The Neurocognitive Determinants of Objective and Subjective Quality of Life in Individuals with Schizophrenia: A Quantitative Meta-Analysis

by

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ABSTRACT

Quality-of-Life (QOL) has been recognized as a crucial domain of outcome in schizophrenia treatment, and yet its determinants are not well understood. While persistent psychiatric symptoms would be a likely determinant, research reveals only small negative relationships between psychiatric symptoms and QOL. Individuals with schizophrenia consistently show 1-2 SD deficits on measures of speed of processing, attention/vigilance, verbal learning and memory, and problem-solving relative to healthy controls, and links between these deficits and objective measures of community functioning (e.g. employment, living status) are well established. While objective measures of community functioning and measures of quality of life (QOL) would appear to be closely related, studies investigating the ability of neurocognitive variables to predict QOL in individuals with schizophrenia have yielded highly conflicting results. One potential explanation for these findings is the interchangeable use of objective and subjective indices of QOL in the schizophrenia literature. This study used quantitative methods of meta-analysis to clarify the relationship between neurocognitive determinants of QOL by evaluating objective QOL (i.e. observable, clinician rated) and subjective QOL (i.e. client life satisfaction) measures separately in individuals with schizophrenia. A total of 20 studies (10 objective, 10 subjective) consisting of 1, 615 clients were aggregated from relevant databases. Weighted effect-size analysis revealed that there were small-moderate relationships ($d \leq .55$) between crystallized verbal ability, working memory verbal list learning, processing speed and executive function and objective indices of QOL. In contrast, results revealed either non-significant or inverse relationships for the vast majority of neurocognitive measures and measures of subjective QOL. Between-group comparison revealed that the neurocognitive domains of crystallized verbal ability, immediate prose recall, list-learning, processing speed, and executive function were differentially related to subjective and objective QOL. Moderating variables and implications for future research and treatment development are discussed.

INTRODUCTION

Schizophrenia is a chronic and profoundly disabling psychiatric disorder. The heterogeneous illness is most often characterized by the presence of positive symptoms (e.g. delusions, hallucinations), and negative symptoms (e.g. flattened affect, social withdrawal) (APA, 1987). Individuals with schizophrenia often also exhibit impoverished social skills and poor vocational and psychosocial function, which have been closely linked to negative symptoms (Dickinson et al., 2007). The economic consequences of the impaired community functioning of individuals with schizophrenia are profound; current estimates suggest that 70-80% of individuals with schizophrenia are unemployed at any one time, and only ½ of 1% of individuals with schizophrenia who receive Social Security Insurance (SSI/SSDI) ever remove themselves from entitlements (Salkever et al., 2007). With prevalence rates in North America ranging from ½ to 1%, the estimated cost of the illness to society, in terms of lost wages and lifelong medical care, is on the order of billions of dollars (Torrey, 1999).

More recently, neurocognitive deficits have been recognized as core aspect of schizophrenia as well (Gold and Harvey, 1993). In addition to their psychiatric symptoms, individuals diagnosed with schizophrenia consistently show 1-2SD deficits on measures of speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, relative to healthy controls, some of which have been linked to regional brain dysfunction in functional and structural neuroimaging paradigms (Nuechterlein et al. 2004). Particular significance has been attached to these deficits as many have been

moderately associated with impaired community functioning (e.g. living and employment status) in individuals with schizophrenia, both cross-sectionally and longitudinally (Green, 1996; Green et al., 2000; Green et al. 2004). Moreover, these deficits, rather than positive or negative symptoms, may actually best account for the diversity of community outcomes in schizophrenia (Elvevag & Goldberg, 2000). In light of such findings, neurocognitive deficits have increasingly become targets for clinical intervention. Based on the assumption that improvements in neurocognitive deficits will lay the foundation for patient functional rehabilitation, researchers have used methods of cognitive remediation to improve neurocognitive functioning (for review, see Kurtz et al., 2001) and the National Institute of Mental Health launched the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative in 2002 to facilitate the development of cognition-enhancing pharmacological agents (Green et al. 2004).

Quality of Life in Individuals with Schizophrenia

With the emergence of more effective pharmacologic management of acute psychiatric symptoms in schizophrenia over the past 20 years, increasing attention has been paid to the development of interventions targeted at improving the long-term functional and subjective outcomes for people with the illness. One of the dominant approaches to measurement of outcome in the schizophrenia literature has been the use of scales designed to assess the construct of quality of life (QOL) (Awad and Voruganti, 2000). Although there is not a single definition of QOL, most agree that it is a multi-dimensional construct that includes a person's subjective sense of well

being, functional status, and access to resources and opportunities (Lehman, 1996). Reflecting this multi-dimensional construct, different approaches have been taken to measuring QOL. Two main approaches can be identified: (1) The "social indicators approach" measures QOL by collecting objective information about an individual's life, with a focus on external conditions such as income, education and housing status. (2) The "psychological indicators approach" measures QOL by collecting information on how people view the conditions own lives, using mainly satisfaction constructs (Priebe and Fakhoury, 2007).

For clinicians and researchers working with the chronically mentally ill post-deinstitutionalization, the project of understanding how to better serve and improve QOL in patients has been of particularly pressing import (Lehman, 1988). Thus, knowledge of the determinants of QOL in patients with schizophrenia is of key importance in tailoring effective interventions to improve the lives of people with the disease. At present, however, an understanding of determinants of QOL in schizophrenia remains elusive. An obvious candidate would be persistent psychiatric symptoms. However, a recent meta-analysis by Eack and Newhill (2007) found only small ($r<-.5$) negative relationships between positive and negative symptoms and QOL, with general psychopathology (e.g. anxiety, depression) showing the strongest associations across all QOL domains. Therefore, although psychiatric symptoms influence QOL in individuals with schizophrenia, they explain only a modest proportion of variance in QOL.

While neurocognitive deficits have been linked to impairment on measures of objective measures of community function, results of studies examining the

relationship between neurocognition and QOL in patients with schizophrenia have been mixed. Some studies have demonstrated a positive relationship between neurocognitive domains and aspects of QOL (e.g. Addington and Addington 2008; Lysaker and Davis, 2004), whereas others show an inverse relationship (e.g. Corrigan and Buican, 1995; Proteau et al., 2005). In other cases, the data revealed no relationship between neurocognitive deficits and QOL (e.g. Heslegrave et al., 1997; Hofer et al., 2005). As just one example, the same measure of executive-function, the Wisconsin Card Sorting Test perseverative error score, has been linked positively to the QOL when measured by the Heinrichs-Carpenter Quality of Life Scale (QLS; Addington and Addington, 2008), but unrelated to QOL when measured by the World Health Organization Quality of Life Scale-BREF (WHOQOL-BREF; Hofer et al., 2005).

