent measures in separate analyses. To limit the number of dependent measures, we restricted our analyses to the following outcomes: CVLT total correct on immediate free recall (sum of Trials 1–5); CVLT delayed free recall; BVRT total errors; and Trails B – A (time in seconds). In addition to mean CFQ total score, age at baseline cognitive assessment, interval in years from baseline, and their interactions with mean CFQ were independent measures, with interval treated as a random effect. All cognitive data between 1993 and 2007 were used in the analyses. Model reductions were performed using backward elimination, whereby non-significant interaction terms were removed sequentially from the model. Secondary analyses were conducted adjusting for depressive symptoms and education, using the mean CES-D score (across visits where the CVLT had been administered) and the highest level of education completed (in years).

Subjective Cognitive Complaints and rCBF using PET—For each participant, PET scans acquired during the same visit as the first CFQ assessment were used in a cross-sectional analysis. First, to establish the typical pattern of activation for this type of memory task, a voxel by voxel activation map was determined across the combined verbal and figural memory conditions relative to rest. Next, to assess the relationship between mean CFQ and brain activity during memory performance, a multiple regression analysis was performed regressing CFQ scores on combined rCBF during the figural and verbal memory

task performance. The results of the regression analysis were then plotted onto the activation map to examine regional overlap between the analyses. Age at the time of PET scan and sex were included as covariates in both analyses and both analyses adjusted for global blood flow. Significant effects for the analyses were based on magnitude ($p < 0.05$ FDR corrected) and spatial extent (50 voxels).

Results

Subjective Cognitive Complaints and Cognitive Decline

Analysis of the effects of mean CFQ on longitudinal change in memory by mixed effects regression showed no significant main effect of baseline age or mean CFQ on CVLT immediate recall scores. There was a main effect of interval, $t(971) = 2.55$, $p = 0.01$, and a significant effect of mean CFQ on change in CVLT immediate recall scores, $t(971) = -2.6$, $p = 0.010$. Higher levels of cognitive complaints were associated with greater longitudinal decline in CVLT immediate recall (Trials 1–5) performance (Figure 1). Figure 2 highlights trajectories of CVLT performance over time for individuals in the highest CFQ quartile compared to the remaining participants. Similarly, no main effects were seen for baseline age, mean CFQ scores, or interval on CVLT delayed free recall, but there was an effect of mean CFQ on longitudinal change in CVLT delayed free recall, $t(973) = -1.98$, $p = 0.048$ (Figure 1). Given that there was a relationship between depression scores and CFQ scores at baseline, we chose to include depression scores as a covariate in the model. Doing so did not influence associations between mean CFQ and declines in immediate and delayed verbal recall. Further, there was no main effect of CFQ on overall performance on any cognitive outcome, and mean CFQ was not related to longitudinal changes in figural memory or executive function.

Subjective Cognitive Complaints and Brain Function

The regression analysis showed significant effects of CFQ on patterns of brain activity during memory performance. High levels of cognitive complaints were associated with higher rCBF in the insula bilaterally, the right inferior parietal cortex (Brodmann Area (BA) 40), the left lingual gyrus (BA 18), the right fusiform gyrus (BA 19), and the cerebellum bilaterally (Table 1). There were no regions showing lower brain activity in association with higher cognitive complaints.

Patterns of memory-related activation and deactivations when comparing memory tasks to the resting condition were similar to previous reports from our laboratory (Beason-Held, Golski, Kraut, Esposito, & Resnick, 2005; Beason-Held, Kraut, & Resnick, 2009). These patterns included task-related increased activation in bilateral prefrontal and posterior occipitotemporal regions, in conjunction with decreased activation in medial frontal, anterior temporal, posterior cingulate and precuneus regions. Superimposing regions showing associations between CFQ and rCBF during memory tasks with the patterns of task-related activations revealed an area of overlap in the lingual gyrus of the occipital lobe (Figure 3).