The Present Study

Given the (1) importance of understanding determinants of QOL in schizophrenia for developing effective interventions, (2) the growing literature on neurocognitive predictors of QOL in patients with schizophrenia over the past 10 years, and (3) and the highly contradictory findings across studies, a quantitative meta-analysis of the literature is warranted. The present study was formulated with the hypothesis that the discordance in findings regarding neurocognition and QOL can be explained by the considerable variance in types of QOL measures used by different research teams. Lack of consensus in both the psychiatric and broader medical community regarding the definition of the construct of QOL, as well as how it should

be measured, has led to a proliferation of QOL instruments focused on different aspects of the construct. For example, in a 1994 review of the general medical literature, Gill and Feinstein found 159 different "Quality of Life" measures used in the 75 studies they evaluated. In schizophrenia research, QOL remains an important, if ill-defined concept. Nevertheless, some efforts to delineate QOL have been especially influential in the field. For the present study, we adopted the model used by Lehman in his seminal article "A Quality of Life Interview for the Chronically Mentally Ill," in which global well-being is understood as being influenced by three distinct factors: personal characteristics, objective QOL indicators, and subjective QOL indicators (Lehman, 1988).

Lehman's QOL measure looks at client functioning (objective QOL) and satisfaction (subjective QOL) across nine different life domains. For Lehman and other researchers adopting his model, objective QOL refers to observable life conditions of the client and may be assessed by clinician ratings or through client self-report, but in either case, the patient's current or recent functional status is under review. In this regard, the construct of objective QOL has considerable overlap with more general constructs and measures of community/social functioning. Subjective QOL, in Lehman's model, specifically refers to patient satisfaction across parallel life domains. For example, in the Lehman Quality of Life Interview, objective QOL in the social relations domain is measured by asking questions about the frequency of the patient's social contacts, e.g. "How often do you spend time with close friends?" In contrast, subjective QOL for social relations measures patient satisfaction, asking for a purely subjective assessment of quality of the patient's interactions with others, e.g.

"How do you feel about the amount of time you spend with other people?" Although we use the influential definition of objective and subjective QOL set forth by Lehman, this categorization is not universal. We note that for the present study we do not view patient self-report as identical to the construct of subjective QOL as posited by some other investigators (e.g. Awad and Voranti, 2000).

To our knowledge, there have been no systematic literature analyses examining the relationship between neurocognition and quality of life in patients with schizophrenia. We sought to use quantitative meta-analytic methods to (1) determine whether there was a differential relationship between neurocognition and objective and subjective QOL in patients with schizophrenia (2) estimate the overall magnitude of these relationships, and (3) examine important demographic and disease variables that might moderate the relationship between neurocognition and subjective and objective quality of life (e.g. age, illness duration, symptoms). We predicted that: (1) Relationships between neurocognitive measures and objective QOL would be larger than those between neurocognition and subjective QOL. (2) Because objective QOL indicators overlap considerably with measures of community functioning, we will replicate previous findings (Green, 1994) and uncover small-medium positive effect sizes between a variety of domains of neurocognitive measures and objective QOL. (3) In contrast, we predicted a negligible relationship between neurocognition and subjective QOL, as previous studies in both schizophrenia and non-psychiatric populations have shown a non-significant relationship between neurocognitive functioning and subjective QOL instruments (Brissos et al., 2008; Chino et al., 2009; Hofer et al., 2005; Bain et al., 2003).

METHODS

Literature Search

We conducted parallel literature searches in the PUBMED and PSYCINFO databases for all peer-reviewed, English-language articles published between 1/1/1980 and 10/1/2009 using the search terms ["cognition" AND "schizophrenia" AND "quality of life"] and ["cognition" AND "schizophrenia" AND "social functioning"] and ["severe mental illness" AND "quality of life"]. Nineteen eighty was selected as the cut-off in light of the introduction of the DSM-III for more reliable diagnostic criteria for schizophrenia illness (APA, 1987). The reference sections of articles located from both searches were studied for relevant citations.

Inclusion Criteria

General study inclusion criteria were as follows: 1) at least one-third participants with schizophrenia or schizoaffective disorder, 2) use of standard neuropsychological test battery, 3) cross-sectional relationship without treatment intervention, 4) use of either an objective and/or subjective QOL measure relied on patients self-report, measured multiple life domains, and that had been validated for use in schizophrenia, and 5) study statistics were convertible to effect size *d* (e.g., Pearson r, beta regression coefficients).

These database searches yielded 518 potential studies. The majority of these studies were excluded because they did not use a standard neuropsychological test battery or a dedicated QOL instrument that met criteria for inclusion, or did not study individuals with schizophrenia. Others measured neurocognitive functioning and

QOL, but did not present data relating the two variables. Studies not using a cross-sectional paradigm were excluded; however, longitudinal studies that presented baseline correlations between neurocognitive measures and QOL were able to be included. Upon review, 27 studies met our study inclusion criteria. Of these, eleven authors who did not publish correlation coefficients between individual neurocognitive measures and total QOL, were solicited for additional data. In total, twenty studies (10 objective, 10 subjective) were included in our analysis. See Table 1 for detailed study descriptions.

Measure Selection

Neurocognitive Measures

To ensure stability of findings, neurocognitive measures were selected for inclusion in this meta-analysis based on their use in at least three different studies. A total of 14 different neurocognitive measures were selected (see Table 2). The following neurocognitive domains were included for analysis: crystallized verbal ability, vigilance, working memory, prose-recall, list-learning, processing speed, and executive-function. Effect-sizes were calculated and aggregated from individual cognitive tests with consistent outcome measures to minimize the combination of effect-sizes from different tests, and different outcome measures from the same test, that could be tapping different neurocognitive constructs. For example, performance on the Wisconsin Card Sorting Test (WCST) is measured with multiple scores, most often either categories achieved or number of perseverative errors. These two outcome measures, while clearly related and from the same test, measure different

presumed underlying constructs, concept formation and flexibility on the one hand, and set-shifting on the other. Thus, we examined these scores separately in this analysis.

In light of their high degree of test similarity, outcome measures were combined across each of three verbal list-learning measures, the Hopkins Verbal Learning Test (HVLT), Rey Auditory Verbal Learning Test (RVLT) and the California Verbal Learning Test (CVLT). Results from Logical Memory subtests from the Wechsler Memory Scale (WMS) and Wechsler Memory Scale-Revised (WMS-R) were also combined, as were results from the paper-and-pencil and computerized versions of the WCST.

Quality of Life Measures

In order to be considered for inclusion in the meta-analysis both subjective and objective QOL measures had to be: 1) validated in samples of individuals with schizophrenia, 2) measure multiple life-domains (e.g., occupation, social interactions, recreation/leisure etc.) and 3) rely on patient self-report. Four objective QOL measures meeting these criteria were selected: 1) the Heinrichs-Carpenter Quality of Life Scale (QLS; Heinrichs et al. 1984), 2) the Lehman Quality of Life Interview objective subscale (QOLI; Lehman, 1988), 3) the Strauss-Carpenter Specific Levels of Function scale (SLOF; Strauss and Carpenter; 1977), and 4) the Sickness Impact Profile (SIP; Bergner et al. 1981). There are differences among the scales chosen in that SIP uses a written questionnaire completed by the patient, whereas the QLS, QOLI, and SLOF use a rated interview format. In addition, the QLS, QOLI, SLOF

and SIP all assess multiple patient life-domains; they include questions specifically related to occupation, social interactions, recreation/leisure, and emotional-status. Other scales that measured patient's multi-dimensional life-function but did not rely on patient self-report were excluded (e.g. Global Assessment of Function). It should be noted that some researchers have categorized the SIP as a "subjective" measure of QOL because it is utilizes patient self-report (Heslegrave, 1997; Voruganti et al. 1998, Sota and Heinrichs, 2004). For the current study, however, we classified the measure as an objective index in light of its focus on objective life-conditions, and lack of inquiry into the subjective ratings of life satisfaction.

Three subjective QOL measures met our criteria: 1) World Health Organization Quality of Life Assessment-Brief Version (WHOQOL-BREF; WHO, 1998), 2) the Lehman Quality of Life Interview subjective subscale (LQOLI; Lehman, 1988), and 3) the Satisfaction with Life Scale (SWL; Stein and Test, 1980). All three of these scales also rely on self-report of the patient, two in the form of a written questionnaire (WHOQOL-BREF, and SWL) and one in the form of a structured interview (QOLI). All included scales assess multiple life-domains, as with the objective QOL scales; however, they are distinct from the objective scales in that they specifically measure the patient's subjective satisfaction with their life conditions, as opposed to assessing objective functional status. We note that scales that combined objective QOL and subjective QOL questions in the same overall measure were excluded due to the comparative nature of the present study (e.g. Lancashire Quality of Life Profile; Oliver et al. 1997).

Data Analysis

The software program *DSTAT v. 1.11* (Johnson, 1993) was used to calculate effect sizes and to carry out subsequent homogeneity and moderator variable analyses. The unit of analysis in a meta-analysis is the effect size (*d*). For purposes of the present study, the *d* score was always defined as the strength of the relationship between each neurocognitive variable and objective or subjective QOL measure expressed in standard deviation units. For 14 studies we converted r into Cohen d-values. One study reported beta coefficients from a multiple regression, not correlation coefficients. In this study we converted beta-values into an approximate *r* for meta-analysis using the method outlined by Peterson and Brown (2005). Nonsignificant results from five studies lacking supporting statistical information were coded as an effect size of zero (Lipsey & Wilson, 2001). Four studies did not present correlations for total QOL score, but instead reported correlations of specific neurocognitive domains with specific QOL domains. As we predicted a positive relationship between neurocognition and objective QOL, we conservatively coded the lowest summary domain correlation for studies of objective QOL. In contrast, because we predicted a negligible relationship between neurocognition and subjective QOL, for subjective QOL studies, we coded the highest domain correlation. Effects were categorized as small (d<.5), medium-large (d=.5-.8) or large (d>.8; Cohen, 1977). All effect sizes were expressed in a way such that positive values indicate better performance on neurocognitive tests.

Individual values of *d* were thereafter combined across studies and weighted according to their variance using a fixed-effects model. Potential differences in effect

size between studies were analyzed using the method of Hedges and Olkin (1985). This procedure computes mean weighted effect sizes and 95% confidence intervals (CI) for each variable subset and allows for the testing of the influence of each individual factor on the overall results using the Q statistic. To assess stability of underlying effects we used a test for heterogeneity Q_T which is based on the sum of squares of the individual effect sizes around the mean when each square is weighted by the inverse of the estimated variance of the effect size. Q has an asymptotic χ^2 distribution and is analogous to the analysis of variance. Studies were evaluated for within-group differences (Q_W) and between-group differences (Q_B) following the same model.

To partially address the "file-drawer" or publication bias problem in meta-analytic investigations, in which null results in a research area are collected but not reported in the literature, we calculated a fail-safe N (N_{FS}) for each class of outcome variable by the method of Orwin (1983). This measure provides an estimate of the number of studies with null results that would be needed to reduce the obtained mean effect-size to a non-significant level. In the absence of a universally accepted significance level for effect sizes, we considered an effect-size of .05 non-significant.

Moderator Analyses

Moderator analyses were conducted when the test for heterogeneity (Q_w) for a specific neuropsychological measure was significant. Results are not reported for non-significant moderator analyses. Study characteristics hypothesized to moderate the relationship of neurocognition and QOL were: treatment setting (inpatient,

outpatient, or mixed), symptomatology (PANSS, Positive and Negative Syndrome Scale, Kay et al. 1987), participant age, gender (%male), illness duration, age of onset, number of hospitalizations, average daily antipsychotic medication dose in chlorpromazine (CPZ) equivalents and type of QOL measure. In addition, we created study quality variable consisting of a 3-point scale with each study getting one point for including a non-psychiatric control group, confirmatory SCID diagnostic interviews (Spitzer, 1990), and/or neuropsychological testers blind to QOL results. These study characteristics were coded by two raters (A.W.T) and (M. M. K.) in a sub-sample of 40% of studies to ensure reliability of extraction of study characteristics. Inter-rater reliability for coding was calculated to be 96%. Continuous moderator variables (e.g. participant age and illness duration) were analyzed with a continuous model (Rosenthal, 1986) with a z-test for significance of model fit. Mean weighted effect-sizes were directly compared for relationships between neurocognition and objective QOL and neurocognition and subjective QOL, when neurocognitive measures between subjective and objective QOL studies overlapped. Direct comparisons in effect-sizes were made only between studies that included independent samples of clients.

RESULTS

Study Characteristics

A summary of sample characteristics of the 10 objective QOL studies the 10 subjective QOL studies that met inclusion criteria for the meta-analysis are presented in Table 3.