In terms of task performance, participants showed no relationship between accuracy during memory performance in the scanner and CFQ scores. A positive relationship was observed between CFQ scores and verbal reaction time ($r = 0.22$, $p = 0.037$). There was no relationship between CFQ scores and performance averaged of the verbal and figural conditions.

Discussion

Our findings indicate that subjective cognitive complaints are associated with both objective memory performance and brain function in older individuals. Although CFQ scores were not associated with baseline verbal memory performance, higher CFQ scores were associated with longitudinal declines in verbal memory over time and with cross-sectional variation in regional brain activity.

Subjective Cognitive Complaints and Objective Cognitive Performance

The first goal was to examine the relationship between CFQ self-reported ratings and objective measures of cognitive performance in individuals free of cognitive impairment. As hypothesized, we found that mean CFQ scores predicted trajectories of decline over time in immediate and delayed verbal recall on the CVLT. The relationship between CFQ and verbal memory suggests that individuals with higher levels of cognitive complaints show greater declines in verbal memory performance over time. The associations between higher mean CFQ and greater decline in verbal memory was observed despite the fact that a large number of individuals showed improvement in performance on repeated CVLT testing, consistent with our previous observations (Lamar, Resnick, & Zonderman, 2003). Yet, prior predominantly cross-sectional studies have yielded mixed support for relationships between subjective and objective measures of cognition (Brown, Dodrill, Clark, & Zych, 1991; Minett et al., 2008; Miranda et al., 2008; Wong et al., 2006; Zelinski, Gilewski, & Anthony-Bergstone, 1990). Like many of the previous cross-sectional results, we did not observe cross-sectional associations between CFQ scores and overall levels of performance on any of the cognitive measures, including verbal memory. In contrast, our analysis of CFQ in relation to longitudinal change in verbal memory revealed that higher CFQ was associated with more rapid decline in verbal memory. In addition, our measure of subjective cognitive complaints is based on a mean CFQ score and multiple follow-up assessments, yielding more stable measures of both cognitive complaints and trajectories of memory decline.

The relationship between subjective memory complaints and longitudinal decline in verbal memory performance lends credence to the possible predictive value of the CFQ. Verbal memory decline and impairment are evident years prior to a diagnosis of dementia (Grober et al., 2008; Howieson et al., 2008). Moreover, performance on the CVLT has been specifically implicated in predicting future dementia type and discriminating between normal aging, MCI, and dementia (Greenaway et al., 2006; Royall, Palmer, Chiodo, & Polk, 2003). Our findings also suggest that associations with subjective cognitive complaints may be specific to verbal memory and may extend to prediction of cognitive decline within the normal range of age-associated changes in verbal memory even prior to overt impairment.

Conflicting results from previous studies of subjective memory may be related to several factors. Among the factors most often discussed are the effects of mood and depressive symptoms on self ratings (Moore et al., 1997; Rabbitt & Abson, 1990, 1991; Simon & Bjork, 2001). Here, we used a mean CFQ score, reflecting an overall level of cognitive complaints over time, which may be less sensitive to temporal variability in mood and cognitive complaints. Furthermore, to address the issue of depression, a measure of depressive symptoms was included as a covariate in secondary analyses. The association between mean CFQ and change in both immediate verbal recall and delayed free recall remained significant after adjusting for depressive symptom scores, suggesting that depressive symptoms did not play a significant role in the relationship between subjective ratings and verbal memory performance over time.

It is also interesting that the relationship between CFQ scores and objective cognitive performance was restricted to verbal memory performance in the current study. Broadbent

and colleagues (1982) believed the CFQ scale measured lapses in perception and motor function as well as memory. Because changes in verbal memory are observed early in the course of cognitive impairment (Grober et al., 2008), it is possible that the CFQ captures these changes before declines in other cognitive domains are evident.