Neurocognitive Deficits and Objective QOL

As can be seen in Table 4, the majority of neurocognitive domains were positively correlated with objective QOL. Small effect sizes were found for the relationship between crystallized verbal ability (WAIS-Vocabulary, d=.34, 95% CI: .13/.55), working memory (Digit Span, d=.26, 95% CI .11/.41; Letter-Number Sequencing, d=.17, 95% CI: .06/.28), verbal list learning (CVLT/HVLT/RVLT-immediate, d=.37, 95% CI: .24/.51; CVLT/HVLT/RVLT-delayed, d=.13, CI: .01/.25), processing speed (WAIS-Digit-Symbol, d=.23, 95% CI: .10/.36) and objective QOL. Executive function was found to have a small-medium effect size relationship to objective QOL (WCST-PE, d=.28, 95% CI: .14/.41; WCST-CAT, d=.55, 95% CI: .38/.72). Attention and prose recall were the only domains that were not significantly correlated (ps>.08) with objective QOL.

Heterogeneity measures suggested that the overall weighted mean effect of the relationship between objective QOL and processing speed, verbal list-learning, working memory (only the Letter-Number Sequencing test) and executive-function (only the PE score) was not stable. Moderator analyses of processing speed revealed that greater age (Z=-3.17, p<.05), more education (Z=-2.8, p<.05), and more hospitalizations (Z=-3.08, p<.05) attenuated the relationship between processing

speed and objective quality of life. In addition, moderator analyses revealed that greater years of education (z=-2.86 p=.04) and antipsychotic medication dose in CPZ equivalents (Z=-2.37 p<.05) attenuated the relationship between list learning (immediate recall) and objective QOL. Greater antipsychotic medication dose (Z=-2.70, p<.05) and more negative symptoms (Z=-2.82, p<.05) attenuated the relationship between executive-function (perseverative errors) and objective QOL. Longer duration of illness correlated with larger effect sizes between both measures of list-learning (Z=2.63 p<.05) and executive function and objective QOL (Z=.284, p<.05). Type of objective QOL measure (QLS, QOLI, LOF or SIP) significantly moderated the relationship between list learning (CVLT/HVLT/RAVLT-immediate, QLS d=.31, QOLI d=.66, QB=4.20, p<.05), working memory (Letter-Number Sequencing, QLS d=.11, QOLI d=.21, LOF d=.78, QB=7.81, p<.05), and executive function (WCST-PE, QLS d=.28, QOLI d=.59, SIP d=.00, QB=8.13, p<.05). Greater percentage of males (Z=-3.57, p<.05), and greater mean sample age of onset (Z=-3.10 p<.05), and greater number of years of education (Z=-2.08, p<.05) attenuated the relationship between working memory (Letter-Number Sequencing) and objective QOL. Higher study quality was correlated with a stronger relationship between list-learning and objective QOL (Z=1.94, p=.05) and processing speed and objective QOL (Z=3.08, p<.05).

Neurocognitive Deficits and Subjective Quality of Life

As can be seen in Table 5, the majority of neurocognitive domains were not significantly correlated with subjective QOL, with the exception of crystallized verbal

ability and processing speed, which were negatively correlated with subjective QOL and letter fluency, which was positively correlated with subjective QOL. Small effect sizes were revealed for verbal IQ (WAIS-Vocabulary, d=-.29, 95% CI: -.49/-.10), processing speed (Digit-Symbol, d=-.19, 95% CI: -.36/-.02), and letter fluency (d=.26, 95% CI: .09/.43). Measures of attention, working memory, verbal list learning and prose recall, and executive function were not significantly correlated with subjective QOL (all ps>.06).

Heterogeneity measures suggested that the overall weighted mean effect of the relationships between subjective QOL and crystallized verbal ability, processing speed, and letter fluency were not stable. Moderator analyses of crystallized verbal ability revealed that greater age was related to smaller mean effect sizes (Z=-3.85, p<.01). Treatment setting (inpatient, outpatient, or mixed) also significantly moderated the relationship between crystallized verbal ability and subjective QOL (inpatient d=.00, outpatient d=-.52, QB=6.83, p=.00), as did QOL measure (WHOQOL d=.00, QOLI d=-.52, QB=6.83, p<.05). Moderator analyses also revealed that greater mean sample age attenuated the relationship between processing speed and subjective QOL (Z=-2.32, p<.05), but that greater percentage of males was related to a stronger relationship between processing speed and subjective QOL (Z=2.89, p<.05). The relationship between letter fluency and subjective QOL was moderated by treatment setting (inpatient d=.84, outpatient d=-.19, QB=26.97, p<.05) and QOL measure (WHOQOL d=.53, QOLI d=-.28, QB=19.35, p<.05).

Comparison of Relationship of Neurocognitive Measures to Objective vs. Subjective Measures of QOL

In addition, we completed between-group analyses to determine if there was significant heterogeneity with regard to QOL measure type (objective v. subjective) for each neurocognitive domain. One study that administered subjective and objective measures of QOL to the same participants was excluded (Narvaez et al. 2008). Results revealed between-group differences in the relationship of neurocognition and subjective and objective quality-of-life for crystallized verbal ability (WAIS-Vocab., QB=13.86, p=.00), immediate prose recall (LM1, QB=6.43, p=.01), list-learning (CVLT/HVLT/RVLT immediate QB=5.66, p=.02), processing speed (WAIS Digit-Symbol, QB=4.56, p=.03), and executive function (WCST-PE: QB=5.42, p=.02; WCST-CAT: QB=11.55, p=.00). The relationship between working memory (digit span) and delayed prose recall was not different for subjective and objective QOL.

File-Drawer Analyses

We sought to determine the extent to which our findings could be influenced by unpublished studies "the file-drawer problem" of non-significant effects. As shown in Table 4, for objective QOL there would need to be 17 unpublished studies for crystallized verbal ability, 17 and 10 for attention (digit span and letter-number sequencing, respectively), 26 and 5 for list learning (CVLT/HVLT/RAVLT-immediate, and delayed, respectively), 18 for processing speed, and 23 and 30 for executive function (WCST-PE and –CAT, respectively). As shown in Table 5, for subjective QOL, there would need to be 14 unpublished studies for crystallized verbal ability, 21 for letter fluency, and 11 for processing speed. These findings suggest that

it is unlikely that enough unpublished studies exist of null effects to make the findings of the present meta-analysis non-significant.

DISCUSSION

Major Findings

This is the first meta-analytic study to directly compare the pattern of relationships between elementary neurocognitive domains and subjective and objective measures of QOL. Our results revealed three major findings. First, consistent with our hypotheses, we found a disparity between the relationship of neurocognitive deficits to measures of subjective QOL and neurocognitive deficits and objective QOL in individuals with schizophrenia. With few exceptions, neurocognitive measures were positively correlated with objective QOL, but either unrelated or negatively correlated with subjective QOL. More specifically, between-group analyses revealed that the neurocognitive domains of crystallized verbal ability, immediate prose recall, list-learning, processing speed, and executive function were differentially related to subjective and objective QOL.

Second, we found positive relationships between measures of crystallized verbal ability, working memory, verbal memory, and processing speed and objective QOL, that were all in the small (d=.17-.34) effect-size range, whereas the relationship between executive-function and objective QOL was in the small-medium (d=.28-.55) effect-size range. These results are consonant with our hypotheses and are consistent with several previous reviews and meta-analyses that have found measures of working memory, verbal memory and executive-function are related to a range of measures of functional outcome in people with schizophrenia in both cross-sectional and longitudinal designs (Green et al, 1996; 2000, 2004). Attention was not related to objective QOL in our study. This finding is also generally consistent with previous

studies of neurocognition and functional outcome, which determined that measures of attention were more strongly associated with performance-based measures of skill acquisition and social problem-solving, than measures of objective community functioning that overlap with the measures of objective QOL selected for the current study (Green et al. 1996).

There is considerable face-validity to the assertion that individuals with higher verbal IQ, working and verbal memory, processing-speed, and executive-function will be more likely to rate more highly on life domains frequently assessed on objective measures of QOL such as vocational status, social networks, and independence in living. However, it is important to note that the effect sizes for the relationship between neurocognitive deficits and objective QOL were generally small, suggesting that there are likely other individual and social determinants of objective QOL in addition to elementary neurocognition. Indeed, research over the past several years has suggested a variety of potential moderating variables between neurocognition and functional outcome, such as social cognition (Green et al. 2005) and learning potential (Green et al. 2000). Already there is preliminary evidence that at least one measure of social cognition, facial affect recognition, moderates the relationship between neurocognitive deficits and objective QOL (Addington et al., 2006).

Third, in contrast to the objective QOL findings, we found a largely non-significant relationship between neurocognition and subjective QOL. Measures of working memory, verbal memory, attention, and executive function were non-significantly ($p>.05$) related to measures of subjective QOL. However, measures of crystallized verbal ability ($d=-.23$) and processing-speed ($d=-.19$) were both

negatively correlated with subjective QOL. Verbal fluency was the only measure found to be positively (d=.26) correlated with subjective QOL.

Moderator Analyses

Tests for heterogeneity revealed that the positive relationship between verbal fluency and subjective QOL was unstable, and further analysis showed that there was a strong positive relationship for studies with inpatient samples (d=.84), but a negligible relationship between verbal fluency and subjective QOL for studies with outpatient samples (d=.00). We speculate that measures of verbal fluency, which ask participants to generate as many words starting with the letter "F," for example, in a short period of time may serve as a proxy measure for more general levels of the social initiative of individuals with schizophrenia. In this way, for individuals who are hospitalized, it may be that those better able, or more willing, to generate many words, also have better general social initiative and are better able to express and address their needs in an inpatient setting and thus report higher life satisfaction.

Our moderator analyses for neurocognitive and objective QOL measures revealed that as the mean study sample age increased, the relationship between working memory (Letter-Number Sequencing) and processing-speed (Digit-Symbol) and objective QOL was attenuated. Similarly, as education increased, the relationships between list learning and working memory and objective QOL weakened. A possible explanation for these findings is that neurocognitive abilities have less of a direct effect on objective QOL in older individuals as they are more educated and have more life experience, enhancing the likelihood of acquisition of

more compensatory skills to cope with the effects of persistent neurocognitive deficits on their day-today life activities than their younger counterparts. The finding that higher study quality was linked to stronger neurocognitive-objective QOL relationships suggests that positive findings from the current analysis for objective QOL were not artifacts of a lack of healthy comparison groups, less rigorous psychiatric diagnostic procedures, or a lack of blinding in a subset of the studies included in this analysis.

In addition, the analysis revealed that relationship between crystallized verbal ability and letter fluency and subjective QOL was moderated by treatment setting (inpatient v. outpatient). For both neurocognitive domains, it was the outpatient samples that accounted for the inverse relationship between cognition and subjective QOL—the inpatient samples had either non-significant or positive relationships between neurocognition and subjective QOL. A possible explanation for this finding is that because outpatient participants are more likely than inpatients to be interacting mainly with non-psychiatric members of the population, those with higher neurocognitive abilities may be more highly attuned to their functional limitations, and thus experience lower life-satisfaction.

Differential Relationship between Neurocognitive Deficits and Objective and Subjective QOL

The very different relationships between neurocognition and objective vs. subjective QOL found in this study are consistent with a wealth of research. Studies have consistently revealed that despite common assumptions, objective QOL

instruments that measures objective social and vocational status do not correlate with subjective QOL instruments that measure satisfaction with these same life domains (Lehman, 1988; Narvaez et al. 2007). For example, Skantze et al. (1992), found no significant association between individuals objective measures of quality of life and their overall ratings of life satisfaction. The standard of life scale scores of their 66 schizophrenia out-patients participants, which included objective indicators of housing quality and current employment, did not correlate with scores on the quality of life scale, which measured participant satisfaction in the same domains (Skantze, 1992). Similarly, Lehman evaluated the construct validity of his objective/subjective QOL distinction and found that objective QOL did not correlate with subjective life satisfaction (Lehman, 1988). Warner et al. (1998) conducted a factor analysis of responses to the Lancashire Quality of Life Profile, a quality of life instrument derived from the Lehman interview that measures both objective and subjective domains, and found that objective QOL variables sorted separately from subjective satisfaction ratings. In other words, better objective life conditions, as measured by employment or number of close friends, for example, do not necessarily correlate with better life satisfaction. This dissociation supports the notion that measures of objective QOL and subjective QOL are indeed measuring very different constructs—and thus, these constructs are likely, as this study has shown, to have different sets of clinical predictors in individuals with schizophrenia.

Neurocognition and Subjective Quality of Life

Overall, our findings suggest that researchers looking to understand the relationship between neurocognition to objective QOL already have a strong foundation of cognition and functional outcome research off of which to build. On the other hand, the relationship between neurocognition and subjective QOL is not as well understood. Again, our results indicate that with the exception of verbal fluency, there is generally a non-significant, and in some cases, negative, relationship between neurocognitive abilities and life satisfaction (subjective QOL) in individuals with schizophrenia. In light of the current findings—two important questions arise. First, how does one explain the seemingly paradoxical finding that better cognitive abilities in certain domains are related to worse subjective QOL? And second, considering the lack of a strong relationship between both neurocognition and subjective QOL, and objective QOL and subjective QOL, what variables, if any, do determine subjective QOL in patients with schizophrenia?

The most common explanation of this inverse relationship in the literature is that individuals with stronger cognitive abilities may have greater insight into their illness and functional disability, and thus lower life satisfaction (Brekke et al. 2001; Karow and Pajonk, 2006; Narvaez et al., 2008). There is ample evidence to support such a hypothesis. Studies have shown that schizophrenia patients with better cognitive abilities had more severe depression (Bowie et al. 2007), and greater insight into their illness (Subotnik et al., 2005). In addition, research has shown that individuals with increased insight into their psychiatric illness had higher rates of depression (Birchwood et al., 2000) and reduced subjective QOL (Pyne et al., 2001).