Subjective Cognitive Complaints and Brain Function

Overall, high levels of cognitive complaints were related to increased levels of activity in insular, occipital, and inferior parietal regions during memory processing. Activity within these regions is not uncommon in PET studies of memory performance (Tulving, Habib, Nyberg, Lepage, & McIntosh, 1999). For example, previous studies have shown that insular activity has a negative relationship to recognition performance (Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Nyberg et al., 1995; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994), suggesting that increased activity is associated with poorer task performance. Although increased cognitive complaints in the present study were not associated with overt differences in task accuracy, it is interesting that differences in rCBF occurred in regions where activation is indicative of memory performance levels. Based on the increased levels of activity observed in these areas, it is possible that subjects with higher levels of complaints have greater difficulty inhibiting insular activity during recognition memory.

Increased activity in the lingual gyrus was also observed in those with higher levels of cognitive complaints. This finding is in contrast with the pattern of memory-related activity seen across the group as a whole, where activation in this region was decreased during task performance. This suggests that those with greater complaints do not inhibit or effectively turn off processes performed by this region during memory performance. Although generally discussed in relation to frontal lobe function, several studies have attributed age-related differences in memory performance to an inability to inhibit regional activity (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003). It is surmised that this lack of inhibition leads to an increase in interference and subsequently poorer task performance. Despite maintaining comparable task performance, these results suggest that there may be different patterns of processing in individuals who complain about their cognitive ability but are not yet demonstrating objective symptoms.

This study is not without limitations. The BLSA is a highly educated cohort and individual with cognitive impairment were excluded from the current analyses. Thus, differences between this study and more population based studies could be due to differences in education level or health status. Although education did not have an effect within our cohort, recent evidence suggests that subjective memory complaints are most strongly related to risk of Alzheimer's Disease in highly educated individuals (van Oijen et al., 2007). The health status of the cohort may not be representative of normal aging, as participants in the BLSA have more opportunities to detect and treat health problems through their involvement in the study.

In summary, although others have argued that subjective cognitive complaints may only relate to cognitive decline in those with existing cognitive impairment (Schofield et al., 1997), our findings demonstrate that overall levels of subjective cognitive complaints predict longitudinal declines in verbal memory performance in a sample free of cognitive impairment. Further, CFQ scores are related to patterns of regional brain activity in regions outside the normal network for memory tasks. Future studies are warranted to determine whether subjective cognitive complaints may be useful as early markers of age related cognitive and brain changes.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. We are grateful to the BLSA participants and neuroimaging staff for their dedication to these studies and the staff of the Johns Hopkins PET facility for their assistance.

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Figure 1. Higher mean CFQ predicts greater decline in CVLT immediate (Trials 1–5) Recall ($p = .009$) and in CVLT delayed free recall ($p = .042$) over time. Rates of change reflect annual rates of change.

Figure 2. CVLT Performance Over Time

Predicted trajectories of longitudinal change in CVLT performance. High Complainers include individuals in the highest quartile of CFQ scores, while Low Complainers represent the remaining participants.

Figure 3. Brain Activation Patterns

The relationship between CFQ and rCBF. Axial slices show brain activation patterns during memory performance (activation in red; deactivation in blue), and regions where rCBF increases in relation to greater cognitive complaints (green). Color bars illustrate the t level of significance (>0.05 FDR corrected).

Brain Activation Patterns

Table 1

CFQ and brain activation during memory performance. Local maxima of regions exhibiting a significant association between CFQ score and rCBF. Stereotaxic coordinates in MNI space are listed, Brodmann areas are indicated in parentheses.

	Coordinate							
Region (BA)	Side	x	y	z	T-value	p value	Size (# of voxels)	
CFQ Positive Correlations								
Insula	L	-40	-42	20	4.39	<.001	88	
Insula	R	42	-34	18	4.28	<.001	151 ^t	
Lingual Gyrus (18)	L	-10	-70	-8	4.61	<.001	516 [*]	
Lingual/Fusiform Gyrus (19)	R	18	-58	-6	4.60	<.001	280 [^]	
Inferior Parietal (40)	R	42	-30	26	3.61	<.001	151 ^t	
Cerebellum	L	-12	-90	-26	4.16	<.001	516 [*]	
Cerebellum	R	12	-70	-12	4.10	<.001	280 [^]	

^{*} [^] Regions contained within the same cluster.