These findings− that cognition and insight are generally unrelated, and in some cases even inversely related to subjective life satisfaction−challenge some basic assumptions concerning the treatment of schizophrenia. Because individuals who lack insight into their illness are less likely to adhere to treatment and thus are more likely to be hospitalized (Amador and Strauss, 1993; Heinrichs et al., 1985), researchers and clinicians often seek to improve patient insight in an effort to provide more favorable clinical outcomes and reduce costs associated with expensive inpatient services (Pyne, 2001). If in fact cognition and insight are key to obtaining favorable objective functional outcome, but are, at least in some domains, inversely related to life satisfaction—treatment intervention paradigms of the future may need to be re-worked.

Clinicians and researchers will need to ensure they attend to both the objective and subjective QOL of the individuals they are seek to help. For example, to buttress cognition-enhancing treatment interventions aimed to improve objective QOL, researchers might aim to incorporate other therapeutic approaches that specifically target subjective QOL alongside their interventions. Experience of stigma has been shown to be negatively correlated with subjective QOL (Switaj et al., 2009); therefore, interventions that work to build patient stigma-resistance may prove to be an especially productive approach in the effort to improve life satisfaction in individuals with schizophrenia (Sibitz et al., 2009). Moreover, for those clinicians and researchers looking to target subjective QOL, focusing simultaneously on treating co-occurring, non-psychotic symptoms such as depression and anxiety is likely to prove more fruitful.

Limitations

Several caveats should be mentioned. First, this is the first meta-analysis to date of a new and rapidly growing research area investigating the relationship between neurocognition and subjective and objective QOL, and thus we had a relatively small number of studies (k=20). Thus, these findings are preliminary and will need to be replicated with larger numbers of studies employing these same neurocognitive measures and QOL indices. As our "fail-safe n" analyses revealed, for some relationships, there would need to be a relatively low number of unpublished studies with non-significant effects required to negate our findings. The fail-safe n range was between 5-30 studies for objective QOL and between 11-21 studies for subjective QOL. Nonetheless, the smaller number of studies also emphasizes the robustnesss of the positive findings evident in this report.

Second, some elementary neurocognitive domains in the current analysis were not well-represented in terms of numbers of measures (e.g., attention) included in the current analysis. Thus, current findings will be strengthened with the addition of other neurocognitive measures designed to measure the same construct. Third, many of our moderator analyses were underpowered with 50% or less of included studies reporting sample duration of illness, negative and positive symptom scores, depression ratings or medication dosage (see Table 3). Fourth, we note that some of our strongest findings were unstable as measured by our heterogeneity statistic (e.g., crystallized verbal ability and subjective QOL). This instability may represent the grouping of very different sample types into the same heterogeneity analysis.

Fifth, moderator analysis revealed that QOL measure type moderated the relationship between some domains of neurocognition and QOL. This finding suggests that the instruments themselves, despite our differentiation into objective and subjective categories, have critical inter-scale differences that significantly moderate the relationship between neurocognition and QOL. Nonetheless, the between-group differences presented in Figure 1 supports the objective/subjective QOL distinction we made in scale categorization. And lastly, important domains of neurocognition, such as non-verbal memory, were not included in the analysis as an insufficient number of extant studies used these measures. Therefore, the relationship of these measures to subjective and objective QOL remains unknown.

Future Research

Given the role that insight has often played in explaining the inverse relationship between neurocognition and subjective QOL, but the lack of direct evidence to test the hypothesis, additional research is necessary. One approach that may prove especially fruitful would be to examine insight as a potential moderator of the relationship between neurocognition and subjective QOL. Secondly, the differential relationship between neurocognition and objective and subjective QOL revealed in this study emphasizes the continuing need for researchers to measure both indices of QOL in the same sample. Doing so would continue to help elucidate the differential determinants of subjective and objective QOL. Perhaps more importantly, using both objective and subjective indices of QOL also helps to ensure that clinicians and researchers attend to a holistic construct of patient well-being.

In addition, we note that preliminary longitudinal research partially supports the findings of this meta-analysis. Some studies show that improvements in neurocognition were associated with improvements in objective QOL, especially for global cognitive functioning and measures of verbal ability (Kasckow et al., 2001; Addington and Addington, 2000). In another study, higher objective QOL at three-year follow-up was found to be associated with improved verbal memory performance, but lower mental-flexibility (Sota and Heinrichs, 2004). In another study, better baseline scores of sustained attention predicted worse subjective QOL following a rehabilitation regime that included cognitive rehabilitation (Proteau et al., 2005). However, additional research using controlled longitudinal paradigms will be necessary to determine the differential impact that cognitive-enhancing interventions have on objective and subjective QOL.

Summary

Taken together, the markedly different pattern of relation between neurocognition and objective and subjective QOL has important implications for those researchers and clinicians working to treat the cognitive deficits of individuals with schizophrenia. Especially in light of the MATRICS initiative work towards the development of cognition-enhancing pharmacological agents (Marder, 2006), the differential relationship between neurocognition and objective and subjective QOL revealed in this study may be a particularly pertinent. Our results confirm the positive link between neurocognition and objective QOL, which supports the hypothesis that improving neurocognition may have a positive impact on objective measures of

patient functioning. However, because the results indicate that neurocognition was largely unrelated to subjective QOL, the current study emphasizes the need for clinicians to craft new interventions alongside those targeting cognition in order to ensure that treatment attends to individuals' subjective life satisfaction in addition to improving objective QOL or social functioning.

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Table 1. Neurocognition and Quality of Life in Schizophrenia

A. Studies of Objective Quality of Life

Study	Sample	Neurocognitive Measures	Quality of Life Measure	Major Findings
Addington and Addington 2008	50 FE participants (88% S), 53 ME participants (100% S), and 55 NPC	WAIS-digit-symbol, letter-number sequencing; CPT; WMS-LMI, LMII; RVLT-immediate, delayed; WCST-CAT, PE	QLS	Cognition predicted QLS scores at time 1 and time 2 for FE, ME, and NPC groups.
Addington and Addington 1999	80 outpatient participants (100% S)	WAIS-vocabulary subtest; CPT; WMS-LMI, LMII; WCST-CAT, PE	QLS	Poor executive-function was significantly correlated with low scores on the QLS.
Dickinson and Coursey 2002	20 outpatient participants (92.5% S or SA)	WAIS-vocabulary, digit-span, letter-number sequencing, symbol-digit subtests	LOF	Neurocognitive measures (except for digit span) were positively associated with LOF.
Fiszdon et al. 2008	151 outpatient participants (100% S or SA)	WAIS-digit span and digit-symbol subtests; WMS-LMI; HVLT-immediate	QLS	At intake, none of the neurocognitive variables were significantly associated with QLS total.
Heslegrave 1997	42 outpatient participants (100% S)	Computerized WCST-PE	SIP	Neurocognitive impairment generally unrelated to objective QOL.
Lipkovich et al. 2009	414 outpatient participants (100% S or SA)	WAIS-letter-number sequencing, RAVLT (with 10min. Crawford alternative)	QLS	At baseline, multiple QLS domains significantly related to processing speed, working memory, and verbal memory.
Lysaker and Davis 2004	65 outpatient participants (100% S or SA)	WAIS-vocabulary subtest; HVLT-delayed, WCST-PE	QLS	All three neurocognitive measures were correlated with at least one domain of the QLS.
Matsui et al. 2008	53 outpatient participants (100% S) and 31 NPC	JVLT-immediate	QLS	QLS total score was significantly predicted by the script and sentence memory tests.
Narvaez et al. 2008	88 outpatient participants (100% S or SA)	WAIS- digit span, digit-symbol, letter number sequencing subtests; WMS-LMI, LMII; WCST-PE, CAT	Objective section of QOLI	List learning and WCST measures were positively associated with objective QOL.
Savilla et al. 2008	57 outpatient participants (100% S)	BACS-list learning-immediate, digit sequencing task, symbol coding	QLS	Cognitive functioning was positively associated objective QOL.

B. Studies of Subjective Quality of Life

Study	Sample	Neurocognitive Measures	Quality of Life Measure	Major Findings
Alptekin et al. 2005	38 outpatient participants (100% S), 31 NPC	WAIS-digit span; COWAT-letter fluency	WHOQOL-BREF	The social domain scores of the WHOQOL were positively correlated with digit span and COWAT.
Brekke et al. 2001	40 outpatient participants (100% S)	WCST-PE	SWL	Negative relationship between WCST and SWL.
Brissos et al. 2008	30 euthymic bipolar I participants, 23 remitted schizophrenia participants (100% S), and 23 NPC	WAIS-digit span subtest, WMS-LMI, LMII; Symbol-Digit Modalities Test; Trail Making Test-A, B; COWAT-letter fluency	WHOQOL-BREF	No correlations between any of the domains of the WHOQOL-BREF and any neurocognitive variables.
Chino et al. 2009	36 outpatient participants (100% S)	RAVLT-immediate; Letter Fluency Test	WHOQOL-BREF	Neurocognitive test results were not correlated with subjective QOL.
Corrigan and Buican 1995	49 participants in transition out of state hospital (80.8% S, SA or mood disorder)	WAIS-vocabulary subtest	Subjective section of QOLI	Verbal ability was inversely related to subjective QOLI.
Dickerson et al. 1998	72 outpatient participants (100% S)	WAIS-vocabulary, digit span, digit-symbol subtests; WMS-LMI, LMII; Trail Making Test-A, B; WCST-PE, CAT	Subjective section of QOLI	Inverse relationship between WMS-LMI and subjective QOLI.
Herman 2004	46 inpatients dually-diagnosed with schizophrenia and substance abuse, 43 inpatients with schizophrenia	WAIS-vocabulary, digit-span, digit symbol; subtests COWAT-letter fluency; WMS-LMI, LMII; Trail Making Test-A, B	WHOQOL-BREF	Subjective QOL was only positively correlated with COWAT.
Hofer et al. 2005	60 outpatient participants (100% S)	CVLT-immediate (German version); WCST-PE, CAT	WHOQOL-BREF	No significant relationship found between neurocognitive variables and subjective QOL.
Narvaez et al. 2008	88 outpatient participants (100% S or SA)	WAIS- digit span, digit-symbol, letter number sequencing subtests; Letter Fluency; WMS-LMI, LMII, Trail Making Test-A, B; WCST-PE, CAT	Subjective section of QOLI	Better neuropsychological functioning independently predicted worse subjective QOL.
Smith et al. 1999	46 outpatient participants (100% S or SA)	CVLT-immediate; WCST-CAT	Subjective section of QOLI	Subjective QOL was not correlated with any neurocognitive variables.

Table 2. Neurocognitive Measures Included in the Meta-Analysis

Neurocognitive Domain	Measure(s)
Crystallized Verbal Ability	Weschler Adult Intelligence Scale-Vocabulary subtest (WAIS-Vocabulary)
Vigilance	Continuous Performance Test (CPT)
Working Memory	Digit Span Subtest of the WAIS (Digit Span)
Prose Recall	Weschler Memory Scale-Logical Memory, Immediate (LMI) and Long Delay (LMII)
List Learning	California Verbal Learning Test, Hopkins Verbal Learning Test, Rey Auditory Verbal Learning Test (CVLT/HVLT/RVLT- Immediate and –Delayed)
Fluency	Letter Fluency, Controlled Oral Word Association Test (COWA-FAS)
Processing Speed	Digit Symbol Substitution Test (DSST), Trail Making Test A (TMT-A)
Executive Function	Wisconsin Card Sorting Test (WCST)-Categories Achieved (CAT) and -Perseverative Errors (PE); Trail Making Test B (TMT-B)

Table 3. Study Characteristics

Variable	Objective QOL Studies N=10	Subjective QOL Studies N=10
Mean Sample Size	**107.40 (106.39)**	**54.1 (22.53)**
% reporting	*100*	*100*
Age in Years	**38.57 (5.77)**	**37.31 (5.21)**
% reporting	*100*	*100*
% Male	**71.33 (11.66)**	**63.47 (6.52)**
% reporting	*100*	*100*
Education in Years	**12.50 (.71)**	**11.63 (1.15)**
% reporting	*60*	*60*
Illness Duration in Years	**13.03 (7.73)**	**14.12 (5.73)**
% reporting	*30*	*60*
Age of Onset	**23.75 (1.01)**	**21.90 (3.56)**
% reporting	*60*	*30*
No. of Hospitalizations	**7.19 (4.51)**	**4.13 (3.16)**
% reporting	*30*	*30*
PANSS Positive	**16.06 (1.70)**	**13.27 (3.26)**
% reporting	*50*	*40*
PANSS NEGATIVE	**18.09 (3.34)**	**16.65 (2.74)**
% reporting	*50*	*40*
HAM-D	**10.90**	**6.97 (5.56)**
% reporting	*10*	*20*
CPZ Equivalents	**636.20 (223.14)**	**399.38 (157.32)**
% reporting	*50*	*50*
Study Quality Score	**.90 (1.1)**	**.40 (.52)**
% reporting	*100*	*100*

Table 4. Estimated Effect Sizes of the Relationship between Neurocognition and Objective Quality of Life

Measure	*k*	N	d	95% CI	z	p	Q_w	N_{FS}
Crystallized Verbal Ability								
WAIS-Vocabulary	3	185	.34	.13/.55	3.23	.00	3.76	17
Vigilance								
CPT	3	271	.15	-.02/ .32	1.70	.09	1.50	N/A
Working Memory								
Digit Span	4	336	.26	.11/ .41	3.35	.00	5.77	17
Letter-Number Sequencing	4	626	.17	.06/.28	2.96	.00	13.23*	10
Prose Recall								
LM-Immediate	4	422	.11	-.02/.25	1.65	.10	4.17	N/A
LM-Long Delay	3	271	.12	-.05/.29	1.35	.18	1.22	N/A
List Learning								
CVLT/HVLT/RVLT-Immediate	4	452	.37	.24/.51	5.57	.00	11.67*	26
CVLT/HVLT/RVLT-Delayed	3	563	.13	.01/.25	2.19	.03	6.16*	5
Processing Speed								
Digit-Symbol	5	439	.23	.10/.36	3.40	.00	19.27*	18
Executive-Function								
WCST-PE	5	439	.28	.14/.41	2.61	.00	10.76*	23
WCST-CAT	3	271	.55	.38/.72	.63	.00	.85	30

Note: CPT=Continuous Performance Test, CVLT=California Verbal Learning Test, HVLT=Hopkins Verbal Learning Test, RVLT= Rey Auditory Verbal Learning Test, LM=Logical Memory,WCST=Wisconsin Card Sorting Test, PE=Perseverative Errors. *K*, number of studies; N, number of participants, 95% CI=95% Confidence Interval, Qw=within-group homogeniety statistic.

*p<.05

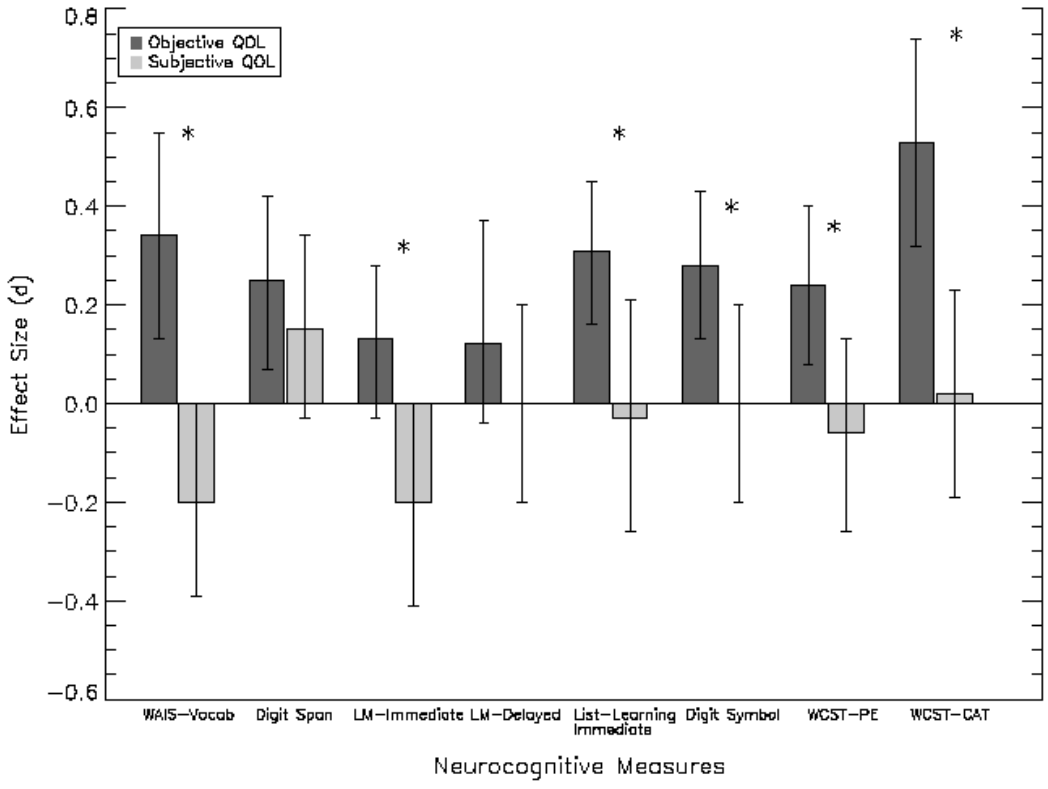
Table 5. Estimated Effect Sizes of the Relationship between Neurocognition and Subjective Quality of Life

Measure	*k*	N	d	95% CI	z	p	Q_w	N_{FS}
Crystallized Verbal Ability								
WAIS -Vocabulary	3	210	-.29	-.49/-.10	-2.96	.00	18.56*	14
Working Memory								
Digit Span	5	310	.01	-.15/.17	.10	.92	22.00	N/A
Prose Recall								
LM-Immediate	4	272	-.16	-.33/.01	-1.89	.06	-2.25	N/A
LM-Long Delay	4	272	-.06	-.23/.10	-.74	.46	1.15	N/A
List-Learning								
CVLT/HVLT/RVLT-Immediate	4	230	.03	-.15/.21	.30	.76	.63	N/A
Fluency								
Letter Fluency	5	274	.26	.09/.43	3.00	.00	32.12*	21
Processing Speed								
Digit-Symbol	4	272	-.19	-.36/-.02	-2.20	.03	10.58*	11
Trail Making Test-A	4	272	-.06	-.23/.11	-.73	.46	1.13	N/A
Executive-Function								
WCST-PE	4	260	.01	-.16/.18	.14	.89	3.38	N/A
WCST-CAT	4	266	.04	-.13/.21	.43	.67	.18	N/A
Trail Making Test-B	4	272	-.04	-.21/.13	-.49	.63	.50	N/A

Note: CPT=Continuous Performance Test, CVLT=California Verbal Learning Test, HVLT=Hopkins Verbal Learning Test, RVLT= Rey Auditory Verbal Learning Test, LM=Logical Memory,WCST=Wisconsin Card Sorting Test, PE=Perseverative Errors. *K*, number of studies; N, number of participants, 95% CI=95% Confidence Interval, Qw=within-group homogeneity statistic.
*p<.05

Figure 1. Neurocognition and Objective and Subjective Quality of Life

Overall effect-size comparison (+/- 95% confidence interval) of the relationship between standardized measures of neurocognition and subjective and objective QOL in individuals with schizophrenia.



* p<.05